

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 SUR-REPLY TO PETITIONER'S REPLY

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<i>Yita LLC v. MacNeil IP LLC</i> , 69 F.4th 1356 (Fed. Cir. 2023)	18

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
EX2053	Transcript from Deposition of Paul Spellman on December 19, 2024

I. CHELL DOES NOT ANTICIPATE CLAIMS 1-30

Petitioner presents two main arguments as to why the '689 patent supposedly cannot claim the benefit of the '487 application and is hence anticipated by the later-filed Chell reference: (1) the '487 application does not describe collecting “whole probes,” and (2) the '487 application does not describe “on-analyte” ligation.

Yet, when it comes to written description, “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.” *Allergan USA, Inc. v. MSN Lab’ys Priv. Ltd.*, 111 F.4th 1358, 1375 (Fed. Cir. 2024) (citation omitted) (emphasis in original). As documented below, Petitioner’s arguments ignore this standard and are instead based on attempting to impose an erroneous and overly-stringent understanding of written description. When the '487 specification is viewed as a whole through the eyes of the POSA, there can be no question that it describes both collecting “whole probes and “on analyte” ligation and hence fully supports the claims.

A. The '487 Application Discloses Collecting “Whole Probes”

Petitioner’s primary argument that the '487 application fails to support the '689 patent claims is based on the notion that, while the claims cover collecting whole probes, the '487 application describes only collecting partial probes. Yet, as a matter of commonsense, there is little difference between partial and whole probes. One is a subset of the other, and Petitioner’s attempt to argue for lack of written

description based on a distinction between the two is dubious on its face. And, as documented below, all the specific arguments that Patent Owner presents on reply lack merit.

1. The '487 Application Does Not Require Probe Cleavage

Petitioner contends that “[c]leavage of probes is not an optional feature, and collecting whole probes is not part of the described methods in the 487 application.” Paper 39 (“Reply”) at 3. In other words, Petitioner contends that collecting whole probes is not disclosed because, in the '487 application, probes are *always* cleaved to release only partial probes for collection.

Yet, when asked on cross-examination whether this truly is the case, Petitioner’s expert, Dr. Spellman, evaded the issue and refused to provide a straightforward answer. *See* EX2053 at 98:3:12-103:2. Dr. Spellman’s attempt to dodge the question was unsurprising because in fact the '487 application’s disclosure is not limited to cleavable probes. Indeed, the very disclosure that Petitioner relies upon to argue the specification is limited to cleavable probes always makes clear that disclosure is non-limiting, using language such as “can comprise,” “in the aspect that,” “can further comprise,” “non-limiting example,” etc. And, as explained in Patent Owner’s Response, a POSA would have understood that the '487 application discloses at least two approaches for releasing entire probes based on (1)

the well-known technique of denaturation and (2) indirect hybridization. Paper 36 (“Response”) at 42-48. Petitioner’s responses to this disclosure are without merit.

a. The ’487 Application Discloses Denaturation To Release Entire Probes Without Cleavage

A POSA would have understood that the ’487 application discloses denaturation to release not just cleaved probes, but *entire probes*. At the outset, both experts agree that the ’487 application itself discloses denaturation. EX1055 ¶¶ 93-95; EX2006 ¶¶ 94-95. Both experts also agree that denaturation is a well-known technique, “a basic concept in genetics and molecular biology.” *Id.* ¶ 94. While Petitioner contends that the disclosure of denaturation in the ’487 application itself is directed to purposes other than releasing entire probes, Petitioner does not deny that the technique is disclosed for releasing one nucleic acid strand from another and is thus applicable to entire probes.

What’s more, as to the specific use of denaturation to release entire probes, Petitioner does not dispute that the incorporated ’386 application discloses precisely this. Petitioner’s expert agreed during cross-examination that the ’386 application discloses hybridization and de-hybridization of sequencing probes:

Q: So do you agree that Exhibit 2008 discloses sequencing probes that hybridize to a target nucleic acid?

A: In Paragraph 11 they are mobilized on a substrate. There’s a set of conditions there, but yes.

Q: Do you agree that Exhibit 2008 discloses de-hybridizing sequencing probes from the target nucleic acid?

...

A: It describes a dehybridization.

EX2053 at 75:13-76:18.¹

Petitioner and its expert nonetheless attempt to discount this disclosure because it is provided in the context of a specific type of probe, specifically, a “sequencing probe.” A POSA, however, would not be so dim as to overlook the import of the disclosure merely because it pertains to “sequencing probes,” particularly given that denaturation is “a basic concept in genetics and molecular biology.” EX2006 ¶ 94. Petitioner never explains why a POSA would not understand a probe to be a probe, particularly given the ’487 application’s guidance that “[a]ny probe or set of probes described herein may be used in methods and kits of the present disclosure.” EX1009 ¶ 259; EX2006 ¶ 100. As the Federal Circuit explained, written description is satisfied “when the essence of the original disclosure conveys the necessary information—regardless of how it conveys such information, and regardless of whether the disclosure’s words are open to different interpretations.” *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354 (Fed. Cir. 2015).

¹ Dehybridization is a type of denaturation. *Id.* at 76:21-22.

Accordingly, the probes in the '386 application being called “sequencing probes” does not undermine its written description support.

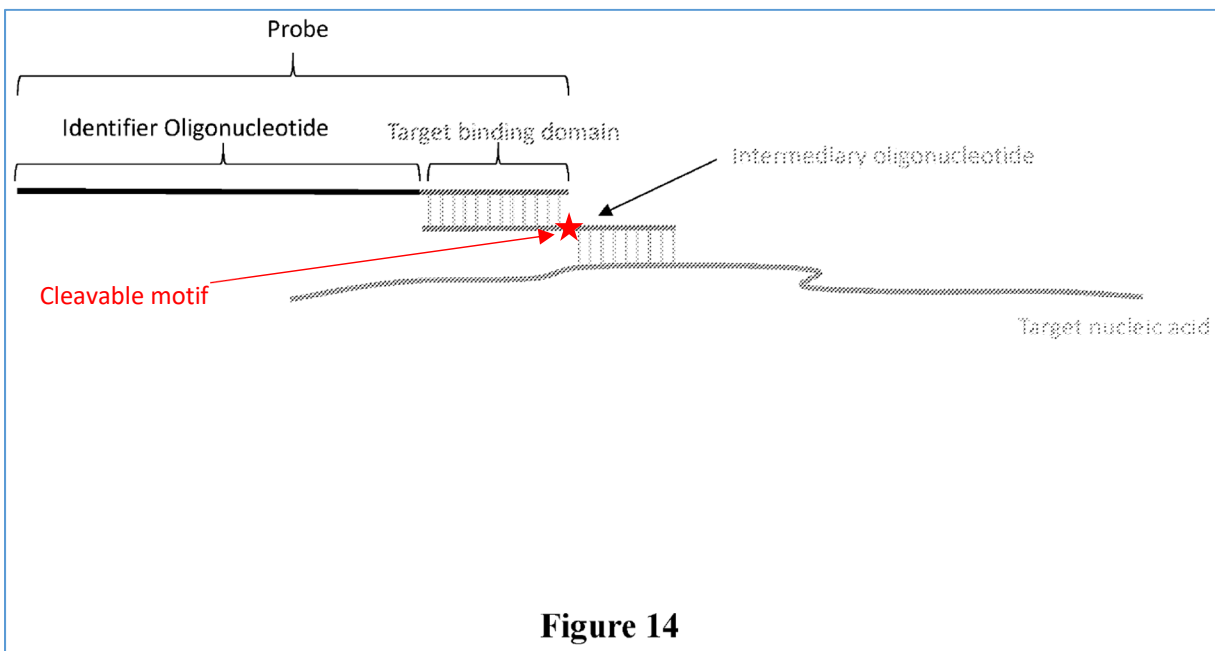
Unable to respond on the merits to the disclosure in the '386 application, Petitioner contends that it is not properly incorporated by reference. The '487 application, however, states that the '386 application is “incorporated herein by reference in its entirety.” EX1009 ¶¶ 216, 227. The '487 further states: “All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.” *Id.* ¶ 64. That is more than sufficient. *See Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 907 (Fed. Cir. 2018) (finding “This application discloses a number of improvements over and enhancements to the hybrid vehicles disclosed in the [reference], which is incorporated herein by this reference” to be “plainly sufficient”).

Petitioner also contends that the '386 application is not incorporated because the '487 application refers to “US2014946386” instead of “US14946386.” This is an obvious typographical error, and a POSA would understand it to be such because there is no US2014946386 document. Importantly, neither Petitioner nor its expert contest that application no. 14/946,386 is the identified document. Moreover, the application publication is identified as a cited reference. EX2012 at 205, 1541; *see also* EX1001 code (56). Petitioner cites no law to suggest that a typographical error

negates a clear incorporation by reference in circumstances such as this. Although Petitioner's expert opined that a POSA would find the incorporation to be ineffective, Dr. Spellman confirmed at cross-examination that he had no independent opinion and was simply relying on counsel. EX2053 at 62:21-63:3.

b. The '487 Application Further Discloses Releasing Entire Probes Via Indirect Hybridization

While the '487 application's disclosure of releasing probes by denaturation is more than sufficient to provide written description support for removal of whole probes, the '487 application further discloses an indirect hybridization scheme that a POSA would have understood to release entire probes when an intermediary oligonucleotide is cleaved. This is depicted in a modified version of Figure 14 that appeared in Patent Owner's response to the Petition:



Response at 47 (red annotations added).

Petitioner nonetheless attempts to discount this disclosure because “none of the 487 application’s indirect hybridization embodiments include a cleavable motif in [the intermediary oligonucleotide].” Reply at 8. Petitioner, however, does not deny that, according to the ’487 application, (1) the intermediary oligonucleotide is a probe; (2) a probe can comprise a cleavable motif; and (3) “[a]ny probe or set of probes described herein may be used in methods and kits of the present disclosure.” Response at 46-48; EX2006 ¶ 103.

Although Petitioner’s expert tried to put his own spin on this disclosure, he could not deny on cross-examination what the ’487 application states in plain-English. See EX2053 at 43:9-13 (“Q. But you do not disagree that Paragraph 233 states, ‘It could be said that the intermediary oligonucleotide is a probe as defined herein’? A. The specification does say that, yes.”); *id.* at 96:19-22 (“Q. Do you agree that the ’487 application teaches a probe with a cleavable linker? A. The ’487 teaches a probe with a cleavable linker, yes.”).

To the extent Petitioner contends that the ’487 application mandates a specific cleavage location, such as on a probe, that is also incorrect. As Dr. Sherman explains, “a POSA would have understood from this broad disclosure that a ‘cleavable moiety’ is not fixed between an identifier oligonucleotide and a target

binding domain of a probe and can be in other locations and be part of other sequences in the method.” EX2006 ¶ 93; *see also* EX2053 at 105:17-106:14 (Petitioner’s expert agreeing that the ’487 application discloses a cleavable sequence that is not on a probe); EX1009 ¶¶ 18, 131 (“The constant nucleic acid sequence can also contain a cleavable moiety”).

Petitioner also contends that a cleavable intermediary oligonucleotide “would eliminate the 487 application’s stated advantages of the indirect hybridization method.” Reply at 8. Specifically, Petitioner alleges that there would be “no economical advantage because it would still require custom synthesis of target-specific probes with a cleavable motif.” *Id.* at 9. Petitioner’s “economical advantage” argument, however, lacks support.

Petitioner relies on its expert’s opinion about the relative cost of probes. But Dr. Spellman admitted on cross-examination that he “can’t actually be certain” and has “no knowledge whether or not [synthetic oligonucleotides with cleavable linkers] were broadly available.” EX2053 at 11:6-12:18. Dr. Spellman also admitted that the specification does not explicitly state why a probe, which Dr. Spellman assumes to be cleavable, is more expensive than an intermediary oligonucleotide. *Id.* at 44:22-45:8.

In any event, the cost and speed advantages identified in the '487 application are maintained with a cleavable intermediary oligonucleotide. The specification teaches that with intermediary oligonucleotides, “a single set of indirectly-binding probes can be used to detect an infinite variety of target nucleic acids (present in a sample) in different experiments simply by replacing the target-specific (synthetic) oligonucleotide portion of the assay.” EX1009 ¶ 233. Regardless of whether an intermediary oligonucleotide is cleavable, it can serve as an indirectly-binding probe that can be switched out between experiments to target the analytes of interest (out of the “infinite variety of target nucleic acids”). The remaining reagents can thus remain constant from one experiment to another.

2. The '487 Application Does Not Require The Target Binding Domain And Identifier Oligonucleotide To Be Distinct Sequences

As a secondary argument, Petitioner contends that the “target binding domain” and “identifier oligonucleotide” of a probe must be distinct because “[n]owhere does the 487 application describe a target binding domain and identifier oligonucleotide as being the same or overlapping sequence.” Reply at 7. In other words, Petitioner contends that the '487 application does not disclose the release of an entire probe when the identifier oligonucleotide is released where the “target binding domain” and “identifier oligonucleotide” of a probe overlap.

As Dr. Sherman explains, however, a POSA would have understood that the same sequence can be both a “target binding domain” and “identifier oligonucleotide” because the ’487 application refers to these terms by their function and never requires two distinct sequences. EX2006 ¶ 102. Petitioner never addresses why a sequence cannot have two functions.

3. The Disclosure Of Negative Purification Further Discloses Removal Of Whole Probes

Petitioner does not substantively address Patent Owner’s Response that the negative purification disclosed in the ’487 application constitutes a disclosure of removing entire probes. Reply at 6-7. It is undisputed that the negative purification described takes place after probes are released and that entire probes are removed to reduce background. Petitioner, who contends that the ’487 application discloses only releasing portions of a probe, fails to address how entire probes are available for purification if probe cleavage is required because the application of the cleavage force affects both bound and unbound probes. In other words, entire unbound probes cannot exist if a cleavage step is required as Petitioner contends. Accordingly, the negative purification disclosure supports the release of entire probes.

B. The '487 Application Discloses “On-Analyte Ligation”

Petitioner’s second written description argument is that the claims require “on-analyte” ligation while the '487 application “exclusively describes ‘off-analyte’ ligation.” Reply at 9. The '487 application, however, adequately discloses “on-analyte” ligation, and Petitioner’s position to the contrary is at odds with recent Federal Circuit law.

1. *Allergan* Forecloses Petitioner’s Arguments

As explained in Patent Owner’s Response, the situation here mirrors that in *Allergan*, where the Federal Circuit found written description for claims that did not require a glidant component. Response at 58-59. While Petitioner contends that *Allergan* is inapposite and *ICU* should instead be applied, it ignores *Allergan*’s analysis of *ICU*.

The Federal Circuit distinguished *Allergan* from *ICU* on at least two bases: (1) “the entirety of the specification in *ICU Medical* described **only** medical valves having spikes” while in *Allergan* “the specification...discloses at least two embodiments in which the formulation does not necessarily include the unclaimed glidant”; and (2) “the specification in *ICU Medical* attributed a particular function to the spike—piercing a seal inside the valve—that could not be accomplished

without a spike” while in *Allergan* “the specification attributes no particular function or significance to the glidant.” *Allergan*, 111 F.4th at 1375 (emphasis in original).

This case is like *Allergan*, not *ICU*. As explained in Patent Owner’s Response and herein, the ’487 application does not **require** ligating a probe pair while “off” a target analyte. Response at 51-58. The ’487 application also attributes no particular function or significance to ligating a probe pair while “off” the target analyte. There is no function, and Petitioner does not contend otherwise, that cannot be done without “off-analyte” ligation.

Allergan is thus directly on point here and confirms the ’487 application provides adequate written description of the ’689 patent claims.

2. The ’487 Application Includes Full Disclosure Of “On-Analyte” Ligation

As explained in Patent Owner’s Response, the ’487 application, including its incorporated references, discloses both (1) probes that bind to target analytes and (2) ligation of probes—the two components of Petitioner’s “on-analyte” ligation. Response at 51-58. Petitioner does not dispute this.

Instead, Petitioner contends there is not a single embodiment of the claimed methods with “on-analyte” ligation. As the Federal Circuit explained, however, “the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and

predictability of the relevant technology.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Here, the two components of “on-analyte” ligation are disclosed, the skill level of a POSA is high, and both experts agree that ligation is a known and fundamental technique. Nothing prevents a POSA from ligating probes while they are “on-analyte” given the disclosure in the collective embodiments in and incorporated into the ’487 application. As Dr. Sherman explains, “[l]igation involves little more than adding the proper ligase in the proper conditions, which a POSA would have understood,” such that “a POSA would have been able to perform a simple ligation step to ligate a probe pair as claimed.” EX2006 ¶ 120.

Petitioner takes issue with the disclosure in the incorporated ’607 publication for not explicitly depicting ligation. Petitioner, however, does not dispute that the ’607 publication discloses a probe pair that hybridizes to a target analyte. Moreover, Dr. Sherman confirmed at deposition that a POSA would have looked at the ’607 publication and understood it to be “a probe pair that could be ligated with a ligase to form a single contiguous fragment.” EX1056 at 68:24-69:4. That the ’607 publication did not include a ligation step does not detract from a POSA’s understanding in light of other disclosures and a POSA’s knowledge of ligation. EX2006 ¶¶ 114-122.

Petitioner likewise takes issue with the incorporated '774 publication's disclosure because the "774 publication's antibody-based proximity ligation methods for protein detection are unrelated to the 689 patent's methods for spatial detection." Reply at 12. Petitioner, however, does not dispute that the '774 publication discloses a "signal oligo" that "is generated by ligating two oligos that are in close proximity, e.g. proximity ligation." EX2010 ¶ 83. Both the '774 publication and the '487 application involve nucleic acid probes, such that the specific terms used in the '774 publication, such as "signal oligo," do not affect the disclosure. *Inphi*, 805 F.3d at 1354. This is particularly so due to the '487 application's guidance that "[a]ny probe or set of probes described herein may be used in methods and kits of the present disclosure." EX1009 ¶ 259. As Dr. Sherman explains, a POSA would have understood that the '774 publication's embodiment is analogous to a probe pair that is ligated after hybridizing to a target nucleic acid. EX2006 ¶ 117.

Petitioner also contends that "Bruker conveniently omits a key feature in the '774 publication's method: the 'signal oligo' generated from the proximity ligation is released from the probe complex to be collected and analyzed." Reply at 12. The '774 publication, however, specifically states that Figures 8B-D depicts

“methods by which the signal oligo shown in FIG. 8A *may be* released and purified.”

Thus, Figures 8B-D are *optional*.

Furthermore, the release and collection of signal oligos support Patent Owner. As Petitioner agrees, the ’774 publication teaches ligating probes before their release and collection, exactly what Petitioner contends is missing in the ’487 application. Petitioner’s contention that the ’774 publication does not disclose collecting entire probes is a red herring—the disclosure is for “on-analyte” ligation. The ’487 application’s disclosure of collecting entire probes is discussed elsewhere. *See, e.g.* Part I.A.

3. The ’487 Application Does Not Require A Specific Order Of Steps

Petitioner contends that “[e]very ligation-based embodiment of the 487 application requires the same order of steps,” such that probe ligation occurs “off-analyte” on the released identifier oligonucleotide. Reply at 14. Not so. Nowhere does the ’487 application state that the steps in an embodiment must take place in an ordered sequence and nothing in the language of the specification requires such an ordering. As Dr. Sherman explains, “a POSA would have understood that the ligation of probes can take place prior to the identifier oligonucleotide’s release.” EX2006 ¶ 116. Petitioner’s expert offers no opinion why, for the purpose of detecting analytes, this is not possible. As such,

Petitioner’s reading of the ’487 application is misguided. The ’487 application provides written description for “on-analyte” ligation.

II. SO-456 DOES NOT ANTICIPATE CLAIMS 1-8, 11-23, 26-30

A. So-456 Does Not Collect The Claimed Probes

“It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify with particularity the evidence that supports the grounds for the challenge to each claim.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016). An “IPR petitioner may not raise in reply an entirely new rationale, not raised in its petition or responsive to arguments raised in the patent owner’s response brief.” *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1366 (Fed. Cir. 2023). “Once the Board identifies new issues presented for the first time in reply, neither this court nor the Board must parse the reply brief to determine which, if any, parts of that brief are responsive and which are improper.” *Intelligent*, 821 F.3d at 1369.

Petitioner contends for the first time on reply that “So-456’s method captures *the original ligated probes* that were bound to the target analytes *along with the amplicons*,” because “*both* the original ligated probes released from the target analyte and amplicons — are captured on the capture probes (Step 825).” Reply at

21. This new theory is nowhere present in the original Petition and should not be considered.

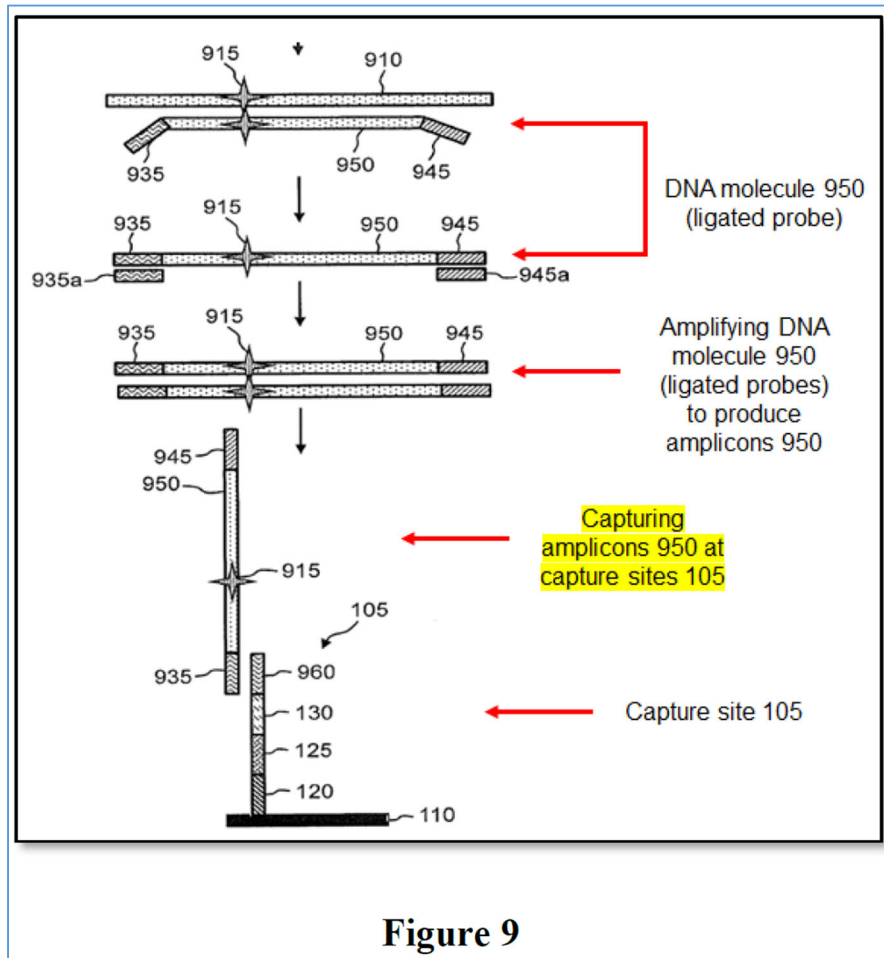
Indeed, the Petition is clear that amplicons—not the “original ligated probes”—are captured:

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.

Paper 2 (“Petition”) at 20. The Board understood the Petition in the exact same way during institution:

Petitioner alleges that So-456’s method discloses amplification of the ligated probes (950) to produce “unbound amplified ligated probes” or “amplicons” (also 950), which are free from the target DNA molecules. Pet. 20. These *amplicons are then “captured”* on a capture array by passive diffusion where they bind to a capture site, 105, as shown in Figure 1A.

Paper 14 at 19. The Petition even included an annotated figure from Dr. Spellman to depict capturing amplicons:



Petition at 21 (yellow highlighting added). Thus, Petitioner identified solely *amplicons* to allegedly disclose the “collecting” claim step. Nowhere does the Petition mention capturing the “original ligated probes.”

Nevertheless, Petitioner’s new theory about capturing the “original ligated probes” ignores So-456’s disclosure. While Dr. Spellman attempts to obfuscate his own annotation to claim that the captured amplicons include the “original ligated probes,” So-456 provides a clear definition that an amplicon is a *copy*:

As used herein, the term “amplicon,” when used in reference to a nucleic acid, *means the product of copying the nucleic acid*, wherein the product has a nucleotide sequence that is the same as or complementary to at least a portion of the nucleotide sequence of the nucleic acid...A first amplicon of a target nucleic acid can be a complementary copy.

EX1005 ¶ 121. Consistent with this definition, So-456 discloses capturing *copies*: “*Genomic amplicon 950 is captured* onto the array by hybridization of universal capture sequence 935 to capture sequence 960.” *Id.* ¶ 183. During deposition, Dr. Spellman agreed that he applied So-456’s definitions in his declaration. EX2053 at 33:10-21. Because it is undisputed that the amplicons were never

“bound to the at least one target analyte,” as required by the claims, Petitioner fails to show that So-456 anticipates the ’689 patent.²

To the extent the Board considers Petitioner’s new theory, Petitioner fails to show that the “original ligated probes” are captured. Dr. Spellman’s testimony confirms the drastically low likelihood of capturing the “original ligated probes.” As he explains, when PCR is performed—a common amplification technique called out in So-456—as many as 2³⁰ amplicons may result. *Id.* at 28:1-6 (“PCR producing...as many as two to the 30th copies.”); *id.* at 52:17-21 (“Q. To clarify, a

² Despite the clear language in his annotated figure, Dr. Spellman refused to acknowledge his original position that the capture of amplicons allegedly satisfied the “collecting” claim step:

Q. Are you able to give me a yes or no on whether the capture of the derived copies of 950, the ones generated at Step 820, do those meet the collecting claim step of the ’689 patent?

A. I don’t believe I comment on that in my clarification [sic].

Q. So you’re not able to say one way or the other today. Is that right?

A. I don't believe I comment on that in my declaration, and I’m not prepared to form an opinion about that right now.

EX2053 at 59:17-60:8. Petitioner’s new theory is nothing more than an attempt to belatedly rewrite the Petition.

million copies is possible. Is that right? A. It is not precluded.”); *see also* EX1005 (“An amplicon can be produced by any of a variety of amplification methods...including, for example...polymerase chain reaction (PCR)....”); *id.* ¶ 122 (“The number of template copies or amplicons that can be produced...can be at least...10,000 copies.”). Of those amplicons, capturing 10% is “a very high fraction.” EX2053 at 39:5-40:5. Out of the captured molecules, sequencing 50% of them would be considered a “high yield.” *Id.* at 40:17-41:7. Taking these numbers together, the “original ligated probes” are far from being necessarily captured and sequenced, as required by the claims.

B. So-456 Does Not Treat Tissue Samples

Petitioner contends that Patent Owner “mischaracterizes So-456’s disclosures in ¶¶[00152]-[00153]” and those paragraphs allegedly teach “treating a tissue sample to facilitate hybridization of probes to a target analyte in the tissue.” Reply at 15.

The alleged teaching in these paragraphs of So-456, however, is threadbare. The two paragraphs, reproduced in their entirety, do not disclose any technique or any indication of a step to modify a tissue sample so as to assist subsequent probe hybridization:

[152] 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.

[153] 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.*

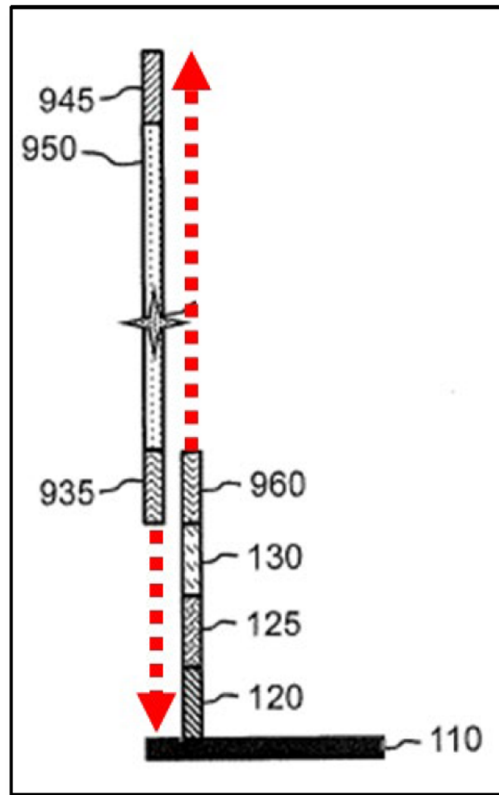
EX1005 ¶¶ 152-153. Petitioner does not dispute that the *only* techniques disclosed in paragraphs 152-153 have nothing to do with facilitating probe hybridization—tissue sectioning, reverse transcription, and amplification reaction. The claimed tissue “treatment” step is thus not disclosed.

Petitioner nonetheless contends that these two paragraphs are not limited to the disclosed techniques because “So-456’s method *must* treat the tissue sample to facilitate binding of the probes to the target analytes because the probes in Figures 8-9 bind to the target analytes and are processed in the subsequent steps.” Reply at 16 (emphasis in original). In other words, Petitioner makes a belated inherency argument. But Petitioner cites no law to support such an inherency theory based on the proposition that a claim limitation is disclosed simply because it must occur

to practice the reference's method. If anything, the law is to the contrary. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd*, 851 F.3d 1270, 1274 (Fed. Cir. 2017) (“*Kennametal* does not stand for the proposition that a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would ‘at once envisage’ the missing limitation.”). So-456 does not disclose the claimed tissue treatment.

C. So-456 Does Not Disclose The Claimed Extension

Petitioner continues to allege that the downward reaction in its annotated Figure 9 inherently occurs to “incorporat[e] a spatial barcode into the capture probes”:



Reply at 21; EX2053 at 85:12-87:10. The downward reaction, in particular, does not necessarily occur, and, even if it did occur, it would not incorporate a spatial location identifier, as the claims require.

As to the requirement to incorporate a spatial location identifier, Petitioner points to item 130 in the figure above. But item 130 is not a spatial location identifier. To the contrary, So-456 explicitly states for Figure 9 that “SBS primer region 130 is SBS3.” EX1005 ¶ 182. That is, item 130 is a sequencing primer.

Petitioner’s contention that a POSA would have recognized that as a typographical error is without merit. According to Petitioner’s expert at cross-

examination, a POSA “would come to the conclusion that there are typographical errors in the annotation for Figure 8 and 9” because in Figure 6 “a different typographical error has occurred in which Segment 130 has two different functions that are incompatible with one another.” EX2053 at 92:4-93:22. In other words, Petitioner’s contention is that So-456 is so full of errors that a POSA would recognize that Figure 9 contains an error and resolve it by assigning segment 130 as the location-identifying sequence. A POSA would more likely understand So-456 as printed. EX2006 ¶¶ 59-60.

Petitioner also contends that region 130 *must* be a location-identifying sequence because one is required somewhere on the capture probe. Nothing, however, prevents a different region from serving as the location-identifying sequence or a location-identifying sequence to be added at a later step. Petitioner fails to show that region 130, what Petitioner identified, is the claimed location-identifying sequence. *See Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1001 (Fed. Cir. 2023) (The “IPR petition, thus, must provide an understandable explanation of the element-by-element specifics of the patentability challenges, including *the identification of particular portions of prior art on which the petitioner is relying.*”).

While Petitioner contends that the methods depicted in the figures with an arrow showing the direction of extension are not analogous to Figure 9, Petitioner does not deny that So-456 depicts the direction of extension where it chooses to and Figure 9 lacks any downward arrow. Moreover, as confirmed by Petitioner's expert, the downward reaction is not necessary for So-456's method as the extension product from an upward reaction alone is sufficient for downstream sequencing. EX2053 at 87:22-88:19.

Petitioner's reliance on Figure 6 to allegedly teach the downward reaction is also unavailing because Petitioner offers only conclusory statements from Dr. Spellman that Figures 6 and 9 allegedly involve the same enzyme and design. When asked at cross-examination for a disclosure in So-456 that the two figures are related, Dr. Spellman was only able to identify a paragraph stating that both Figures 6 and 9 can contain a universal capture region that can comprise "a poly-T oligonucleotide that can be used to capture total mRNA in a tissue sample." EX2053 at 89:8-22; EX1005 ¶ 142. A similar capture region on the end of an immobilized capture probe does not explain how bidirectional extension is inherent in Figure 9. As Dr. Sherman explains, "[m]erely adding enzymes would not necessarily cause a bi-directional extension reaction to occur." EX2006 ¶ 64.

Accordingly, Petitioner fails to show that So-456 discloses the claimed extension step.

D. So-456 Does Not Disclose The Claimed Ligation

Petitioner contends that “claim 16 requires that the first and second nucleic acid probes are ligated together, and does not limit the nucleic acid probes to those that are adjacent and non-overlapping.” Reply at 17. Petitioner, however, ignores the difference between So-456 and the ’689 patent.

As Dr. Sherman explained at deposition, “visually, [So-456’s] Figure 9, you can see that it’s a large gap...it’s a region that needs to be extended through a evidently large region.” EX1056 at 77:24-78:1. That is because the purpose of Figure 9’s large gap is for an extension to capture a mutation in the target analyte. EX2006 ¶ 70. In contrast, the ’689 patent discloses a small gap extension before ligation where the nucleic acid probes are not adjacent and not overlapping. EX1056 at 78:2-7. No mutations are incorporated into the ligated probe.

Accordingly, So-456 does not disclose the claimed ligation.

III. SO-456 DOES NOT RENDER THE CLAIMS OBVIOUS

As documented above, So-456 fails to disclose several key claim limitations and is far from the claimed invention. Petitioner falls far short of identifying any

evidence to show that a POSA would find it obvious to bridge the gulf between the prior art and the claimed invention.

The most glaring omission from the Petition that Petitioner’s Reply does not remedy is the lack of motivation to modify So-456. Petitioner contends on reply that “a POSA armed with the high level of skill in the art would have understood ‘how to bridge the gaps between one or more disclosures of So-456 and the challenged claims.’” Reply at 28. But Petitioner offers no reason *why*—not to mention the lack of any details on *how*—So-456 may be modified to meet the missing limitations. Petitioner offers “no argument about common sense,” “no evidence that there are a finite number of identified, predictable solutions,” and “no evidence of a design need or market pressure.” *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 887–88 (Fed. Cir. 2024). The Petition is thus deficient—“obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (emphasis in original).

For Petitioner’s obviousness ground, the Petition discussed only the extension limitation. Even if a POSA modifies segment 130 so that it is the location-identifying sequence, the “upward reaction” that extends the capture probe would

then have a location-identifying sequence that can be subsequently sequenced when the strand is cleaved. In such a circumstance, as Petitioner's expert stated, the extended capture probe alone is sufficient for downstream sequencing. EX2053 at 87:22-88:19. Petitioner provides no reason to modify Figure 9 to ensure that the "downward reaction" occurs.

The Board should also disregard Petitioner's obviousness contentions regarding the treated tissue and probe ligation limitations as new theories,³ similar to *Virtek* where the Federal Circuit did not credit petitioner's expert for "rely[ing] on an entirely new rationale to explain why one of skill in the art would have been motivated to combine" on reply. 97 F.4th at 888 n.3. Here, the Petition stated only that to "the extent NanoString argues that So-456 does not disclose all the elements of claims 1 and 16... claims 1-30 still would have been obvious over So-456." Petition at 39. Nothing more was alleged.

³ Petitioner's Reply and Dr. Spellman's Reply Declaration do not address the collecting probe limitation.

Dated: January 3, 2025

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 5,592 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: January 3, 2025

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY** and **EXHIBIT EX2053** were served on January 3, 2025, via email pursuant to 37 C.F.R. § 42.6(e) to counsel for Petitioner at the addresses below:

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