

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 B2

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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PETITIONER’S UPDATED EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 11,377,689 to Beechem <i>et al.</i> , issued July 5, 2022 (“689 patent”)
1002	Declaration of Paul Spellman, Ph.D.
1003	<i>Curriculum Vitae</i> of Paul Spellman, Ph.D.
1004	File History of U.S. Patent No. 11,377,689
1005	International Patent Application Publication No. WO 2017/019456 A2 to So <i>et al.</i> , published February 2, 2017 (“So-456”)
1006	International Patent Application Publication No. WO 2021/133849 A1 to Chell <i>et al.</i> , published July 1, 2021 (“Chell”)
1007	“Explore Illumina sequencing technology,” Illumina, Inc., accessible at https://www.illumina.com/science/technology/next-generation-sequencing/plan-experiments/paired-end-vs-single-read.html
1008	“Visium Spatial Gene Expression Reagent Kits for FFPE,” 10x Genomics, Inc., Document No. CG000407, Rev. D, 2022
1009	U.S. Patent Application No. 16/272,487, filed February 11, 2019
1010	U.S. Provisional Application No. 62/771,212, filed November 26, 2018
1011	U.S. Provisional Application No. 62/629,180, filed February 12, 2018
1012	File History of U.S. Patent Application No. 16/272,487
1013	Merritt, <i>et al.</i> , “Multiplex digital spatial profiling of proteins and RNA in fixed tissue,” <i>Nature Biotechnology</i> 38:586-599 (May 2020)
1014	<i>Intentionally Left Blank</i>

Exhibit No.	Description
1015	<i>Intentionally Left Blank</i>
1016	Stahl <i>et al.</i> , “Visualization and analysis of gene expression in tissue selections by spatial transcriptomics,” <i>Science</i> 353(6294):78-82 (July 1, 2016), with attached Supplementary Materials
1017	International Patent Application Publication No. WO 2012/140224 A1 to Frisen <i>et al.</i> , published October 18, 2012
1018	Spatial Transcriptomics Workflow, accessible at https://spatialtranscriptomics.com/workflow/
1019	Kivioja <i>et al.</i> , “Counting absolute numbers of molecules using unique molecular identifiers,” <i>Nature Methods</i> 9(1):72-76 (January 2012), with attached Supplementary Information
1020	NanoString Technologies, Inc.’s Initial Infringement Contentions with Attachment A and Exhibit 1, <i>10x Genomics, Inc. et al. v. NanoString Technologies, Inc.</i> , Case No. 1:22-cv-00261 (D. Del.), filed November 23, 2022
1021	Nanostring Technologies, Inc. First Amended Answer, Affirmative Defense, and Counterclaims to Plaintiffs’ First Amended Complaint, <i>10x Genomics, Inc. et al. v. NanoString Technologies, Inc.</i> , Case No. 1:22-cv-00261 (D. Del.), filed August 16, 2022
1022	<i>Intentionally Left Blank</i>
1023	Scheduling Order, <i>NanoString Technologies, Inc. v. 10x Genomics, Inc.</i> , Case No. 1:22-cv-01375 (D. Del.), filed April 13, 2023
1024	Joint Claim Construction Statement with Exhibits A through C, <i>NanoString Technologies, Inc. v. 10x Genomics, Inc.</i> , Case No. 1:22-cv-01375 (D. Del.), filed August 4, 2023
1025	Duncan <i>et al.</i> , “A method for detecting single mRNA molecules in <i>Arabidopsis thaliana</i> ,” <i>Plant Methods</i> 12:13 (2016)

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1026	Lieben, L., “Spatial transcriptomics in plants,” <i>Nature Reviews Genetics</i> 18:394 (2017)
1027	Jemt <i>et al.</i> , “An automated approach to prepare tissue-derived spatially barcoded RNA-sequencing libraries,” <i>Scientific Reports</i> 6:37137 (2016)
1028	Asp <i>et al.</i> , “Spatial detection of fetal marker genes expressed at low level in adult human heart tissue,” <i>Scientific Reports</i> 7:12941 (2017)
1029	“Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation,” United States Patent and Trademark Office Memorandum, June 21, 2022
1030	Fantini <i>et al.</i> , “Assessment of antibody library diversity through next generation sequencing and technical error compensation,” <i>PLOS One</i> 12(5):e0177574 (2017)
1031	U.S. Patent Application Publication No. 2007/0172873 to Brenner <i>et al.</i> , published July 26, 2007 (“Brenner 873”)
1032	U.S. Patent No. 9,567,645 to Fan <i>et al.</i> , issued February 14, 2017 (“Fan 645”)
1033	U.S. Patent No. 8,835,358 to Fodor <i>et al.</i> , issued September 16, 2014 (“Fodor 358”)
1034	International Patent Application Publication No. WO 2016/138496 A1 to Fodor <i>et al.</i> , published September 1, 2016 (“Fodor 496”)
1035	U.S. Patent No. 9,902,950 to Church <i>et al.</i> , issued February 27, 2018 (“Church 950”)
1036	U.S. Patent Application Publication No. 2016/0122753 to Mikkelsen <i>et al.</i> , published May 5, 2016 (“Mikkelsen 753”)

Exhibit No.	Description
1037	“An Introduction to Next-Generation Sequencing Technology,” Illumina, Inc. (2017), accessible at https://www.illumina.com/content/dam/illumina-marketing/documents/products/illumina_sequencing_introduction.pdf
1038-1050	<i>Intentionally Left Blank</i>
1051	Transcript of Teleconference between Board and Parties, December 8, 2023
1052	Memorandum Opinion and Order, <i>NanoString Technologies, Inc. v. 10x Genomics Inc.</i> , Case No. 1:22-cv-01375 (D. Del.), February 1, 2024
1053	Motion of 10x Genomics, Inc. for Entry of an Order (i) Modifying the Automatic Stay with Respect to the 653 Action and the IPR Proceedings and (ii) Granting Related Relief, <i>In re: Nanostring Technologies, Inc., et al.</i> , Case No. 24-10160 (Bankr. D. Del.), February 22, 2024
1054	Order (A) Approving Asset Purchase Agreement, (B) Approving the Sale of the Debtors' Assets Free and Clear of Liens, Claims, Interests, and Encumbrances, (C) Approving the Assumption and Assignment of Certain Executory Contracts and Unexpired Leases, and (D) Granting Related Relief, <i>In re: Nanostring Technologies, Inc., et al.</i> , Case No. 24-10160 (Bankr. D. Del.), April 19, 2024
1055	Declaration of Paul Spellman, Ph.D. in Support of Petitioner's Reply
1056	Transcript of the Deposition of David Sherman, Ph.D., October 30, 2024

TABLE OF AUTHORITIES

Cases

<i>Allergan USA, Inc. v. MSN Lab 'ys Priv. Ltd.,</i> 111 F.4th 1358 (Fed. Cir. 2024)	15, 16
<i>Ariad Pharms. v. Eli Lilly and Co., Inc.,</i> 598 F.3d 1336 (Fed Cir. 2010)	1, 6, 12
<i>D Three Enters., LLC v. SunModo Corp.,</i> 890 F.3d 1042 (Fed. Cir. 2018)	6, 12
<i>ICU Medical v. Alaris Medical Systems,</i> 558 F.3d 1368 (Fed. Cir. 2009)	16
<i>LizardTech, Inc. v. Earth Resource Mapping, Inc.,</i> 424 F.3d 1336 (Fed. Cir. 2005)	10
<i>Mformation Techs. v. Research in Motion,</i> 764 F.3d 1392 (Fed. Cir. 2014)	14
<i>Net MoneyIN, Inc. v. Verisign, Inc.,</i> 545 F.3d 1359 (Fed. Cir. 2008)	25
<i>Waldemar Link GmbH & Co. v. Osteonics Corp.,</i> 32 F.3d 556 (Fed. Cir. 1994)	10

Regulations

37 C.F.R. § 1.57(c)	4
37 C.F.R. § 1.57(d)	4
37 C.F.R. § 1.57(h)	4

The Petition demonstrated that the challenged claims are unpatentable under multiple different Grounds, and the Board should accordingly cancel the challenged claims. As shown below, Bruker's response fails to show otherwise.

I. CHELL ANTICIPATES CLAIMS 1-30.

There is no dispute that if the 689 patent is not afforded its claimed priority date, Chell anticipates claims 1-30. Pet., 52-75; EX1002, ¶¶271-378; Paper 14 (“DOI”), 33-34. Bruker only challenges Chell’s prior-art status, disputing that the 487 application’s methods lack written description of (1) collecting whole probes and (2) on-analyte ligation. “[T]he hallmark of written description is disclosure,” and the test “requires an objective inquiry into the four corners of the specification from the perspective of a [POSA].” *Ariad Pharms. v. Eli Lilly and Co., Inc.*, 598 F.3d 1336, 1351 (Fed Cir. 2010) (en banc). Bruker and its expert go well outside the four corners of the specification to fabricate hypothetical embodiments—many of which are incompatible with the claimed methods—described nowhere in the 487 application. EX1055, ¶¶83-145.

A. The 487 application does not describe collecting whole probes.

The challenged claims encompass collecting *whole* nucleic acid probes or portions thereof, yet the 487 application exclusively describes methods that collect a *portion* (identifier oligonucleotide) of the nucleic acid probes. Pet., 53-55; EX1009, ¶¶[0005]-[0007], [0024]-[0027], [00174]-[00180]. Bruker raises five

flawed arguments, none of which show written description of collecting whole probes. POR, 43-48; EX1055, ¶¶85-123.

1. Bruker’s cited evidence requires collecting portions of probes.

Bruker argues that because the 487 application discloses “non-limiting example[s]” of cleavable probes, it must also describe non-cleavable probes (which Bruker alleges could then be collected as whole probes). POR, 43; EX2006, ¶¶92-93. Each of these “non-limiting examples” is in a method that involves collecting a probe portion.

For example, the 487 application’s (EX1009) ¶¶[00106]-[00107], [00125]-[00128], [00143]-[00146], [00159]-[00160], [00184]-[00185], [00200]-[00201], [00211]-[00212], [00221]-[00222], and [00246] all relate to methods that provide a force to *release the identifier oligonucleotide portions* of the probes and collect them for subsequent analysis. EX1055, ¶¶87-88. Here, the “non-limiting example[s]” are of the *type* of cleavable linker (e.g., photo-cleavable or enzymatically cleavable linker) in the probe or the *type* of force applied to cleave the probe (e.g., UV light or enzyme). *Id.* None of these disclosures describes releasing a portion of the probe as a “non-limiting example.” *Id.*

Similarly, the 487 application’s ¶¶131, 137, 176, 180 refer to a “non-limiting example” for steps that occur *after* the released identifier oligonucleotide portion of the probe has been collected. EX1055, ¶89; EX1009, ¶¶[00131]-[00137]

(ligating the *released identifier oligonucleotide* to a nucleic acid adaptor), 140-142 (same), 176 (hybridizing the *released identifier oligonucleotide* to a pair of secondary probes), 180 (same). Further, the disclosures in ¶¶236 and 315-317 refer to a “non-limiting example” of target analytes detected in the methods. EX1055, ¶89; EX1009, ¶¶[00236] (“protein P53,” “protein P97”), [00315]-[00317] (“target analyte X”).

Braker also relies upon the 487 application’s ¶¶14-15, 18, 131, and 199 to argue that a cleavage site is an optional probe feature. POR, 43; EX2006, ¶93. Again, the methods disclosed in these paragraphs all involve collecting the probe’s *released identifier oligonucleotide portion*. EX1055, ¶90; EX1009, ¶¶[0014]-[0017], [00199]-[00203] (disclosing providing a force to release the probes’ identifier oligonucleotide portions), [0018], [00131] (disclosing ligating adaptors to the released identifier oligonucleotides). Cleavage of probes is not an optional feature, and collecting whole probes is not part of the described methods in the 487 application. EX1055, ¶¶87-91.

2. The 487 application never describes using denaturation to release whole probes.

Braker alleges that because the 487 application mentions “denaturation,” a POSA would have known that “the entire probe *can be* released from the target analyte” for collection using denaturation. POR, 43-45; EX2006, ¶¶94-100. There is no such description in the 487 application. Dr. Spellman’s acknowledgement at

deposition that, “as an *abstract concept*, denaturation is well known to a POSA,” does not alter this fact. EX2007, 113:25-114:7; EX1055, ¶103.

Bruker’s reliance on the 487 application’s ¶285 does not support its argument. POR, 43-44. Paragraph 285 refers to using denaturation during *the downstream cleanup steps for sequencing* described in ¶¶279-287 (i.e., after release and collection of the identifier oligonucleotide portion). EX1055, ¶93.

Bruker’s reliance on disclosures in “patent application No. 14/946,386” (allegedly incorporated by reference) also misses the mark. POR, 44-45. First, the 386 application is not effectively incorporated by reference. To incorporate material, the 487 application must (i) “[c]learly identify” the reference; and (ii) if essential material, the reference must be “a U.S. *patent* or U.S. patent application *publication*.” 37 C.F.R. §§1.57(c)-(d), (h). The 487 application purports to incorporate a document identified as “US2014946386.” “US2014946386” is neither an application serial number nor an application publication number, and thus is not an effective incorporation by reference. Even if the 386 application were incorporated, it is incorporated for disclosure of *sequencing methods*, which occur *after* the collection step. EX1009, ¶¶[00216], [00227]; EX2008, Abstract; EX1055, ¶¶97-99; EX2006, ¶¶97-99.

Additionally, the 487 application states that “[i]n the case of *conflict*, the

present Specification, including definitions, will control.”¹ EX1009, ¶[0064];

EX1055, ¶¶97-99, 102. A POSA reading these disclosures thus would have understood that the 386 application’s *sequencing probes* and sequencing methods are separate and distinct from the collecting step of the claimed methods. *Id.*

Dr. Sherman misreads the 487 application disclosures regarding a double-stranded identifier oligonucleotide. EX2006, ¶95; EX1009, ¶[00240]. Paragraph 240 describes “denaturing of the probe’s *identifier oligonucleotide*” portion, *not* denaturing to release whole probes. EX1009, ¶[00240]; EX1055, ¶¶94-86. Indeed, this embodiment still requires releasing and collecting *the identifier oligonucleotide portion*. EX1055, ¶¶94-96; *see also*, DOI, 36 (“all references to ‘collecting probes’ refer only to cleaved off identifier oligonucleotides, not release of entire probes.”). Having a double-stranded identifier oligonucleotide portion of the probe prevents the identifier oligonucleotide from hybridizing non-specifically with the target analyte. *Id.* This reduces the amount of non-specific hybridization between the identifier oligonucleotide and the target analyte, which further improves efficient release of the identifier oligonucleotide portion. *Id.*

Paragraphs 64 and 259 of the 487 application likewise do not support Bruker’s denaturation argument. POR, 43-45; EX1055, ¶¶102. Paragraph 259

¹ Emphasis has been added throughout unless otherwise stated.

merely provides a generic reference to “[a]ny probe,” and is limited by ¶64’s caveat that “[i]n the case of conflict, the present Specification, including definitions, will control.” EX1009, ¶¶[0064], [00259].

Bruker argues throughout its response what *could be done* from the 487 application’s disclosures combined with disclosures taken from disparate sections of other patent applications, rather than what *is actually disclosed* in the 487 application. *See, e.g.*, POR, 44 (arguing that “the entire probe *can be* released ... through denaturation”), 45 (arguing that “‘whole probes’ *can be* released via denaturation”); EX2006, ¶95 (same). But “the hallmark of written description is *disclosure*.” *Ariad*, 598 F.3d at 1351. Bruker’s obviousness-themed arguments cannot create *disclosure* where there is none. *Id.* at 1352 (“a description that merely renders the invention obvious does not satisfy the [written description] requirement.”); *see also D Three Enters., LLC v. SunModo Corp.*, 890 F.3d 1042, 1052 (Fed. Cir. 2018).

3. “Negative purification” is not written description of collecting whole probes.

Bruker’s response cites the 487 application’s “negative purification” disclosure (POR, 45), but this is not a description of collecting whole probes *for use in the claimed methods*.² Rather, as the Board already found, “the 487

² Bruker admits that “an extension, or amplification step, is performed on the

application does not describe the use of whole/intact probes *that are collected and extended* as recited in the challenged claims." DOI, 35-36. This is a disclosure of removing "intact," i.e.—whole probes, from the assay via negative purification to reduce "[b]ackground noise." EX1009, ¶[00252]; EX1055, ¶¶104-110; EX1056, 60:17-24, 61:18-62:2.

4. The 487 application never describes the identifier oligonucleotide and target binding domain as the same or overlapping sequences.

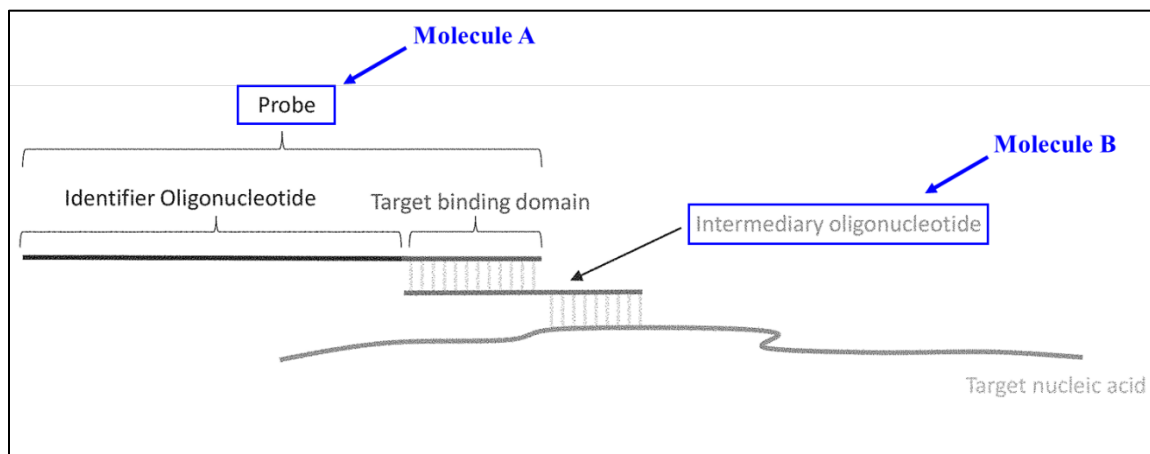
Bruker argues that the 487 application describes the target-binding domain and identifier oligonucleotide as overlapping or even the same sequence. POR, 45-46; EX2006, ¶102; EX1009, ¶¶[00106], [00126], [00144], [00158], [00183], [00199]. But Bruker ignores the fact that the 487 application repeatedly and explicitly identifies the identifier oligonucleotide as distinct from the target binding domain, including when it states that the probe "further" comprises an identifier oligonucleotide in Bruker's cited paragraphs. EX1009, ¶¶[00106], [00126], [00144], [00158], [00183], [00199]; EX1055, ¶111-114. Nowhere does the 487 application describe a target binding domain and identifier oligonucleotide as being the same or overlapping sequence.

collected probes." EX2006, ¶38.

5. The “indirect hybridization” method does not describe collecting whole probes.

Braker continues its obviousness theme, arguing that the 487 application’s indirect hybridization method could be reformatted into an alternative, *hypothetical* cleavable duplex molecule. POR, 46-48 (citing EX1009, FIG. 14 and ¶¶[00106], [00233], [00310]). This imagined scheme is not only absent, but would eliminate the 487 application’s stated advantages of the indirect hybridization method.

As shown in Dr. Spellman’s annotated Figure 14 below, the indirect hybridization embodiment includes three molecules: “Target nucleic acid”; “Probe” (Molecule A); and “Intermediary oligonucleotide” (Molecule B).



EX1009, FIG. 14 (annotated in blue); EX1055, ¶¶116-118.

Braker argues that Molecule B could *hypothetically* include a cleavable motif, in which case the entirety of Molecule A would be released upon cleavage. POR, 46-48. But none of the 487 application’s indirect hybridization embodiments include a cleavable motif in Molecule B. *See, e.g.*, EX1009, ¶¶[0080], [00106]-

[00108], [00126]-[00128], [00144]-[00146], [00158]-[00160], [00174]-[00176], [00178]-[00179], [00183]-[00185], [00199]-[00202], [00210]-[00212], [00220]-[00222], [00233], [00310], [00420], FIGs. 14, 26, 27; EX1055, ¶118. Rather, the cleavable motif is in Molecule A. *Id.*

Moreover, as Dr. Spellman explains, it makes no sense for Molecule B to have a cleavable motif, because doing so renders Molecule A needless. EX1055, ¶¶119-123. The 487 application discloses that indirect hybridization “allows economical and rapid flexibility in an assay design” by including “target (present in the sample)-specific components ... in inexpensive and widely-available synthetic DNA oligonucleotides [i.e., Molecule B] rather than the more expensive probes [i.e., Molecule A].” EX1009, ¶[00233]; EX1055, ¶¶119-122. Adding a cleavable motif in Molecule B, as Bruker speculates, would make the indirect hybridization method superfluous with no economical advantage because it would still require custom synthesis of target-specific probes with a cleavable motif. *Id.* Molecule B with a cleavable motif is no different than the standard direct-hybridization probes of the 487 application. EX1055, ¶¶121-122.

B. The 487 application does not describe “on-analyte” ligation.

Claims 16-30 require “on-analyte” ligation of probe pairs to create the ligated probes, yet the 487 application exclusively describes “off-analyte” ligation. Pet., 55-57; EX1002, ¶¶287-292; EX1009, ¶¶[0024]-[0027], [0033]-[0036],

[0047], [00161], [00168]-[00169], [00174]-[00180], [00183]-[00186], [00389].

Bruker's response fails to show otherwise. POR, 49-59; EX1055, ¶¶124-145.

1. The 487 application does not describe the full scope of the claims.

Bruker first argues that the 487 application need not describe 10x's accused product. POR, 49-51. The issue here, however, is not a missing description of 10x's accused product per se, but rather Bruker's failure to "demonstrate that the inventor[s] possesse[d] the full scope of the invention." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005); Pet., 52-57; EX1002, ¶¶287-292. The written description must still permit a POSA to "immediately discern the limitation at issue." *Waldemar Link GmbH & Co. v. Osteonics Corp.*, 32 F.3d 556, 558 (Fed. Cir. 1994). As shown below, a POSA reading the 487 application would not have immediately discerned on-analyte ligation as part of the claimed methods because there is no such disclosure. Bruker's proffered written description is made from stitched-together disclosures taken from other patent applications—none of which fit together with the claimed methods.

2. Neither US 2010/0015607 nor the indirect hybridization scheme provides written description of "on-analyte" ligation.

Bruker's reliance on US 2010/0015607 (allegedly incorporated by reference in the 487 application) and the 487 application's indirect hybridization scheme

further fails to show written description support for “on-analyte” ligation in the claimed methods. POR, 51-54.

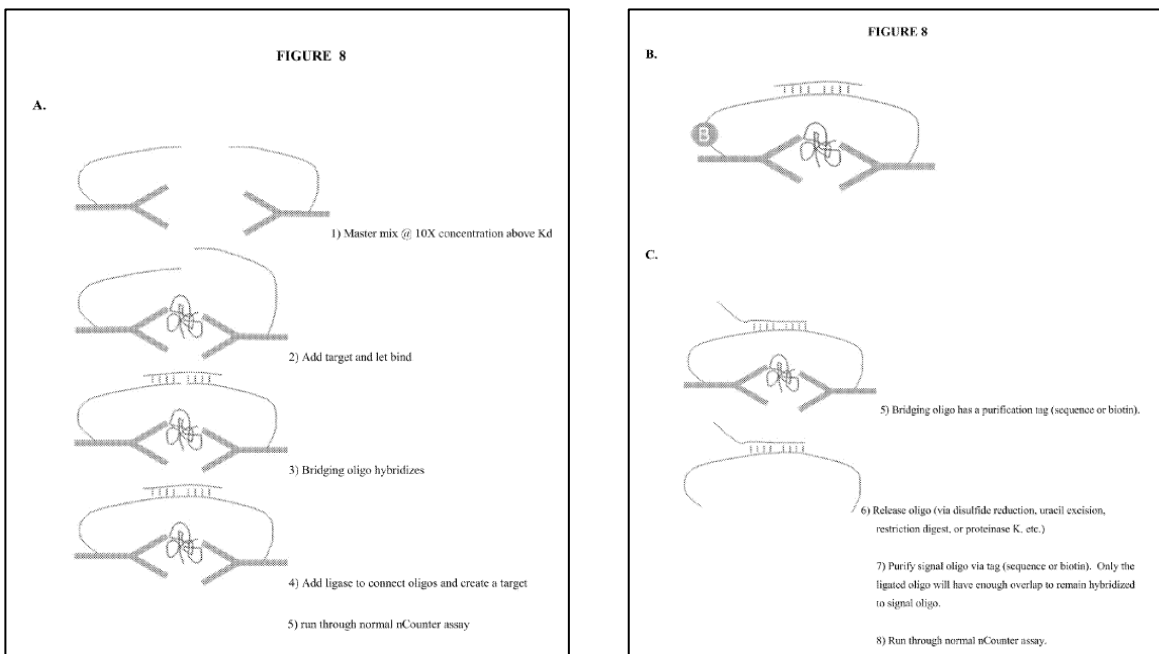
Bruker relies on the 607 publication only for the proposition that it “teaches two probes that hybridize to a target analyte.” POR, 51-52 (citing EX2009, ¶13, FIG. 1A-C). Neither ¶13 nor Figure 1A-C in the 607 publication describes “on-analyte” ligation. *Id.*; EX1055, ¶¶125-127. Bruker then argues that the 487 application’s indirect hybridization embodiment teaches that “probe pairs can indirectly hybridize to a target analyte... *prior to ligation*.” POR, 54. However, Dr. Sherman admitted at deposition that in this hypothetical embodiment, *there is no ligation of probe pairs*. EX1056, 68:10-13 (“In this case, there is no need for that.”); 68:14-20 (“the probe pair ... comprises this intermediary oligonucleotide with two hybridizing regions, so there's no need for a ligase or a ligation.”); EX1055, ¶¶128-131. Thus, by Dr. Sherman’s admission, this embodiment does not depict *any ligation at all*, let alone “on-analyte” ligation. EX1055, ¶132.

3. US 2011/0086774 does not provide written description support for “on-analyte” ligation.

Bruker’s response then jumps to rely on a completely different disclosure in a different patent application (“the 774 publication”), directed to antibody-based proximity ligation methods. POR, 54-55 (citing US 2011/0086774 (EX2010), ¶37 and FIG. 8A). According to Bruker, the 774 publication discloses “designing two oligonucleotides that can be ligated while hybridized to a third,” and this is

somehow “analogous to the allegedly missing feature” (“on-analyte” ligation).

POR, 54-55. The 774 publication’s antibody-based proximity ligation methods for protein detection are unrelated to the 689 patent’s methods for spatial detection, nor would they have conveyed to a POSA that the inventors had “possession” of using “on-analyte” ligation in the claimed methods. EX1055, ¶¶133-136. Bruker again attempts obviousness themes, not evidence of *written description*. *Ariad*, 598 F.3d at 1352; *D Three*, 890 F.3d at 1052. Moreover, 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. EX2010, ¶86, FIGs. 8A-C; EX1055, ¶137; EX1056, 74:9-15. Bruker omits Figure 8C (copied below):



EX2010, FIGs. 8A, 8B, 8C; EX1055, ¶137.

Thus, even if the 774 publication's antibody-based proximity ligation were relevant for probe pair ligation in the claimed methods (it is not), the methods still require collecting *a portion* of the probes—not whole ligated probes. EX1055, ¶¶133-141; EX1056, 73:22-74:14.

4. US 2011/0245111 cannot provide written description support for “on-analyte” ligation.

Bruker relies on US 2011/0245111 (EX2012) to argue the “longstanding and fundamental nature of ligation of probes.” POR, 56. Whether or not “ligation of probes” was generally known in the art is not the issue. EX1055, ¶142. The question is whether the 487 application adequately describes methods that include “on-analyte” ligation of nucleic acid probes as part of the claimed methods. As explained in the Petition and above, it does not.

5. The claims require a specific order of steps that the specification does not describe.

There can be no dispute that claims 16-30 require that ligation take place “on-analyte,” before collection. Claim 16(b) recites forming ligated probes by ligating probe pairs *bound to target analytes* (on analyte), and 16(c)-(d) recite collecting the ligated probes from step 16(b). *Mformation Techs. v. Research in Motion*, 764 F.3d 1392, 1398 (Fed. Cir. 2014) (“a claim requires an ordering of steps when the claim language, as a matter of logic or grammar, requires that the steps be performed in the order written” (internal citation omitted)).

Bruker argues that the 487 application description “does not require disclosed steps to take place in order” and therefore describes ligation of probe pairs on analyte, before the collection step. POR, 54; EX2006, ¶116. Bruker is wrong. Every ligation-based embodiment of the 487 application requires the same order of steps: collecting the released identifier oligonucleotides (off analyte); hybridizing secondary probe pairs to the collected identifier oligonucleotides (off analyte); and ligating the secondary probe pairs (off analyte). EX1009, ¶¶[0024]-[0027], [0033]-[0036], [0047], [00161], [00168]-[00169], [00174]-[00180], [00183]-[00186], [00389]; Pet., 55-57. Nowhere does the 487 application describe ligation of probe pairs on the target analyte *before* the collection step. *Id.*

6. *Allergan* does not support Bruker’s argument.

Bruker relies on *Allergan v. MSN Labs* to argue that, even though the 487 application’s methods exclusively utilize “off-analyte” ligation, the specification nevertheless provides written description of “on-analyte” ligation. *Allergan USA, Inc. v. MSN Lab’ys Priv. Ltd.*, 111 F.4th 1358, 1373 (Fed. Cir. 2024); POR, 58.

The facts in *Allergan* are easily distinguished from the present case. In *Allergan*, the issue was whether the specification described a composition that lacked a “glidant.” *Allergan*, 111 F.4th at 1366. The Federal Circuit found written description support because (i) the specification “describe[d] at least two embodiments in which a glidant is not required”; and (ii) the original claims in the

priority application recited ligand-optional compositions. *Id.* at 1373.

Here, there are *no examples* in the 487 application where ligation optionally occurs on analyte *before collection*. Pet., 55-57; EX1002, ¶¶278-286. And the original claims in every priority application require ligation *after collection* (off analyte). EX1009, claim 1; EX1010, claims 1-3, 35-36, 87-90, 95-98, 142; EX1011, claims 1-3, 35-36, 87-90, 95-98; EX1055, ¶¶143-145. The facts here align not with *Allergan*, but with *ICU Medical v. Alaris Medical Systems*, 558 F.3d 1368 (Fed. Cir. 2009). In *ICU*, the Federal Circuit found that the specification lacked written description for *spikeless* valves because the entirety of the specification “repeatedly and uniformly” described *spiked* valves. *Id.* at 1375-1376. The same is true for the 487 application’s repeated and uniform description of “off-analyte” ligation.

II. SO-456 ANTICIPATES CLAIMS 1-8, 11-23, AND 26-30.

A. So-456 discloses treating a tissue sample as claimed.

The Petition showed that So-456 teaches treating a tissue sample to facilitate hybridization of probes to a target analyte in the tissue. Pet., 18-19 (citing EX1005, ¶¶[00152]-[00153], [00178], [00182], FIGs. 2, 8, 9); EX1002, ¶¶125-127. Bruker mischaracterizes So-456’s disclosures in ¶¶[00152]-[00153] as relating only to “sectioning a sample onto a slide” and “reverse transcription” and “in situ amplification” reactions. POR, 20.

So-456's ¶¶[00152] and [00153] describe Steps 210 and 215, respectively, of Figure 2, both of which occur *before* the nucleic acid probes bind to the target analytes. EX1005, ¶¶[00152]-[00153], FIG. 2; EX1055, ¶15. Paragraph 152 teaches that in Step 210 “a tissue sample is prepared for analysis.” EX1005, ¶[00152]; EX1055, ¶16. A POSA would therefore understand that Step 210 is not limited only to sectioning the tissue sample as Bruker alleges, and *includes* treating the sample to facilitate binding of the probes for further analysis. EX1002, ¶¶125-127; EX1055, ¶16. Paragraph 152 explains that “[i]n some embodiments [i.e., not all], the tissue sample is a FFPE tissue sample that is sectioned onto a slide.” EX1005, ¶[00152]; EX1055, ¶16.

Similarly, So-456's ¶[00153] disclosures are not limited to reverse transcription and in situ amplification reactions. EX1055, ¶17. Again, So-456 lists these reactions as non-limiting. EX1005, ¶[00153]; EX1055, ¶17. Moreover, 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. Pet., 18-19; EX1002, ¶126; EX1055, ¶18; EX1056, 50:22-52:2.

Additionally, Bruker's relied-upon evidence relates only to specific treatments for an FFPE tissue sample. POR, 18-19; EX1001, FIG. 21B; EX1055, ¶19. Neither the challenged claims nor So-456's method is limited to such specific

treatments. EX1001, 145:51-150:17; EX1005, ¶¶00125]. As Dr. Spellman explains, sample treatment varies with the type of tissue sample and even the same tissue type can be treated in different ways. EX1055, ¶¶19-20; EX1056, 50:22-52:2. To anticipate, So-456 need not disclose the same specific treatment as the 689 patent examples. Rather, So-456's disclosure of *any* tissue treatment that facilitates binding meets this claim limitation. Accordingly, So-456 discloses treating the tissue sample as claimed. EX1055, ¶¶13-21.

B. So-456 discloses the claimed ligation step.

Bruker argues that So-456 “does not disclose ligating probes *as they are ligated in the '689 Patent.*” POR, 33. According to Bruker, “ligating probes” in the challenged claims refers to ligating adjacent, non-overlapping probes. *Id.* This unduly narrow construction is inconsistent with the scope of the claims and the 689 patent's own disclosures. EX1055, 22-34.

The plain language of 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. EX1001, 147:54-148:11. This is consistent with the 689 patent specification, which discloses an embodiment in which “the first and the second nucleic acid probes are *not* adjacent and are *not* overlapping,” in which case the probes are ligated together “by performing a gap extension reaction

and a nick repair reaction,^[3] such that the first and the second nucleic acid probes are ligated together.” EX1001, 25:66-26:6; Pet., 19; EX1002, ¶¶128-130; EX1055, ¶¶22-26.

So-456 discloses the same gap extension and ligation embodiment (referred to as “extension/ligation” in So-456) taught in the 689 patent when the probes are not adjacent and non-overlapping. Pet., 19-20; EX1005, ¶[00182]; EX1002, ¶¶128-130; EX1055, ¶¶27-33. A POSA would have understood that So-456’s extension/ligation reaction and the 689 patent’s gap extension and ligation reaction are the *same reactions*, using the *same extension enzyme* (DNA polymerase) and the *same ligation enzyme* (DNA ligase). EX1055, ¶33; EX1056, 35:11-17, 55:9-57:3. Bruker attempts to distinguish the two reactions by arguing that the 689 patent’s gap extension and ligation embodiment is “not meant to ... collect *meaningful data*,” whereas So-456’s extension/ligation reaction is an “intentional step” meant to “capture a *meaningful extension product*.” POR, 37; EX2006, ¶71. This is a meaningless distinction. Claim 16 has no user intent requirement for the ligation step, and does not exclude capturing “meaningful data” in an extension/ligation reaction. EX1001, 147:54-148:11; EX1055, ¶32.

³ Dr. Sherman testified that “nick repair includes the ligation.” EX1056, 56:23-57:3; EX1055, ¶25.

Both Bruker and Dr. Sherman admit that in So-456's method, an extension *and ligation* reaction occurs with the two nucleic acid probes. POR, 33-34 ("the 'extension/ligation reaction' is a step wherein ... each probe is *ligated* to the extension product."⁴); EX2006, ¶70 ("the referenced *ligation* is the extension product with the probe ... This *ligated molecule* is then used ..."). Dr. Sherman attempted to retreat from this admission at deposition, arguing for the first time that So-456's method involves *no ligation at all*—contradicting his own declaration testimony and Bruker's POR. EX1056, 35:23-36:14. Regardless, Dr. Sherman's new, contradictory position does not and cannot undermine the disclosure in So-456, which explicitly discloses ligation in step 815 of Figure 9. EX1005, ¶[00182], FIG. 9; EX1002, ¶¶128-130; EX1055, ¶¶22-34.

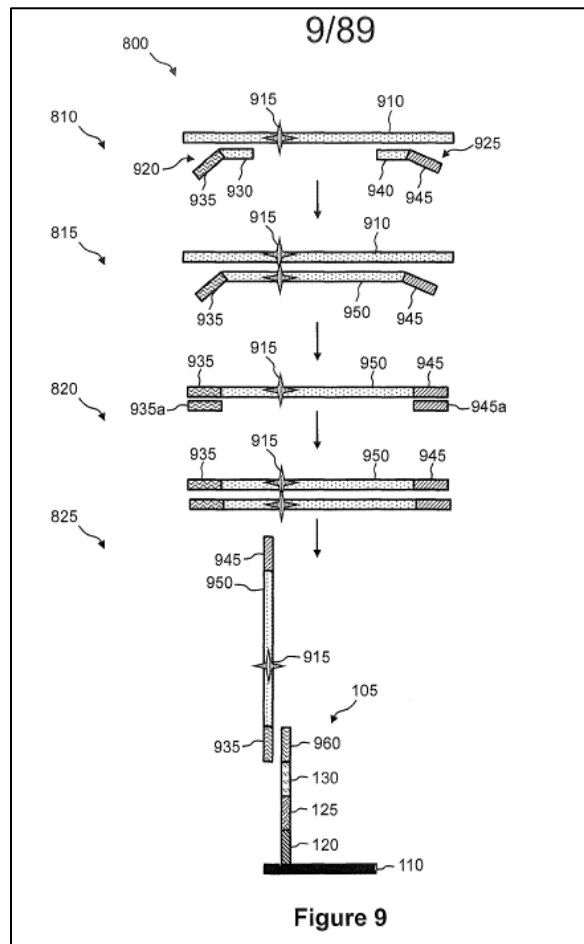
C. So-456 collects nucleic acid probes as claimed under Bruker's construction.

Bruker alleges that So-456's method only collects amplicons of the ligated probes, and those amplicons were not bound to the target analytes, as required by the claims. POR, 14-16. Bruker mischaracterizes the full extent of the Petition's

⁴ Contrary to Bruker's portrayal (POR, 38), So-456's extension/ligation reaction extends one probe and ligates the extended probe to the second probe, just like the 689 patent's gap extension and ligation embodiment. EX1055, ¶¶26-27; EX1056, 34:13-35:10, 56:6-14.

arguments.

The Petition explained that So-456's Figure 9 labels both the original ligated probe (generated in Step 815) and its amplicons (generated in Step 820) as molecule "950." Pet., 10-11. As shown below, the original ligated probe 950 and its amplicons 950 are identical molecules with the same features (935, 915, 945):



EX1005, FIG. 9; Pet., 10-11, 21; EX1002, ¶¶166-169; EX1055, ¶38. Dr. Sherman admitted at deposition that the original ligated molecule 950 contains the same segments as the captured molecule 950. EX1056, 44:13-45:5.

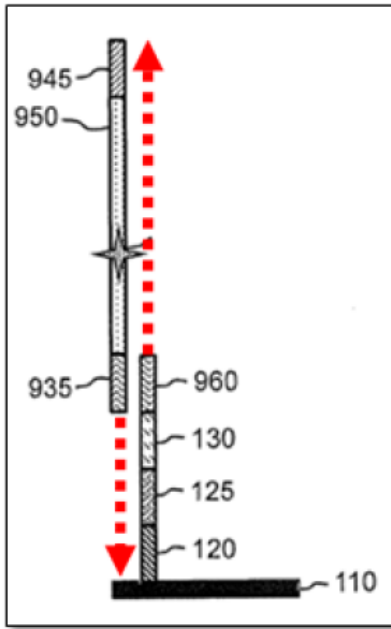
Figure 9 further depicts the original ligated probe (950) being *released from*

the target analyte (910) after Step 815, where amplification primers 935a and 945a for isothermal amplification bind to it (Step 820). EX1009, FIG. 9; EX1055, ¶¶39; EX1002, ¶69. Next, “950”—i.e., both the original ligated probes released from the target analyte and the amplicons—are captured on the capture probes (Step 825). EX1005, FIG. 9; EX1055, ¶40; EX1002, ¶¶169 (“capturing whole ligated probes (formed by ligating the primary probe pairs)”), 104 (p. 54) (“captured ligated products (950)”), 237 (“amplicons (950) (i.e., ligated probes of the claims)”); EX2007, 117:5-7 (“the 950 that is ligated is amongst the 950s that bind to 960 at the capture oligo....”). Thus, So-456’s method captures the original ligated probes that were bound to the target analytes along with the amplicons. EX1055, ¶¶37-41; EX1002, ¶¶166-169; Pet., 19-22, 29. And So-456 does not teach removing the released original ligated probes before capturing molecules 950 on the capture probe. EX1055, ¶40. Accordingly, So-456 discloses the claimed collecting steps under Bruker’s construction. EX1055, ¶¶35-41.

D. So-456 discloses the claimed extension steps.

The Petition explained that So-456 discloses an extension reaction that inherently proceeds in both directions, incorporating a spatial barcode into the captured probes (950) in the reaction depicted by the downward arrow in Dr.

Spellman's annotated Figure 9 (copied below). Pet., 22-27.⁵



EX1005, FIG. 9 (annotated); EX1002, ¶¶148-149.

Bruker's response fails to show otherwise. EX1055, ¶¶42-69.

1. **Because So-456's method collects original ligated probes (molecule 950), it extends probes that were bound to the target analyte.**

Bruker argues that because So-456 does not disclose collecting bound probes or their portions, it cannot disclose the claimed extension reaction that must be performed on those collected probes or portions. POR, 23-24. As explained above in Section II.C, So-456's method collects the original bound probes (along

⁵ Bruker misrepresents 10x's argument as "attorney argument" when clearly the Petition cites ¶¶148-149 of Dr. Spellman's Declaration (EX1002). Pet., 25-26.

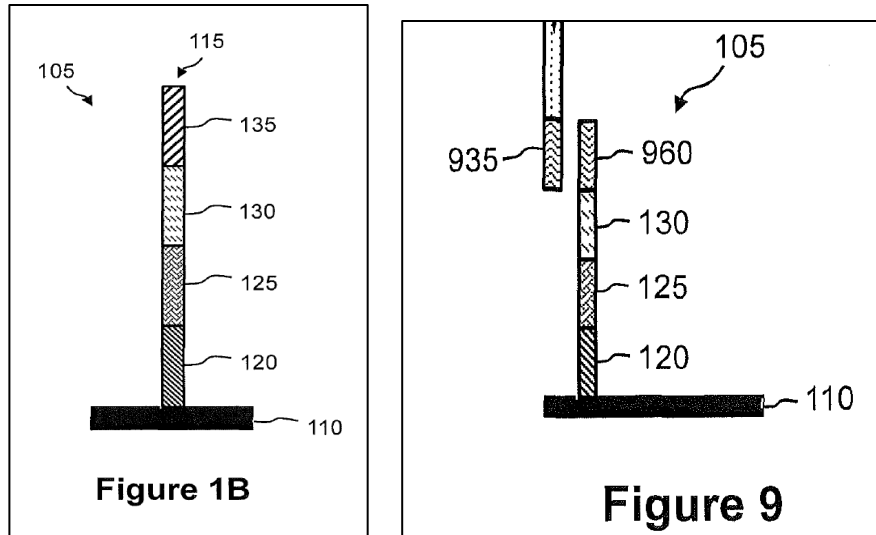
with their amplicons) and extends them. EX1002, ¶¶131-137, 166-169; EX1055, ¶¶35-41.

2. So-456 discloses that segment 130 in the capture probe is the spatial barcode.

Bruker alleges that the Petition “mix[es] and match[es]” embodiments in So-456 to show that segment 130 in Figure 9’s capture probe is the spatial barcode, because, according to Bruker, segment 130 is “the sequencing by synthesis primer region.” POR, 24-26. As explained below, Bruker is wrong. EX1055, ¶¶42-66.

So-456 expressly discloses that Figure 8-9’s method *uses Figure 1A’s capture array*. EX1005, ¶[00177]; EX1055, ¶¶51-54. The Petition did not improperly “mix and match different embodiments” because So-456’s disclosures in Figure 1 and 9 are *directly related* to each other. *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (anticipation cannot require “picking, choosing, and combining various disclosures *not directly related to each other* by the teachings of the cited reference.”).

So-456’s Figure 1A and 1B illustrate different views of the same capture array, which comprises capture sites (105) with capture probes comprising a cleavable region (120), an SBS primer sequence (125), and spatial address sequence (130). EX1005, FIGs. 1B, ¶¶[00141], [00183]; EX1055, ¶¶52-54. These same features are depicted in the capture probe of Figure 9:



EX1005, FIGs. 1B , 9.

A POSA would have identified segment 130 of Figure 9’s capture probe as a spatial barcode. Pet., 20-21, 26, 34-35, 41, 46. So-456 identifies segment 130 in Figure 1B as a spatial barcode. EX1005, ¶[00141]; EX1055, ¶¶55-59. In fact, So-456 repeatedly discloses that segment 130 is a spatial barcode throughout its specification. *See e.g.*, EX1005, ¶¶[00141], [00145]-[00146], [00189], [00201]-[00202], [00213]-[00214], FIGs. 1B-1C, 3, 4, 7, 11, 13A-13B, 15B-15C; EX1055, ¶55.

Bruker’s argument relies on a typographical error in So-456 that refers to segment 130 in Figure 9 as “SBS primer region 130.” POR, 24. But this error would have been readily apparent to a POSA. EX1005, ¶¶[00172]-[00173], [00182]-[00183]; EX1055, ¶56. For example, Figure 6’s description identifies segment 130 both as a spatial address region *and* an SBS sequencing primer. EX1005, ¶¶[00172] (“SBS sequencing primer 130 is SBS3”), [00173] (“spatial

address region 130”). Figure 9’s description inadvertently repeats the same error, identifying segment 130 as an SBS primer region. EX1055, ¶56; EX1005, ¶[00182]. A POSA would have known that segment 130 in Figure 8-9’s capture probe is a spatial barcode. EX1055, ¶¶55-57. This would have made logical sense to a POSA, because Figure 8-9’s capture probes must include a spatial barcode for the spatial identification methods to be useful. Pet., 23-24; EX1002, ¶140; EX1005, ¶¶[0001], [0002], [0085], [0089]; EX1055, ¶¶57-58.

The POSA would have known that the spatial barcode must be downstream (3’) of the SBS primer region in the capture probe so that the target analyte’s spatial information coded in the spatial barcode is copied over to the molecules that are ultimately analyzed in the sequencing step. EX1055, ¶57. Bruker’s annotated Figure 9 showing segment 130 as “SBS primer region” depicts a flawed design where the molecules analyzed by sequencing would not contain any spatial information. POR, 25; EX1055, ¶58. As Dr. Sherman admitted at deposition, if the spatial barcode were below segment 130 of the capture probe (e.g., segment 125), it would not be sequenced. EX1056, 46:16-21. A POSA would have recognized the typographical error and known that the only logical location for the spatial barcode in Figure 9 is segment 130. EX1055, ¶¶50-59.

3. So-456’s extension reaction in Figure 9 incorporates a spatial barcode as claimed.

Bruker alleges that the “only extension” in So-456’s Figures 8-9 “is the

extension/ligation reaction” of step 815. POR, 31. But Bruker again ignores the full context of So-456’s disclosure. EX1055, ¶¶43-48. So-456's Figure 2 discloses its overall workflow including sequencing library preparation (Step 225). Pet., 23-25, 27-28; EX1005, ¶¶[00156]-[00158], FIG. 2; EX1002, ¶¶141-142; EX1055, ¶44. Following Figure 2’s workflow, Figure 9’s method after Step 825 includes extension of the capture probes and captured ligated probes, followed by amplification of the extension products. EX1005, ¶¶ [00182]-[00183], FIG. 9; EX1055, ¶44.

Bruker also alleges that Figure 8-9’s extension reaction is not a bidirectional extension because So-456 discloses examples of unidirectional extension of capture probes in other figures, depicted by a unidirectional arrow. POR, 26-27 (citing, EX1005, FIGs. 22, 23A, 24, 25A, 25B, 29A, 39, 40, ¶¶[00297]-[00301], [00307]-[00320], [00332]-[00334], [00391]-[00395], [00410]-[00412]). The fact that certain figures in So-456 include a unidirectional arrow does not alter So-456’s bidirectional extension teaching in Figures 8-9. EX1055, ¶60.

This is because the methods depicted in Bruker’s selected figures were not designed for bidirectional extension. EX1055, ¶¶61-66. Specifically, the methods in So-456’s Figures 22-23A (Step 2215), 24-25A (Step 2415), 28-29A (Step 2815), and 38-39 (Step 3810) are designed to synthesize a “first strand cDNA” for subsequent steps, which is the product of the extension reaction depicted by a

single arrow. EX1055, ¶¶62-63. Similarly, Figures 24-25B (Step 2425), 28-29A (Step 2820), and 38-39 (Step 3820) are designed to synthesize a “second strand cDNA” for use in the subsequent steps, which is the extension product of the reaction depicted by a single arrow. EX1055, ¶64. Further, Figure 40 discloses a probe bound within *the interior* of the target, such that the probe’s 3’-end is the only end available for extension. EX1055, ¶65.

Meanwhile, another example involving the same enzyme (DNA-dependent DNA polymerase) and design as Figure 9 is Figure 6. EX1005, ¶¶[00172]-[00174]; EX1002, ¶149; EX1055, ¶67. And just like Figure 9, Figure 6 does *not* depict a unidirectional extension arrow. EX1005, FIGs. 6, 9; EX1055, ¶67. Rather, So-456 states in Figure 6 that *both* the capture region 660 and capture region 630 “can also function as primers for an extension reaction” (bidirectional extension), and that “[b]oth extension products can be used for downstream library generation.” EX1005, ¶[00173]; Pet., 25; EX1002, ¶149; EX1055, ¶¶67-68. Thus, Figure 9’s extension reaction proceeds in both directions. Pet., 26; EX1055, ¶¶42-69.

III. CLAIMS 1-30 WERE OBVIOUS OVER SO-456, AND CLAIMS 9-10 AND 24-25 WERE OBVIOUS OVER SO-456 AND STAHL.

As explained in the Petition and underscored above, So-456 discloses all elements of claims 1-8, 11-23, and 26-30. Pet., 15-38. The Petition also showed that claims 1-30 would have been obvious over So-456, and claims 9-10 and 24-25 would have been obvious over So-456 and Stahl. Pet., 49-52.

As the Board noted, even if So-456 did not teach all the elements of the challenged claims, 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.” DOI, 30-31; EX1055, ¶71. For example, there is no dispute that treating a tissue sample to facilitate probe hybridization to a target analyte would have been obvious to a POSA. *Id.*, 31 (a POSA “would have known how to prepare tissue for in situ histochemistry.”); EX1012, 1560 (treating a tissue sample to facilitate probe hybridization “is a routine laboratory procedure that is commonly performed in both research and industrial labs within the field of the present disclosure.”); EX1056, 50:6-52:2; EX1055, ¶¶72-74. There is also no dispute that a POSA would have understood basic methods for ligating nucleic acids. POR, 56 (“ligation of probes is yet another skill that was fundamental and well-known in the art.”); EX2006, ¶119 (“[l]igation is a basic skill well within the competency of a POSA.”); EX1055, ¶¶75-76.

Bruker argues that “adding a spatial barcode by extension is actually an inventive step,” but this step was obvious in view of So-456. POR, 38; EX1055, ¶¶77-81. A POSA would have obviously collected all of So-456’s molecule “950” depicted in Figure 9—including both original ligated probes (950) and the identical amplicons (950)—because there is no way (or reason) to separate the two populations of molecules. EX1055, ¶78. The POSA would have further been

motivated to include a spatial barcode in the capture probe of So-456 (segment 130) because that is precisely what So-456 teaches for its spatial mapping methods. EX1005, ¶¶[0089], [00182]-[00183], FIG. 9; EX1055, ¶¶79-80. And given the specific setup in So-456's Figure 9, the POSA would have reasonably expected a bidirectional extension reaction to occur, thereby incorporating the spatial barcode into the captured ligated probe on the array. *Id.* Bruker's response fails to undermine the Petition's *prima facie* obviousness showing. EX1055, ¶¶70-82.

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Petitioner's Reply complies with the type-volume limitation of 5,600 words, comprising 5,566 words, excluding the parts exempted by 37 C.F.R. § 42.24(c).

2. This Petitioner's Reply complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

Respectfully submitted,

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PETITIONER'S REPLY TO PATENT
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