

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIO BIOSCIENCE, INC.,
Petitioner,

v.

PROGNOSYS BIOSCIENCES INC. and 10X GENOMICS, INC.,
Patent Owner.

IPR2025-00236
Patent 10,662,468 B2

Before MICHAEL J. FITZPATRICK, ANNETTE R. REIMERS, and
SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

REIMERS, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Curio Bioscience, Inc. (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 of U.S. Patent No. 10,662,468 B2 (“the ’468 patent,” Ex. 1002). Paper 1 (“Pet.”). Prognosys Biosciences Inc. and 10x Genomics, Inc. (collectively, “Patent Owner”) filed a Preliminary Response to the Petition. Paper 8 (“Prelim. Resp.”).

Prior to the due date for filing the Preliminary Response in this proceeding, the Acting Director of the U.S. Patent and Trademark Office issued a memorandum titled “Interim Processes for PTAB Workload Management.” *See* Memorandum from Coke Morgan Stewart to All PTAB Judges (Mar. 26, 2025), *available at* <https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf> (“Interim Process Memo”). Under the Interim Process, decisions on whether to institute *inter partes* review are bifurcated between discretionary considerations and merits and other non-discretionary considerations. Patent Owner had the opportunity to file a brief arguing for discretionary denial, but Patent Owner declined to file such a brief by the due date. Afterwards, the proceeding was referred to this panel. Paper 9.

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b) (2018); 37 C.F.R. § 42.4(a) (2024). An *inter partes* review may not be instituted “unless . . . the information presented in the petition . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon consideration of the Petition and the evidence of record, we determine that Petitioner has not demonstrated a

reasonable likelihood of success in proving that at least 1 claim of the '468 patent is unpatentable.

A. Real Parties in Interest

Petitioner Curio Bioscience, Inc. asserts it alone is the real party in interest. Pet. 8. Prognosys Biosciences Inc. and its exclusive licensee, 10x Genomics, Inc., are identified as the real parties in interest for Patent Owner. Paper 3, 1.

B. Related Matters

The parties indicate that the '468 patent is asserted against Petitioner in *10x Genomics, Inc. and Prognosys Biosciences Inc. v. Curio Bioscience, Inc.*, No. 23-cv-01375-MN (D. Del.). Pet. 8; Paper 3, 1.

The parties also indicate that the '468 patent issued from application No. 16/660,234 (the '234 application), which claims priority to application No. 16/443,771 (the '771 application), which claims priority to application No. 16/437,726 (the '726 application), which claims priority to application No. 16/430,015 (the '015 application), which claims priority to application No. 16/414,213 (the '213 application) now Patent. No. 10,787,701, which claims priority to application No. 16/402,098 (the '098 application) now Patent. No. 10,472,669, which claims priority to application No. 16/276,235 (the '235 application) now Patent. No. 10,480,022, which claims priority to application No. 15/187,661 (the '661 application), now Patent No. 10,308,982, which claims priority to application No. 13/080,616 (the '616 application) now Patent No. 9,371,598, which claims priority to provisional application No. 61/321,124 (the '124 provisional). Pet. 8–10; Paper 3, 1.

Petitioner also filed for *inter partes* review of Patent Owner's related patents: IPR2024-01289 (Patent No. 10,480,022), IPR2025-00192 (Patent

No. 11,549,138) and IPR2025-00193 (Patent No. 11,761,030) and IPR2025-00237 (Patent No. 11,001,879).¹

C. The '468 patent (Ex. 1002)

The '468 patent discloses “spatially encoded biological assays” that are “capable of high levels of multiplexing where reagents are provided to a biological sample in defined spatial patterns,” “instrumentation” that is “capable of controlled delivery of reagents according to the spatial patterns,” and “a decoding scheme” that “provid[es] a readout that is digital in nature.” *Id.*, code (57). Thus, the '468 patent “relates to assays of biological molecules . . . for determining spatial distributions of a large number of biological molecules in a solid sample simultaneously.” *Id.* at 1:28–31.

According to the '468, patent, “gene expression analysis and protein analysis have been useful tools in understanding mechanisms of biology” and “[c]onventional methods such as in situ hybridization and other multiplexed detection of different transcripts have revealed spatial patterns of gene expression and have helped shed light on the molecular basis of development and disease.” *Id.* at 1:42–51. But these methods “do not enable simultaneous measurement of the expression of many genes or the presence and/or activity of multiple proteins at many spatial locations in a sample,” they can be very expensive, laborious, and do not scale well, and

¹ In March 2025, the Board denied institution in IPR2024-01289, which addressed related Patent No. 10,480,022. *See* Paper 10 in IPR2024-01289. The Board recently denied a Rehearing Request for IPR2024-01289. *See* Paper 15 in IPR2024-01289. Petitioner presents the same art and similar arguments for the subject IPR as those presented in IPR2024-01289.

they can have low spatial resolution. *Id.* at 1:60–66. The '468 patent purports to resolve these problems. *Id.* at 2:6–11.

Figure 1, reproduced below, is a simplified overview of the assay system of the '468 patent.

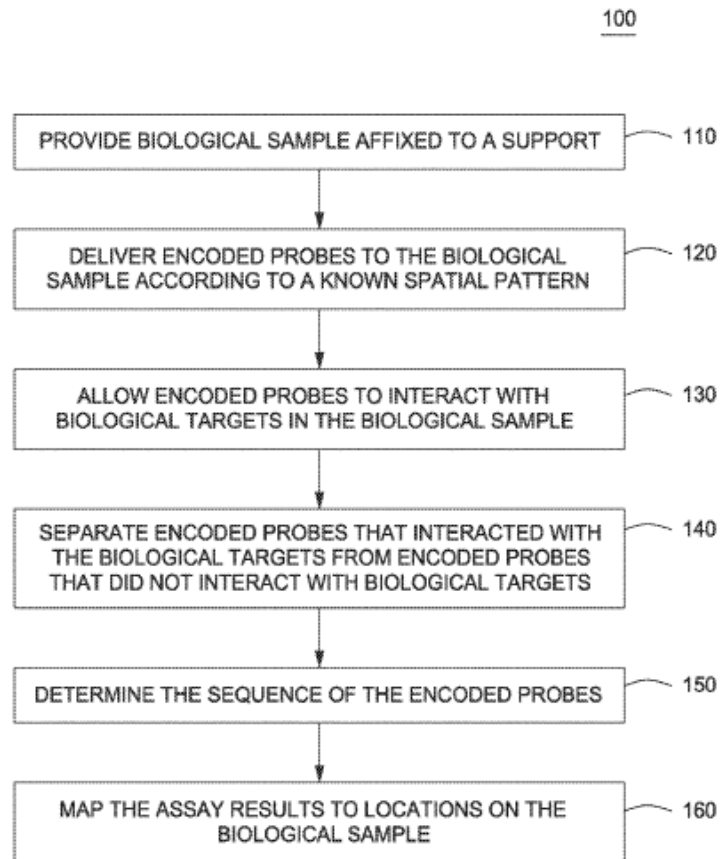


FIG. 1

Figure 1 shows assay system 100 having a starting step 110 of providing a biological sample affixed to a support, in which the biological sample has biological targets of interest such as molecules of nucleic acids, i.e., RNA transcripts, cDNA, and the like. *Id.* at 9:17–24. At the next step 120, encoded probes are delivered to the biological sample “according to a known spatial pattern,” in which the encoded probes comprise a probe and a coding tag. *Id.* at 9:24–30. The probe can interact with the biological target

of interest from the biological sample and the coding tag can be oligonucleotides, mass tags, fluorescent labels, or other moieties, that are used to identify the positions of the biological targets. *Id.* at 9:26–33. As an example, “both the probe and coding tag sequence can be synthesized as a single oligonucleotide.” *Id.* at 9:36–39. At the next step 130, the encoded probes are allowed to interact with the biological targets and hybridize. *Id.* at 9:51–65. At the next step 140, the encoded probes that interacted with the biological targets are separated from those that did not interact, via washing and capturing. *Id.* at 9:66–10:9. At the next step 150, the sequence of the interacted encoded probes is determined, preferably by sequencing. *Id.* at 10:24–28. At the final step 160, the sequence of the encoded probes is used to map the assay results “back to locations in the biological sample.” *Id.* at 10:28–30.

In another embodiment, an assay system 200 includes steps in which “the probes and encoding agents (encoding oligonucleotides) are delivered in separate steps.” *Id.* at 10:31–34, 10:56–58, Fig. 2. “[T]he information in the encoding oligonucleotides can be transferred by using a DNA polymerase to extend a probe oligonucleotide that acts as a primer, and thereby copy and incorporate the sequence of the encoding oligonucleotides.” *Id.* at 10:63–67.

In yet another embodiment, “the assay system is used to analyze nucleic acids, e.g., by genotyping, quantitation of DNA copy number or RNA transcripts, localization of particular transcripts within samples, and the like.” *Id.* at 12:28–31, Fig. 3. A step is provided in which one of the oligonucleotide probes is extended to incorporate, for example, a single nucleotide polymorphism (SNP) sequence and ligated to another probe to

form an extended probe comprising a target nucleic acid region and ligation regions. *Id.* at 12:40–44. Then, two encoding agents, both comprising a coding tag, a ligation region, and a primer region, are combined with and ligated to the extended probe to form an encoded target-specific oligonucleotide. *Id.* at 12:45–49. The '468 patent discloses that the “[g]enotyping may be performed using any technique known to those of skill in the art” such as nucleic acid arrays and bead arrays. *Id.* at 24:54–61. As an example, “[a] microarray is used as a proxy for a tissue section.” *Id.* at 30:46. A tissue section can come from animal sectioning and biopsies, frozen samples, and paraformalin-fixed, paraffin-embedded (FFPE) samples. *Id.* at 12:4–17. “[W]here high-throughput digital sequencing is employed, the sequences of at least 1,000 encoding probes are typically determined in parallel.” *Id.* at 11:44–46.

D. Illustrative Claim

Independent claim 1, the sole independent claim, is reproduced below and is illustrative of the claimed subject matter of the '468 patent.

1. A method for determining the presence or abundance of a nucleic acid at a location in a tissue section comprising:
 - (a) contacting the tissue section with an array comprising a plurality of features, wherein a feature of the plurality of features comprises a capture agent, wherein the capture agent comprises:
 - (i) a first sequence that specifically binds the nucleic acid, and
 - (ii) a second sequence comprising a coding tag, wherein a sequence of the coding tag corresponds to a location of the capture agent on the array;
 - (b) determining all or a portion of the sequence of the coding tag, or a complement thereof, and all or a portion of the sequence of

the nucleic acid specifically bound to the capture agent, or a complement thereof, and using the determined sequences to determine presence or abundance of the nucleic acid at a location in the tissue section.

Ex. 1002, 32:66–33:17.

Claims 2, 6, 7, 12, 18, 20, 21, 23, 25, 26, and 30 depend from independent claim 1. *Id.* at 33:18–20, 33:29–35, 33:46–47, 34:9–10, 34:13–17, 34:21–23, 34:28–31, 34:45–50. Claim 13 depends from claim 12. *Id.* at 33:48.

E. Evidence

Petitioner relies upon information that includes the following:

Ex. 1020, Frisen et al., WO 2012/140224 A1, published Oct. 18, 2012 (“Frisen”).

Ex. 1022, Armani et al., *2D-PCR: a method of mapping DNA in tissue sections*, Lab Chip, 2009, 9(24), 3526–3534; NIH Public Access Author Manuscript (“Armani”).

Ex. 1031, Cantor, WO 2009/091934 A1, published July 23, 2009.

Petitioner also relies upon the Declaration of Dr. Joseph D. Puglisi (Ex. 1102) to support its contentions.

Patent Owner relies upon the Declaration of Dr. Charles R. Cantor (Ex. 2002) to support its contentions.

F. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1, 2, 6, 7, 12, 18, 20, 21, 23, 25, 26, and 30 would have been unpatentable on the following grounds:

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, 30	103	Cantor, knowledge of a POSA ²
2	1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, 30	103	Cantor, Armani, knowledge of a POSA
3	1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, 30	102	Frisen

II. ANALYSIS

A. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Petitioner does not argue construction for any claim terms. Pet. 23–24. Likewise, Patent Owner takes the position that “no claim terms require explicit construction” for purposes of determining whether to institute *inter partes* review. Prelim. Resp. 19.

We determine that no express construction of any claim term is necessary to determine whether to institute *inter partes* review. *Nidec Motor*

² Person of ordinary skill in the art.

Corp. v. Zhongshan Broad Ocean Motor Co., 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))). To the extent further discussion of the meaning of any claim term is necessary to our decision, we provide that discussion below in our analysis of the asserted grounds of unpatentability.

B. Level of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art (“POSA” or “POSITA”) at the time of the invention

would have had a doctorate degree (or equivalent) in bioengineering, genetics, genomics, chemistry, biochemistry, biophysics, molecular imaging or a related discipline with at least 2-4 years of academic, research, or industry experience in genomic technology. In the course of their training and experience, the POSA would have acquired a working knowledge of nucleic acid arrays, combinatorial chemistry techniques for making and using such arrays, nucleic acid sequencing and sample preparation techniques, such as barcoding, imaging methods for signal detection, as well as histopathology techniques for cell permeabilization and tissue handling.

Pet. 13–14 (citing Ex. 1102 ¶¶ 30–32).

Patent Owner does not contest the level of ordinary skill in the art set forth in the Petition. Prelim. Resp. 19.

Because Petitioner’s unopposed definition is consistent with the ’468 patent and the prior art of record, we adopt that definition. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1354–55 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579–80 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

C. Summary of Cited Prior Art

1. Summary of Cantor (Ex. 1031)

Cantor “pertains generally to the field of nucleic acid sequence analysis and methodology and components for use in such analysis.” Ex. 1031, 1.³ Cantor provides improvements in “efficiently preparing nucleic acids that comprise nucleotide sequences identical to or substantially identical to one or more target nucleotide sequences of a sample nucleic acid, or complement thereof,” by using reference sequences that facilitate sequence analysis and solid supports. *Id.* A probe sequence is used to hybridize to a sample nucleic acid when the probe sequence is complementary to a nucleotide sequence in the sample nucleic acid, and a solid support and the sample nucleic acid are contacted to allow hybridization of the solid phase nucleic acid to the sample nucleic acid. *Id.* at 1–2.

According to Cantor, “the invention in part provides a substrate comprising a collection of beads oriented in an array” in which “each bead is in association with single-stranded nucleic acid” and “the solid phase nucleic acid comprises an identifier sequence and a probe sequence.” *Id.* at 4. In one embodiment, “the solid support is in a collection of solid supports” and “at least one nucleic acid of the solid phase nucleic acid of each of the solid supports in the collection has a unique probe sequence different than a probe sequence of the solid phase nucleic acid of the other solid supports.” *Id.* Tissues can be used as a biological sample. *Id.* at 6. “The density of solid phase nucleic acid molecules per solid support unit (e.g., one bead) can be

³ As Exhibit 1031 is not sequentially numbered starting at the first page, we refer to the original page number of the WO document.

selected” and “[i]n certain embodiments, the density of the solid phase nucleic acid per unit solid support is about 1 to 1 (e.g., one molecule of solid phase nucleic acid to one bead).” *Id.* at 13.

Figure 1A, reproduced below, shows an exemplary solid support.

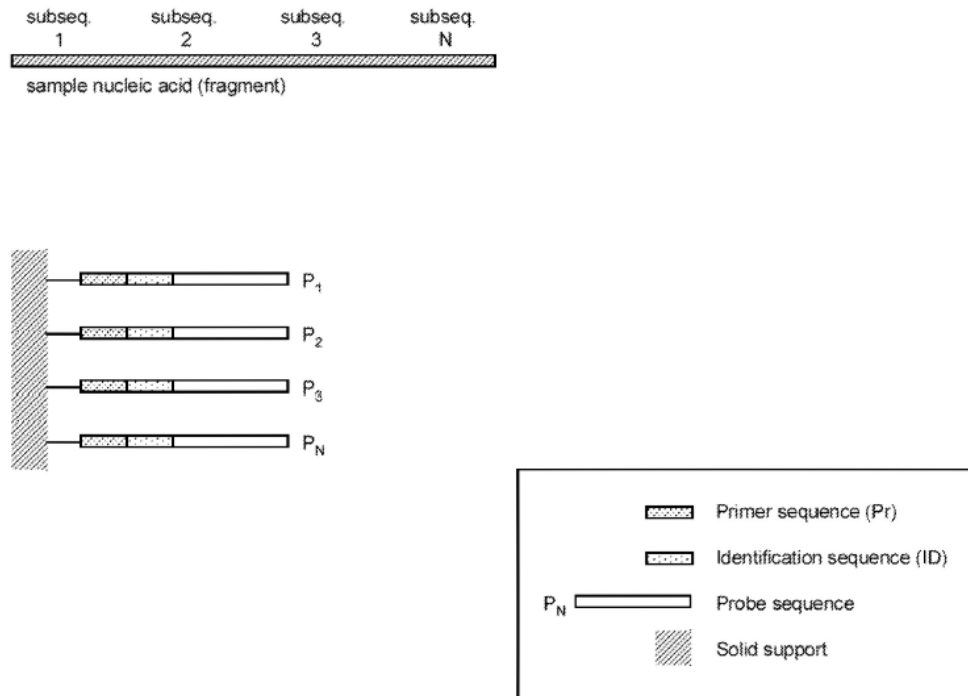


Figure 1A

Figure 1A shows that a solid phase nucleic acid “may contain an identification sequence . . . which may be useful in part for constructing partial sequence reads into larger sequence constructions” wherein the identification sequence is unique for each solid support species and is for analyzing the nucleotide sequence or partial nucleotide sequence of sample nucleic acid. *Id.* at 15. The solid phase nucleic acid often includes a primer sequence (Pr) or a “primer hybridization sequence” that can hybridize to a complementary nucleotide sequence in a primer nucleic acid that can be utilized to amplify extended solid phase nucleic acid previously hybridized to a sample nucleic acid. *Id.* The solid support species have a particular

combination of solid phase nucleic acid differing by probe sequence species $P_1, P_2, P_3, \dots P_N$ and these probe sequence species are complementary to subsequences in sample nucleic acid, namely, subsequences 1, 2, 3, $\dots N$, respectively. *Id.* at 16–17. In another embodiment, a collection of three solid support species is provided, in which each solid support species includes solid phase nucleic acid having a unique identification sequence and the same probe sequence species. *Id.* at 17, Fig. 1C. Further, “solid supports may be provided in an array” such as an “X by Y array.” *Id.*

2. *Summary of Armani (Ex. 1022)*

Armani is titled “2D-PCR: a method of mapping DNA in tissue sections.” Ex. 1022, 3526. Armani discloses 2-dimensional mapping of the gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH) from a tissue section to show correlation with the spatial area of a tissue sample for assessing the status of multiple genes within tissue sections, and “yielding a molecular map that directly correlates with the histology of the sample.” *Id.* According to Armani, “[t]his will provide investigators with a new tool to interrogate the molecular heterogeneity of tissue specimens.” *Id.*

Armani explains that “[v]ariations in DNA status (mutation, epigenetic modification, insertions, deletions) by location within a tissue section are of interest for elucidating their roles in biology and as clinical markers for diseases.” *Id.* A “first lab-on-a-chip method to visualize target DNA across a tissue section” is presented. *Id.* at 3527. The method is “mapping DNA as a step towards the more challenging task of mapping mRNA and microRNA.” *Id.*

Figure 1, reproduced below, illustrates a 2D-PCR concept for DNA mapping methodology.

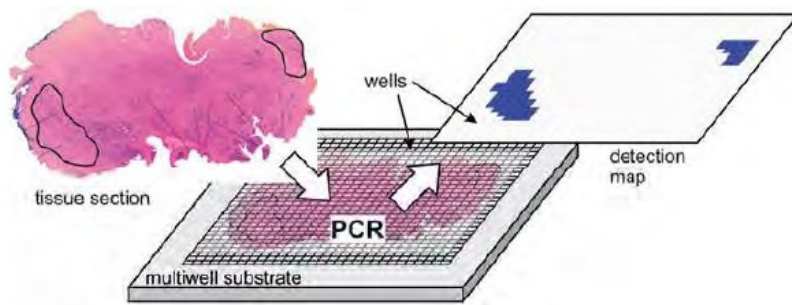


Figure 1 shows that “2D-PCR is achieved by transferring a tissue section vertically into a multi-well array device, isolating tissue subregions.” *Id.* “The DNA is extracted and then amplified by the polymerase chain reaction,” and a detection map “is created by imaging the amplified DNA, for example using a DNA-intercalating dye.” *Id.*

Figure 2, reproduced below, illustrates schematically the steps to create the 2D map of DNA in tissue.

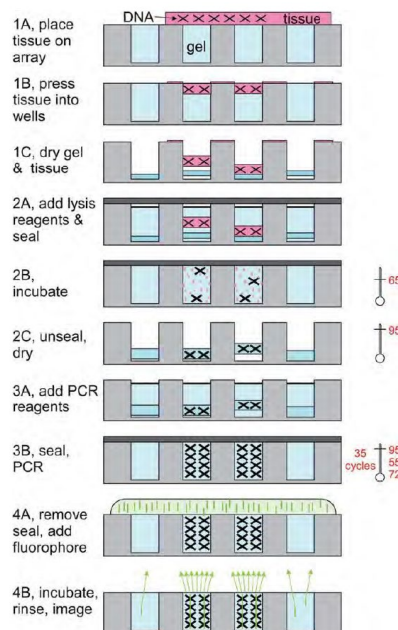


Figure 2 shows steps 1A–4B in an experimental protocol that is “used to demonstrate the 2D-PCR concept.” *Id.* “Tissue is transferred into wells, isolated, and lysed to extract the genomic DNA (represented by ‘x’s),” and

“PCR is performed to amplify the target DNA, and the targets are visualized with fluorescent dye (indicated by vertical lines ‘|’).” *Id.*

3. *Summary of Frisen (Ex. 1020)*

Frisen “relates to methods and products for the [localized] or spatial detection of nucleic acid in a tissue sample” comprising providing an array of a substrate in which multiple species of capture probes are immobilized “such that each species occupies a distinct position on the array.” Ex. 1020, code (57). The method further includes contacting the array “with a tissue sample such that the position of a capture probe on the array may be correlated with a position in the tissue sample and allowing nucleic acid of the tissue sample to [hybridize] to the capture domain” in the capture probes and then “generating DNA molecules from the captured nucleic acid molecules” using the capture probe as extension or ligation primers. *Id.* Frisen discloses that “[t]he capture domain may be capable of binding selectively to a desired subtype or subset of nucleic acid” such as “a particular mRNA species e.g. corresponding to a particular gene or group of genes.” *Id.* at 19:15–19.

Frisen discloses that a positional tag in a cDNA molecule can be “correlated with a position within the tissue sample” so that the cDNA can be sequenced, “which results in a transcriptome with exact positional information.” *Id.* at 6:5–7. According to Frisen, “[a] number of standard arrays are commercially available” that can be used for sequence analysis, such as “an Illumina bead array.” *Id.* at 15:21–33.

D. Ground 1: Obviousness of Claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 over Cantor and knowledge of a POSA

Petitioner asserts that claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 would have been obvious over Cantor and knowledge of a POSA. Pet. 24–50. In support of its assertion, Petitioner provides a detailed discussion explaining how each claim limitation allegedly is disclosed by Cantor. *Id.* Petitioner also asserts that the knowledge of a person of ordinary skill in the art would have provided sufficient motivation and a reasonable expectation of success for using Cantor’s arrays to identify the spatial location of nucleic acids in a tissue section. *Id.*

Patent Owner contends that Cantor does not disclose spatial analysis of a tissue section and therefore fails to teach or suggest all elements of the challenged claims. Prelim. Resp. 33–48.

For the reasons that follow, we determine that Petitioner has not demonstrated a reasonable likelihood that any of claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 would have been obvious over Cantor and knowledge of a POSA.

1. Petitioner’s Contentions

Petitioner asserts that Cantor discloses a “method for determining the presence or abundance of a nucleic acid at a location in a tissue section,” as recited by claim 1. Pet. 24. Petitioner asserts that “Cantor discloses methods for analyzing biological samples using nucleic acid capture agents affixed to solid supports such as beads.” *Id.* (citing Ex. 1031, 13 (a “solid support unit (e.g., one bead) can be selected”). Those beads may be used to form an array, for example “an ‘X by Y array’ . . . , where the array includes X number of sample locations or solid supports,” such as beads, “in one dimension and Y number of sample locations or solid supports,” such as

beads, “in a perpendicular dimension.” *Id.* at 25–26 (citing Ex. 1031, 17); *see also id.* at 26 (“Cantor explains that each bead has a unique identification sequence, such that each bead at its unique (X,Y) coordinate location would have a unique identification sequence as part of its capture agent.”). Each of those beads may comprise nucleic acids configured to hybridize to target nucleic acids in a tissue section.⁴ *Id.* at 28–29. Relying on the testimony of Dr. Puglisi, Petitioner further contends that Cantor discloses an identification sequence⁵ that uniquely identifies a specific bead, and thus, identifies the location at which that particular bead’s capture agent interacted with the target nucleic acid of the tissue section. *Id.* at 25–26 (citing Ex. 1102 ¶¶ 127–133). Dr. Puglisi testifies as follows:

Cantor explains that each bead has a unique identification sequence, such that each bead at its unique (X, Y) coordinate location would have a unique identification sequence as part of its capture agent. Such capture agents would also include a “probe” sequence as part of the same single-stranded nucleic acid. Thus, the “identification sequence” corresponds to the location at which the “probe” portion of the capture agent interacts with the tissue section.

Ex. 1102 ¶ 133.

Additionally, Petitioner points to Figure 1A of Cantor as demonstrating “a solid support (e.g., a bead), comprising a plurality of ‘capture agents,’ each having the same ‘identification sequence (ID)’ and

⁴ Petitioner asserts that “Cantor’s plurality of beads comprise the claimed ‘capture agents’ because bound to each bead are nucleic acid constructs that include a ‘probe sequence’ that ‘specifically binds’ with a target nucleic acid. Pet. 25.

⁵ Petitioner asserts that Cantor’s “identification sequence” corresponds to the “coding tag” recited in the challenged claims. *Id.*

different ‘probe sequences.’” Pet. 25 (citing to Ex. 1102 ¶ 132); *see supra* Sec. II.C.1 (Figure 1A). With reference to Figure 1A, Petitioner asserts that

Cantor explains that its “[s]olid supports may be provided in an array” including “an ‘X by Y array’ ..., where the array includes X number of sample locations or solid supports,” such as beads, “in one dimension and Y number of sample locations or solid supports,” such as beads, “in a perpendicular dimension.” EX1031, 17. Thus, a POSA would have understood Cantor to disclose an array of beads at which each bead is necessarily deposited at a particular (X,Y) coordinate location. Cantor explains that each bead has a unique identification sequence, such that each bead at its unique (X,Y) coordinate location would have a unique identification sequence as part of its capture agent. Such capture agents would also include a “probe” sequence as part of the same single-stranded nucleic acid. Thus, the “identification sequence” corresponds to the location at which the “probe” portion of the capture agent interacts with a tissue section contacting the array. EX1102, ¶133.

Id. at 25–26.

Petitioner contends that a person of ordinary skill in the art would have had “motivation to correlate Cantor’s bead ‘identification sequences’ with the bead’s location in array, and thus the location of the ‘specifically bound’ nucleic acid in the tissue section.” *Id.* at 38. Relying on the testimony of Dr. Puglisi, Petitioner contends that

multiple references disclosed the use of nucleic acid arrays, such as bead arrays, to (1) capture nucleic acids from a tissue sample through the use of complementary probes; (2) amplify the captured nucleic acid; and (3) determine the identity of the captured nucleic acid and the location at which it interacted with the complementary probe, and thus its location in a tissue sample.

Id. (citing Ex. 1102 ¶ 171).

Petitioner further contends that

a POSA would have appreciated that Cantor's disclosure of a unique identification sequence for each bead constituted a unique "barcode" nucleic acid sequence to distinguish one bead from another. In addition to Cantor's express disclosures of providing the beads according to an (X,Y) array, a POSA would have found it obvious to determine the identity and location of each bead in the array before using it in Cantor's analytical procedures at least by (i) selective loading of particular beads to particular locations on the array and/or (ii) decoding the array. EX1102, ¶177 (discussing EX1038); ¶¶65-71.

Id. at 40; *see also id.* at 40–41 ("A POSA would have reasonably expected success in correlating such sequences with particular (X, Y) coordinates given the disclosure of success in using such systems in the prior art.").

Petitioner supports this contention with the expert declaration of Dr. Puglisi, who states the following,

Other references within the knowledge of a POSA similarly use and disclose the use of devices and assays similar to Cantor (i.e., array-based capture and amplification of target nucleic acid) to successfully capture nucleic acids, including mRNA, from tissue samples on bead arrays to preserve and determine the spatial location of the captured target nucleic acids in said tissue samples.

Ex. 1102 ¶ 175; Pet. 39–40.

Petitioner contends that this knowledge of a POSA would further confirm a POSA's motivation and reasonable expectation of success in using the "identification sequences" in Cantor's "capture agents" "to determine the location at which the probe of a given capture agent interacted with a target nucleic acid from a tissue sample" because "a POSA would . . . have found it obvious to map the rest of the sequence readout (i.e., the sequence of the target nucleic acid or a complement thereof) to the bead location, thereby

determining a spatial location of the biological molecule of the tissue sample.” Pet. 40–42.

2. *Patent Owner’s Contentions*⁶

Patent Owner counters by asserting Petitioner erred in its argument that, “because Cantor’s beads can be placed on a substrate,” they “correspond to the location at which the ‘probe’ portion of the capture agent hybridizes with a sample nucleic acid.” Prelim. Resp. 34. Patent Owner contends “[t]his is wrong” because “Cantor’s methods relate to **bulk analysis** of sample nucleic acid, **not to spatial analysis** (e.g., the presence or abundance of a nucleic acid at a location) of a solid material such as a tissue.” *Id.*

Patent Owner explains that “Cantor teaches preparing a ‘**sample nucleic acid**’ and contacting that sample nucleic acid to solid supports (e.g., beads).” *Id.* at 38. Those “beads are arranged on the substrate in a manner suitable for the sequencing and manufacturing processes disclosed”—that is, in a bead array—but that bead arrangement “[does] not provide or seek to provide spatial information—to obtain information about the presence or abundance of a nucleic acid at a location in a tissue section.” *Id.* at 34–36; *see also* Ex. 2002 ¶ 68 (Dr. Cantor explaining that the use of “bead arrays on a solid substrate facilitates the ease of handling of the beads for use in the described methods” in Cantor.). Rather, the methods disclosed by Cantor “facilitate sequence analysis of a sample nucleic acid to determine **if** a particular nucleic acid of interest was present in a sample (but not where in

⁶ Patent Owner references the Board’s recent decision denying institution in IPR2024-01289 throughout the Preliminary Response. *See* Prelim. Resp., *passim*.

the sample).” Prelim. Resp. 35. Cantor provides no information as to “the location of a bead and its corresponding identification sequence.” *Id.* Thus, according to Patent Owner, “Cantor has ***nothing*** to do with spatial analysis.” *Id.*

Here, Patent Owner relies on the Declaration of Dr. Cantor who testifies that a person of ordinary skill in the art would first have to derive a nucleic acid from a tissue source before continuing to the next step of “preparing a mixture comprising sample nucleic acid and a solid support.” Ex. 2002 ¶ 132 (quoting Ex. 1031, 1); Prelim. Resp. 40. Dr. Cantor testifies that “a POSA would have understood that ‘the sample nucleic acid’ is derived from a sample or source ‘by any means commonly known in the art, including but not limited to cell lysis procedures using chemical, physical or electrolytic lysis methods.’” Ex. 2002 ¶ 133 (citing Ex. 1031, 54); Prelim. Resp. 41. Dr. Cantor further testifies that, “after derivation of the sample nucleic acid, a POSA would understand that the ‘sample nucleic acid’ exists in the form of a homogenized (blended) mixture that does not retain the original spatial distribution of cells or nucleic acids that an intact tissue would have.” Ex. 2002 ¶ 134; Prelim. Resp. 41.

Thus, according to Dr. Cantor, “a POSA could obtain information about whether a [target nucleic acid] is present in the [sample nucleic acid] but could not obtain information about the spatial distribution of those [target nucleic acids] relative to one another within the original [tissue sample].” Ex. 2002 ¶ 134; *see also id.* ¶¶ 142, 143; Prelim. Resp. 48 (Patent Owner asserting that, “even if Cantor suggested that an identification sequence could be traced back to a location ***of a bead on the substrate*** . . . ,

it would not and *could not* correlate to the location of the target nucleic-acid sequence in the original *tissue sample*.” (citing EX. 2002, ¶¶142–143))

3. Discussion

We begin with a simplified summary of the elements of claim 1 relevant to the dispute between the parties. Claim 1 is directed to the use of features (e.g., beads)⁷ comprising a capture agent having first and second sequences; the first sequence specifically binding a nucleic acid; the second sequence comprising a coding tag that corresponds to a location of the capture agent; the beads are brought into contact with a tissue section so that all or a portion of (1) the sequence of the nucleic acid specifically bound to the capture agent; and (2) the sequence coding tag are determined. The determined sequences of the coding tag are used to determine the presence of the nucleic acid at a location in the tissue section.

The parties dispute whether the claims encompass the methods disclosed by Cantor, and more specifically, whether determining the location of a bead in Cantor’s bead array achieves the challenged claims’ requirement for determining the location of a captured nucleic acid in a tissue section. In short, Petitioner contends that the ability to identify the location of a target nucleic acid within a nucleic acid binding array, such as an “X by Y array,” achieves the requirement of the challenged claims for determining the presence of a nucleic acid at a location in a tissue section. Pet. 25–26 (Ex. 1031, 17; Ex. 1102 ¶ 133); *see also id.* at 32–33 (Ex. 1102 ¶ 155); Ex. 1102 ¶ 128 (“Because each bead necessarily occupies a different spatial address on the array, each ID sequence and its linked probe is necessarily correlated

⁷ Both Petitioner and Patent Owner agree that the claimed “features” includes beads. Pet. 24, fn.2, 27; Prelim. Resp. 44.

to a unique location (such as an (X,Y) coordinate) on the array.”). We have considered the parties’ positions and evidence of record on that issue, summarized above, and find Patent Owner to have the better position.

In particular, we agree with Patent Owner that Cantor does not teach or suggest contacting a ‘tissue section’ with its beads, let alone that its beads could be contacted with a tissue section to identify spatial location. Prelim. Resp. 37–44. In this case, we are persuaded by the testimony of Dr. Cantor, sole inventor of Cantor (Ex. 2002 ¶ 29), that Cantor’s nucleic acid samples are made in bulk from the extraction of nucleic acids from a biological sample and mixed together “to create the sample nucleic acid prior to mixing that with the solid phase nucleic acids to capture molecule(s) from the sample nucleic acid.” *Id.* at ¶ 36 (citing EX.1031 1:5–6). More specifically, according to Dr. Cantor, “[f]or bulk-analysis methods, nucleic acids are extracted from the different types of cells within a tissue sample without preserving their spatial distribution.” *Id.* at ¶ 19. Dr. Cantor further explains that in bulk-analysis methods,

the mixture is analyzed to determine *if* a particular nucleic acid was present in the tissue sample or not. They cannot, however, determine *where* the molecule was in the tissue sample. As such, bulk-analysis techniques provide no information about spatial location of biological molecules in tissue samples. This is in contrast to spatial analysis methods such as those claimed in the ’468 patent which can determine both *if* a biological molecule was present in a tissue sample and *where* the molecule was in the tissue sample.

Id. at ¶¶ 16–17.

Although we recognize that Cantor discloses “providing the beads according to an (X,Y) array” (Pet. 25–26, 32–33 (citing to Dr. Puglisi, Ex. 1102 ¶¶ 133, 135, respectively), this disclosure makes no mention of using

this array to map where the nucleic acids of Cantor came from relative to the original sample, let alone when that original sample is a tissue. *See e.g.* Ex. 1031, 17. The only mention of “tissue” made in Cantor is in reference to where the sample may be obtained, for example, “[t]he biological sample can be in any form, including without limitation a solid material such as a tissue.” *Id.* at 6. Cantor provides no teaching, however, regarding how to use a tissue sample with the probes and methods described in Cantor to identify where the target nucleic acids of Cantor were spatially located within the tissue section itself. *See* Ex. 2002 ¶¶ 142, 143 (Dr. Cantor testifying that (1) “a POSA would only be able to determine where on the array a target nucleic acid was captured, but not where in the original tissue section the nucleic acid came from,” because “all information about the spatial location of a target nucleic acid in a tissue sample is lost when the nucleic acid sample is prepared as Cantor teaches”; and (2) “Cantor [] does not teach or suggest contacting its solid supports (e.g. beads) with a tissue section and certainly not with its beads at known locations to obtain spatial information.”).

Incidental to the parties’ dispute is whether Petitioner’s reliance on and characterization of Cantor’s use of the terms “sample” and “nucleic acid sample” as equivalent in meaning to “tissue section” recited in the challenged claims is persuasive. Pet. 25 (citing Ex. 1031, 6). Here, we note that Cantor discloses that “[s]ample nucleic acid may be derived from one or more samples or sources.” Ex. 1031, 5; Ex. 2002 ¶ 35. Cantor refers to “sample” as the thing that contains the sample nucleic acid. Ex. 1031, 5. For example, Cantor discloses that “[a] sample may be collected from an organism.” Ex. 1031, 6; Ex. 2002 ¶ 42. When a “sample” comes from a

living (or formerly living) source, Cantor refers to that sample as a “biological sample,” which can “be in any form, including without limitation a solid material such as a tissue, cells, a cell pellet, a cell extract, or a biopsy, or a biological fluid” *Id.* Those samples, however, are further processed in bulk to obtain the nucleic acid sample. *Id.* 1; 5–6; Ex. 2002 ¶ 36.

Cantor further discloses that the “sample nucleic acid may be a result of nucleic acid purification or isolation and/or amplification of nucleic acid molecules from the sample.” Ex. 1031, 6; *see also id.* at 54 (The “sample nucleic acid” is derived from a sample or source “by any means commonly known in the art, including but not limited to cell lysis procedures using chemical, physical or electrolytic lysis methods.”); Ex. 2002 ¶ 39. In view of the above, we are not persuaded by Petitioner’s attempts to characterize Cantor’s “nucleic acid sample” as synonymous to “tissue section” recited in the challenged claims. Rather, as correctly noted by Dr. Cantor,

the “sample nucleic acid” may come from many different sample sources, including a “biological sample,” which itself may have any form, including a solid form (e.g., tissue, cell, etc.) or fluid form (e.g., urine, blood, etc.). (EX1031, 6.) But the biological sample is ***not*** the sample nucleic acid assayed in Cantor’s methods. The sample nucleic acid in Cantor is extracted from the sample source (e.g., a biological sample) and mixed together in bulk to create the sample nucleic acid prior to mixing that with the solid phase nucleic acids to capture molecule(s) from the sample nucleic acid. (EX1031, 1; 5– 6.) But whatever the source, the sample nucleic acid is in solution. It is not a solid material such as a tissue.

Ex. 2002 ¶36.

Stated differently, we agree with Dr. Cantor that a tissue is simply the source of the sample nucleic acid used in Cantor's methods, but it is not the sample nucleic acid itself. *Id.* Petitioner does not direct us to any persuasive evidence to the contrary.

In view of the above, we find that, on this record, Petitioner has failed to establish that Cantor teaches or suggests each element of the challenged claims. Specifically, we are not persuaded that Cantor teaches or suggests contacting a tissue section with beads at known locations to obtain information about a nucleic acid in the tissue section.

4. Conclusion

For the foregoing reasons, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing on its challenge that any of claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 would have been obvious over Cantor and knowledge of a POSA.

E. Ground 2: Obviousness of Claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 over Cantor, Armani, and knowledge of a POSA

Petitioner asserts that claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 would have been obvious over the combination of Cantor, Armani, and knowledge of a POSA. Pet. 51–57. Consistent with Ground 1, Petitioner asserts that the challenged claims would have been obvious over Cantor and further relies on Armani to “provide[] additional specific implementations of how to successfully prepare and process effectively a nucleic acid sample for localized detection.” *Id.* at 55. Specifically, Petitioner relies on Armani's method for analyzing nucleic acids in a tissue section having the following steps:

- (1) “the tissue section is transferred onto the surface of the multi-well array (step 1A) and then pressed onto the surface (1B),”

after which “[t]he contents of the well are dehydrated to enable the addition of lysis reagents (1C); (2) “the tissue is lysed to release genomic DNA into solution”; (3) the “DNA is amplified” using PCR; and (4) “the DNA is imaged” using fluorescent detection techniques. EX1022, 3527.

Id. at 52. Petitioner contends that a person of ordinary skill in the art would have combined Armani’s method with Cantor’s bead array having a plurality of beads disposed in wells in order “to detect nucleic acids from a tissue sample, while specifically using the identification probes to identify the location at which beads were provided.” *Id.* at 55.

We have considered Petitioner’s reliance on Armani in this ground, but are not persuaded that Armani cures the deficiencies of Cantor discussed above with regard to Petitioner’s Ground 1. Specifically, although Armani uses tissue as the nucleic acid source, the nucleic acid source “is lysed to release genomic DNA into solution.” *Id.* at 52. Thus, the combination of Cantor and Armani likewise fails to disclose determining spatial locations of nucleic acids within the tissue section because the sample itself is lysed and therefore fails to retain the information of the sample nucleic acids within the tissue section. *See* Prelim. Resp. 34 (“Cantor says nothing about placing beads in a known location on a substrate, or determining their location prior to use, because Cantor’s beads contact a sample nucleic acid, which itself has no spatial information.”). We therefore agree with Patent Owner’s conclusion that

Ground 2 still suffers from the same critical flaws as Ground 1: because the target nucleic acids are non-uniformly distributed in the tissue sample **and** the probes of Cantor’s bead collections are not repeated, hybridization will only happen by chance (or not at all) and the spatial location of the nucleic acid cannot be determined. [Prelim Resp.] §VII.B.2; *see also* EX2002, ¶161.

Prelim. Resp. 71.

Accordingly, for the foregoing reasons, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing on its challenge that any of claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 would have been obvious over the combination of Cantor, Armani, and knowledge of a POSA.

F. Ground 3: Anticipation of Claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 by Frisen

Petitioner asserts that claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 are anticipated by Frisen. Pet. 58–77. Frisen has an effective filing date of April 13, 2011. Ex. 1020, code (30). Petitioner contends that Frisen qualifies as prior art to the '468 patent because the challenged claims are not entitled to a priority date earlier than February 14, 2019, the filing date of the '468 patent. Pet. 58–67.

For the reasons set forth below, we find that the '468 patent is entitled to its earliest claim priority date of April 5, 2010, the filing date of the '124 provisional. Frisen therefore does not qualify as prior art to the '468 patent. Accordingly, we determine that Petitioner has not demonstrated a reasonable likelihood that claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 are anticipated by Frisen.

1. Petitioner's Contentions

The '468 patent issued from application No. 16/660,234, filed October 22, 2019,⁸ which is a continuation of application No. 15/187,661, filed on

⁸ In the Priority Date table provided by Petitioner for the '468 Patent, the application No. and filing date are listed as 16/276,235 and February 14, 2019, respectively. Pet. 57. We note that this application No. and filing date

June 20, 2016, which is a continuation of application No. 13/080,616, filed on April 5, 2011, which claims benefit of provisional Application No. 61/321,124, filed on April 5, 2010. Ex. 1002, codes (21), (22), (63), (60).

Petitioner contends that “[a]t least one limitation of independent claim 1 is not disclosed by the Priority Documents, as there is no disclosure of “contacting the tissue section with an array comprising a plurality of features.” Pet. 60. Petitioner further contends that the ’661 Application does not disclose (1) delivering a tissue sample to a previously generated array of substrate-affixed probes or (2) contacting an array with a tissue section such that nucleic acids in the tissue section “specifically bind” to the capture probes. *Id.* at 60–67.

Petitioner contends that because “there has to be a continuous chain of copending applications each of which satisfies the requirements of §112 with respect to the subject matter presently claimed,” this break in the priority chain precludes [Patent Owner] from relying on any earlier date.” *Id.* at 58–59 (quoting *Holmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012)).

2. Patent Owner’s Contentions

Patent Owner responds that the ’124 provisional application “provides written[]description support for the claim elements.” Prelim. Resp. 19–31. First, Patent Owner contends that the ’124 provisional provides written description support for the limitation of “delivering a tissue sample to a previously generated array of substrate-affixed probes.” *Id.* at 25–30. Specifically, Patent Owner asserts that

are to Patent No. 10,480,022. We consider this an inadvertent typographical error.

Paragraphs 17 and 18 of the '124 provisional explain that, in one embodiment of the invention, binding agents (e.g., capture agents) are “immobilized directly or indirectly to the **substrate** surface.”¹ EX1009, ¶¶17-18; EX1002, 22:13-21; EX2002, ¶¶114-115. And in one embodiment, a “substrate surface” is described as having “wells or channels.” *Id.* As Dr. Cantor explains, a POSA would understand that a tissue section **does not** have features like wells or channels. EX2002, ¶115. Instead, as Dr. Cantor explains and supports with evidence, “wells or channels” are features of manufactured solid supports. *Id.* (citing EX1031). A POSA would understand that a “surface” of a “substrate” with “wells or channels” is **not** a tissue section, but instead is a manufactured solid support. *Id.*

Moreover, paragraphs 15-18 of the '124 provisional explain that in some embodiments, binding agents are immobilized (e.g., onto beads) and are **then** placed on the substrate surface, for example in wells or channels. EX2002, ¶114; *see also* EX1009, ¶17; EX1002, 22:22-33 (“In another aspect, the binding agents are immobilized onto beads or other separate structural elements that are then provided in known locations on the substrate surface.”). These passages describe an array as depicted in Petitioner’s “Figure A” because, once constructed, that array would then be contacted with a tissue section as depicted in “Figure A” to carry out the types of spatial distribution analyses described. EX2002, ¶114

Even more passages in the '124 provisional discuss the use of these types of pre-generated arrays—with binding agents immobilized directly or indirectly onto a “substrate surface.” EX2002, ¶116. One passage does so in the context of peptide binding agents. EX1009, ¶21; EX1002, 22:52-62; EX2002, ¶116. Another does so in the context of chemical binding agents. EX1009, ¶22; EX1002, 22:63- 23:5; EX2002, ¶116.

Prelim. Resp. 26–27.

Second, Patent Owner contends that the '124 provisional provides written description support for the limitation “contacting an array with a tissue section such that nucleic acids in the tissue section specifically bind to

the capture probes.” *Id.* at 30–31. In particular, Patent Owner contends that, “as Dr. Cantor testifies and supports with evidence, techniques for preparing tissues to interact with biological molecules were well known to a POSA by April 5, 2010, and therefore would not have needed to be explained to a POSA in the specification.” *Id.* at 30 (citing Ex. 2002 ¶¶ 124–127 (citing EX. 2009, EX. 2010)). Additionally, Patent Owner contends that

Both Petitioner and Dr. Puglisi *agree* with Dr. Cantor stating: “techniques for local release of nucleic acids or other biological molecules from tissue samples for capture on probes in bead or other arrays were known” to a POSA at the time the ’124 provisional was filed. Pet., 66; EX1102, ¶264; EX2002, ¶125. As Dr. Cantor elaborates, conventional techniques such as in situ hybridization (referenced in the ’124 provisional) have been around since the 1970s and would not need to have been explained to a POSA circa 2010. EX2002, ¶124; EX1009, ¶3. The ’124 provisional itself points a POSA to “standard laboratory manuals” that describe such conventional techniques. *Id.* One of those manuals includes detailed protocols for liberating nucleic acids from a variety of different samples, including the local release of nucleic acids from tissue samples for in situ analysis. *Id.*; EX2009; EX2010.

Prelim. Resp. 31.

Patent Owner contends that the ’468 patent’s priority chain back to the ’124 provisional is intact because “[e]ach intervening application and the ’234 application expressly and unambiguously incorporated by reference the disclosure of the ’124 provisional.” Prelim. Resp. 23 (citing EX. 1012, 5; EX. 1011, 2; EX. 1010, 6; EX. 1057, 15; EX. 1056, 16; EX. 1055, 21; EX. 1064, 23; EX. 1063, 22; EX. 2011, 17 (“Cross-Reference to Related Applications”)).

Patent Owner concludes that “Frisen is not prior art,” asserting that “Frisen’s earliest possible priority date [is] April 13, 2011” and that the ’468

patent “traces its priority back to the [] ’124 provisional application,” which is April 5, 2010. Prelim. Resp. 33. Additionally, Patent Owner urges the Board to deny institution on Ground 3 “[b]ecause Petitioner cannot cure this defect in the Petition at trial.” *Id.*

3. Discussion

Petitioner challenges whether certain elements of independent claim 1 are supported by the ’124 provisional and/or whether the ’468 patent’s priority chain is intact. Pet. 58–67. Having considered the parties’ positions and evidence of record, however, we agree with Patent Owner’s written description analysis, summarized above, and find that (1) the ’124 provisional provides adequate written description support for each of the challenged claim elements; (2) the ’468 patent’s priority chain is intact; and (3) the ’468 patent is therefore entitled to the priority date of April 5, 2010. Consequently, Frisen is not prior art to the challenged claims. Because Frisen is not prior art, we do not specifically comment on its teachings, nor the factual assertions regarding its teachings provided by Petitioner or Patent Owner.

4. Conclusion

For the foregoing reasons, we determine that Petitioner has not established a reasonable likelihood of showing that Frisen anticipates any of claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30.

III. CONCLUSION

Petitioner has not established a reasonable likelihood of prevailing in demonstrating that any one of claims 1, 2, 6, 7, 12, 13, 18, 20, 21, 23, 25, 26, and 30 is unpatentable over prior art set forth in the Petition.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and no trial is instituted.

For PETITIONER:

Andrew E. Krause
Henry White
IRELL & MANELLA LLP
akrause@irell.com
hwhite@irell.com

For PATENT OWNER:

Anita L. Meiklejohn
Michael J. Kane
Katie E. Hyma
Kristi L. R. Sawert
FISH & RICHARDSON P.C.
meiklejohn@fr.com
kane@fr.com
hyman@fr.com
reiter@fr.com
sawert@fr.com

Kiley A. White
TENSEGRITY LAW GROUP
Kiley.white@tensegritylawgroup.com