

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.

IPR2025-00193
Patent 11,761,030 B2

Before MICHAEL J. FITZPATRICK, SHERIDAN K. SNEDDEN, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

A. *Background and Summary*

Curio Bioscience, Inc., (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 of U.S. Patent No. 11,761,030 B2 (“the ’030 patent,” Ex. 1005). Paper 1 (“Pet.”). Prognosys Biosciences Inc. and 10x Genomics, Inc., (collectively, “Patent Owner”) filed a Preliminary Response to the Petition. Paper 7 (“Prelim. Resp.”).

To institute an *inter partes* review, we must determine that the information presented in the Petition shows “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). After considering the evidence and arguments presented in the Petition, we determine that Petitioner has not demonstrated a reasonable likelihood of success in proving that at least 1 claim of the ’030 patent is unpatentable.

B. *Real Parties in Interest*

Petitioner Curio Bioscience, Inc., asserts it alone is the real party in interest. Pet. 7–8. Patent Owner Prognosys Biosciences Inc. and 10x Genomics, Inc.,¹ assert they are the real parties in interest. Paper 4, 1.

C. *Related Matters*

The parties indicate that the ’030 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. 7; Paper 4, 1.

¹ 10x Genomics, Inc. is an exclusive licensee but the parties refer to 10x Genomics, Inc., and Prognosys Biosciences Inc., collectively, as “Patent Owner” or “PO.” Pet. 4, n1; Paper 4, 1.

Petitioner also filed the following *inter parte* review petitions challenging Patent Owner's related patents: IPR2024-01289 (Patent No. 10,480,022) and IPR2025-00192 (Patent No. 11,549,138).

D. The '030 patent (Ex. 1005)

The '030 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.” Ex. 1005, code (57). Thus, the '030 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 1:38–41.

According to the '030 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 1:52–61. 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 they can have low spatial resolution. *Id.* at 2:4–15. The '030 patent purports to resolve these problems of those existing methods. *Id.* at 2:16–21.

Figure 1, reproduced below, is a simplified overview of the assay system of the '030 patent.

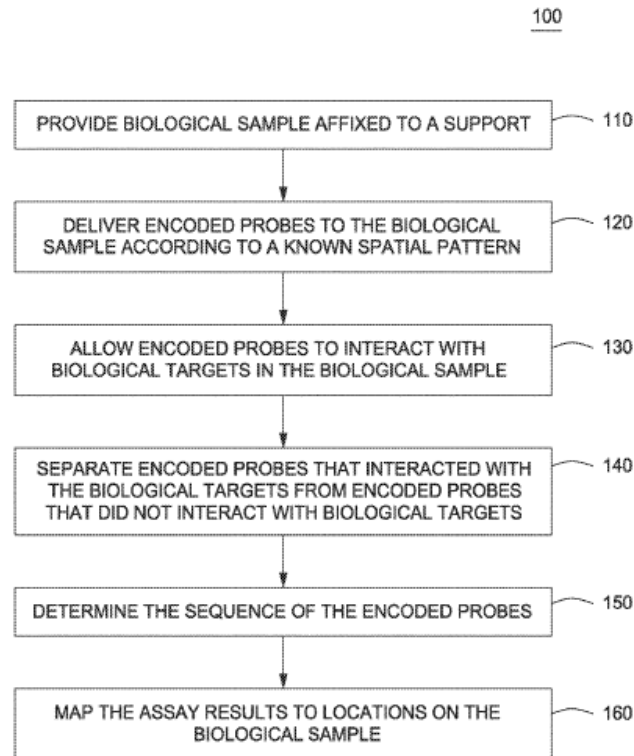


FIG. 1

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 9:26–33. 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 9:33–37. 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 9:35–42. As an example, “both the probe and coding tag sequence can be synthesized as a single oligonucleotide.” *Id.* at 9:43–48. At the next step 130, the encoded probes are allowed to interact with the biological targets and hybridize. *Id.*

at 9:60–10:7. 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 10:8–32. At the next step 150, the sequence of the interacted encoded probes is determined, preferably by sequencing. *Id.* at 10:33–37. 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 10:37–39.

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 10:40–67, 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 11:5–9.

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 12:39–44, Fig. 3. In this embodiment, one of the two provided 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 12:44–55. 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 12:56–60.

The '030 patent discloses that analysis of nucleic acids by 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 25:6–13. As an example, “[a] microarray is used as a proxy for a tissue section.” *Id.* at 30:64. A tissue section can come from animal sectioning and biopsies, frozen samples, and paraformalin-fixed, paraffin-embedded (FFPE) samples. *Id.* at 11:58–12:4. “[W]here high-throughput digital sequencing is employed, the sequences of at least 1,000 encoding probes are typically determined in parallel.” *Id.* at 11:53–55.

E. Illustrative Claims

Independent claims 1 and 16, reproduced below, are illustrative of the claimed subject matter of the ’030 patent.

1. A composition comprising an array comprising a substrate, a plurality of beads, and a plurality of capture probes, wherein:

the plurality of beads are attached to the substrate;

each of the capture probes of the plurality of capture probes comprises a nucleic acid sequence comprising from the bead surface: (i) a primer binding site, (ii) a nucleic acid sequence that identifies a unique location on the substrate and is not configured to hybridize to a target nucleic acid that binds to a target nucleic acid binding domain, and (iii) the target nucleic acid-binding domain;

the target nucleic acid-binding domain of each of the plurality of capture probes comprises a nucleic acid sequence capable of hybridizing to at least a portion of the target nucleic acid that binds to the target nucleic acid-binding domain; and

the plurality of beads was previously positioned on the substrate in a random pattern.

16. A composition comprising (i) an array comprising a substrate, a plurality of beads, and a plurality of capture probes, and (ii) a tissue section, wherein:

the tissue section is disposed on the array;

the plurality of beads are attached to the substrate;

each of the capture probes of the plurality of capture probes comprises a nucleic acid sequence comprising from the bead surface: (i) a primer binding site, (ii) a nucleic acid sequence that identifies a unique location on the substrate and is not configured to hybridize to a target nucleic acid that binds to a target nucleic acid binding domain, and (iii) the target nucleic acid-binding domain;

the target nucleic acid-binding domain of each of the plurality of capture probes comprises a nucleic acid sequence capable of hybridizing to at least a portion of the target nucleic acid that binds to the target nucleic acid-binding domain; and

the plurality of beads was previously positioned on the substrate in a random pattern.

Ex. 1005, 33:16–34, 34:8–26.

Claims 3, 6, 10, and 11 depend from independent claim 1. *Id.* at 33:37–39, 33:46–47, 33:54–57. Claims 18, 21, 24–26, and 30 depend from independent claim 16. *Id.* at 34:29–31, 34:38–39, 34:44–49, 34:57–60.

F. Evidence

Petitioner relies upon information that includes the following:

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.

Ex. 1045, Frisen et al., WO 2014/060483 A1, published Apr. 24, 2014 (“Frisen”).

Petitioner also relies upon the Declaration of Dr. Joseph D. Puglisi (Ex. 1103) to support its contentions.

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

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 would have been unpatentable on the following grounds (Pet. 10):

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1, 3, 6, 10, 11, 16, 18, 21, 24–26, 30	103	Cantor, knowledge of a POSA ²
2	1, 3, 6, 10, 11, 16, 18, 21, 24–26, 30	103	Cantor, Armani, knowledge of a POSA
3	1, 3, 6, 10, 11, 16, 18, 21, 24–26, 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 that any claim term requires construction. Pet. 22–23. Likewise, Patent Owner takes the position that “no claim terms

² Person of ordinary skill in the art.

require explicit construction” for purposes of determining whether to institute *inter partes* review. Prelim. Resp. 19.

Having considered the parties’ positions and evidence of record, we determine that no express construction of any claim term is necessary to determine whether to institute *inter partes* review. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Matal*, 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))).

B. 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.

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

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.* Tissue 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 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.

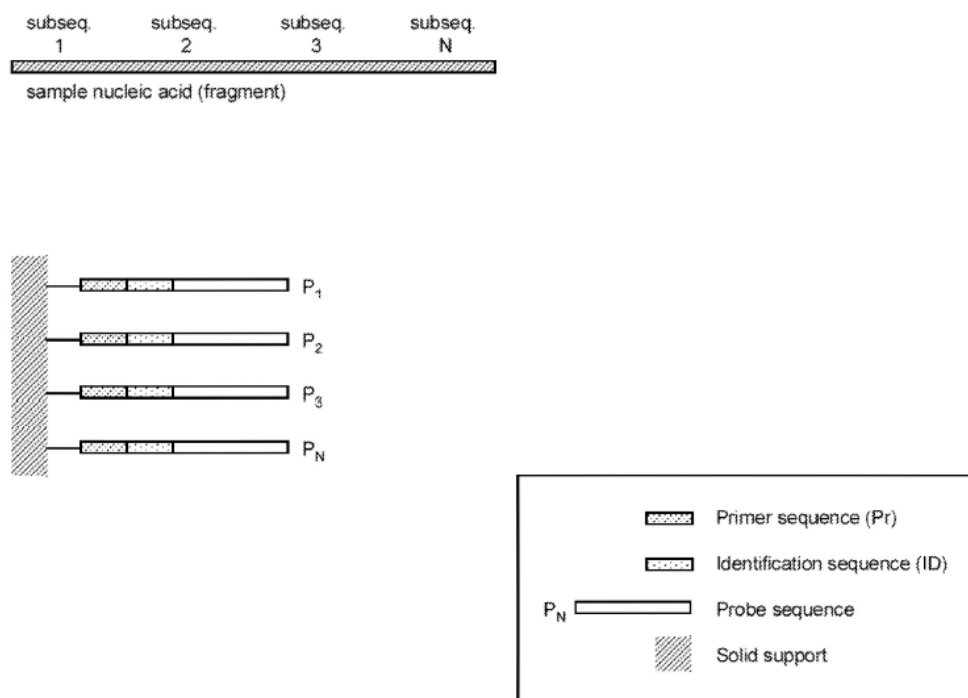


Figure 1A

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, . . . 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, “[s]olid 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.

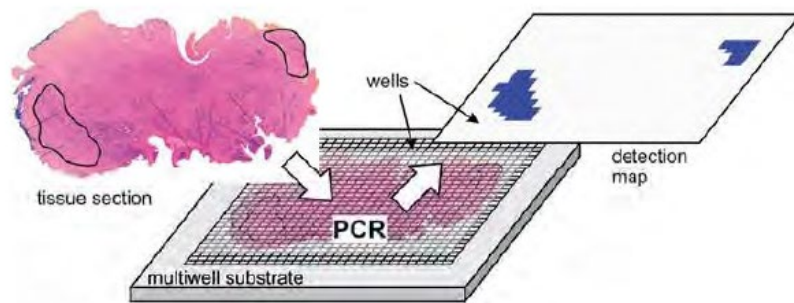


Figure 1 shows that “2D-PCR is achieved by transferring a tissue section vertically into a multi-well array device, isolating tissue subregions.”

Ex. 1022, 3526. “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.

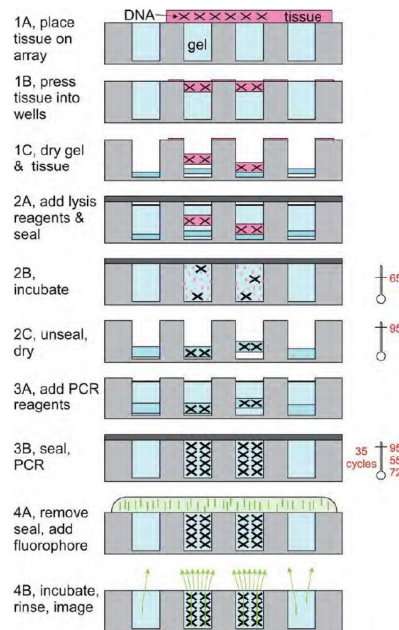


Figure 2 shows steps 1A–4B in an experimental protocol that is “used to demonstrate the 2D-PCR concept.” Ex. 1022, 3526. “Tissue is transferred into wells, isolated, and lysed to extract the genomic DNA (represented by ‘x’s),” and “PCR is performed to amplify the target DNA, and the targets are visualized with fluorescent dye (indicated by vertical lines ‘|’).” *Id.*

3. Summary of Frisen (Ex. 1045)

Frisen “relates to methods and products for localized or spatial detection and/or analysis of RNA in a tissue sample” comprising “providing an object substrate on which at least one species of capture probe, comprising a capture domain, is directly or indirectly immobilized such that the probes are oriented to have a free 3’ end to enable said probe to function as a reverse transcriptase (RT) primer.” Ex. 1045, code (57). The method further includes “contacting said substrate with a tissue sample and allowing RNA of the tissue sample to [hybridize] to the capture probes” and “generating cDNA molecules from the captured RNA molecules using said capture probes as RT primers.” *Id.*

Frisen discloses that it “provides an object substrate, such as a chip or slide (e.g. an array) for performing the method.” *Id.* at 2:6–7. “[T]he probes may be immobilized on beads, e.g. plastic microbeads, which can be used to immobilize the probes on the substrate.” *Id.* at 20:12–13.

Frisen summarizes its invention as

requir[ing] reverse transcription (RT) primers to be [immobilized] on an object substrate, e.g. a glass slide or chip. Thin tissue sections are placed onto the substrate and a reverse transcription reaction is performed in the tissue section on the substrate. The RT primers, to which the RNA in the tissue sample binds (or hybridizes), are extended using the bound RNA as a template to obtain cDNA, which is therefore bound to the surface of the substrate. The synthesized part of the cDNA is labelled, e.g. with a visibly detectable label, such as a fluorescently labelled nucleotide which may be incorporated into the synthesized cDNA molecules. A consequence of labelling the synthesized cDNA is that each cDNA strand provides a detectable signal that corresponds to the presence of a RNA molecule in the tissue section, and the location of the cDNA on the surface of the substrate corresponds to its original location in the tissue section. The signal from the labelled cDNA is detected, e.g. the surface of the substrate is imaged, and accordingly, the relative abundance of transcript present in each part of the tissue section, e.g. each cell, can be detected and quantified. Optionally, the tissue section may be [visualized] or imaged, e.g. stained and photographed, before or after the cDNA synthesis step to enable the labelled cDNA molecule to be correlated with a position within the tissue sample.

Id. at 6:9–27.

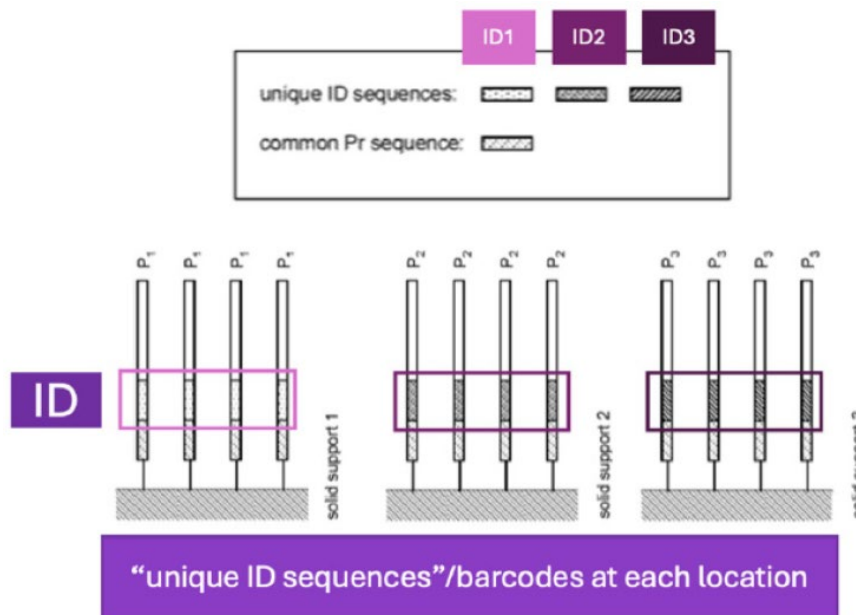
Frisen discloses that “[t]he capture domain may be capable of binding selectively to a desired subtype or subset of nucleic acid” such as “a particular mRNA species e.g. corresponding to a particular gene or group of genes.” *Id.* at 26:2–5.

The capture domain comprises a nucleotide sequence that is capable of hybridizing to nucleic acid such as mRNA that is present in the cells of the tissue sample contacted with the array and may be selected or designed to bind selectively or specifically to the particular nucleic acid. *Id.* at 24:35–25:5. A positional domain such as a feature identification domain or tag can be included in the capture probe, and can be “located directly or indirectly upstream, i.e. closer to the 5’ end of the capture probe nucleic acid molecule, of the capture domain.” *Id.* at 26:19–21. This positional domain “comprises the sequence which is unique to each feature or a group of directly or indirectly adjacent features, and acts as a positional or spatial marker (the identification tag)” such that “each region or domain of the tissue sample, e.g. each cell in the tissue, may be identified by spatial resolution across the array linking the nucleic acid, e.g. RNA (e.g. the transcripts) from a certain cell to a unique positional domain sequence in the capture probe.” *Id.* at 28:12–18. “[T]he positional domain should not interfere with (i.e. inhibit or distort) the interaction between the RNA of the tissue sample and the capture domain of the capture probe,” meaning that “the positional domain should be designed such that nucleic acid molecules in the tissue sample do not hybridize specifically to the positional domain.” *Id.* at 29:32–30:2.

C. Obviousness of Claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 over Cantor and knowledge of a POSA

Petitioner asserts that claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 would have been obvious over Cantor and knowledge of a POSA. Pet. 23–43. For the reasons set forth below, we determine that Petitioner has not demonstrated a reasonable likelihood that claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 would have been obvious over Cantor and knowledge of a POSA.

Independent claims 1 and 16 recite a plurality of capture probes, each comprising a nucleic acid sequence that identifies *a unique location on the substrate* and is not configured to hybridize to a nucleic acid that binds to the target-binding domain. Ex. 1005, 33:16–34, 34:8–26. For this element of the challenged claims, Petitioner relies on Cantor’s disclosure of solid supports (i.e., beads) “coded with a unique nucleic acid ‘identifier sequence’ that differs from the ‘identifier sequence’ coding of every other bead.” Pet. 28 (citing Ex. 1031, 2). Here, Petitioner directs our attention to a schematic interpreting of Cantor’s Figure 1C. *Id.* at 29–30. Petitioner’s schematic, which places solid supports 1, 2, and 3 of Cantor’s Figure 1C side-by-side and adds annotations, which is reproduced below.



Petitioner’s annotated schematic “depicts a single bead, each capture probe on a given bead shares a common identifier sequence, each identifier sequence (i.e., each identifier sequence is the same).” *Id.* at 28–29 (citing Ex. 1103 ¶ 131). Petitioner states that “separate solid supports, such as

beads, each hav[e] ‘unique ID sequences’ that are correlated to the specific solid supports.” *Id.* at 29–30.

Petitioner further contends that Cantor teaches that “[s]olid supports may be provided in an array” including for example “an ‘X by Y array’ for square or rectangular arrays, where the array includes X number of sample locations or solid supports.” *Id.* at 28–29 (citing Ex. 1031, 17; Ex. 1103

¶ 132). Further to that point, Petitioner contends that

a POSA would understand that Cantor discloses an array of beads at which each bead is necessarily deposited at a particular (X, Y) coordinate location, and thus, each identification sequence necessarily corresponds to, and thus identifies, the unique location (such as an (X,Y) coordinate) of the bead on the array. EX1103, ¶134.

Pet. 29.⁴

Independent claims 1 and 16 also recite that each of the plurality of capture probes are immobilized on the substrate in a random pattern.

Ex. 1005, 33:16–34, 34:8–26. Petitioner does not contend that Cantor expressly teaches this limitation. Rather, Petitioner contends that

a POSA would appreciate that “the beads may be randomly distributed on the array,” and “can later be ‘decoded’, i.e. after the array is made, a correlation of the location of an individual

⁴ We note that Petitioner does not argue that Cantor’s “identification sequence” identifies a unique location on the substrate, but that Cantor’s capture probes identify a bead that may be placed on bead arrays. Pet. 29; *see also* Ex. 1003 ¶ 108 (“Cantor discloses bead arrays in which each bead is labelled or barcoded with a unique ‘identification sequence’ that differs from one solid support (e.g., bead) to another, thereby differentiating different beads at different locations in its arrays.”). Thus, we understand Petitioner’s argument to be that Cantor’s “identification sequence” identifies a bead that “necessarily occupies a distinct physical location on [bead] arrays.” Pet. 29; Ex. 1103 ¶ 109.

site on the array with the bead or candidate agent at that particular site can be made.” EX1038, [0042].^[5] A POSA would have been motivated to use such a random loading procedure to simplify and expedite the array generation and fabrication process. EX1103, ¶145.

A POSA also would have found it obvious to decode the array by using any of a number of known decoding procedures. For example, a POSA would have found it obvious to use the decoding by sequencing procedure disclosed in Chee-824, which allows simultaneous decoding of many bead types in a single experiment. *Id.*, [0046]. For example, Chee-824 discloses “decoding by sequencing” of bead arrays comprising probes structured similarly to those used in Cantor’s bead array, comprising an encoding sequence used to identify the particular bead as well as a gene-specific sequence that may be used to assay target nucleic acids. *Id.*, [0037]-[0038], Figs. 12-13. A POSA would have reasonably expected success in performing such decoding, as doing so would have involved the mere application of well-known techniques, including those described in Chee-824. EX1103, ¶¶146-147.

Pet. 35–36; *see also* Ex. 1103 ¶ 145 (“Selectively loading the beads in a defined pattern becomes more difficult as more beads are added to the array.”).

We have considered Petitioner’s argument and evidence summarized above, but are not persuaded on this record that Cantor teaches or suggests all elements of the challenged claims. As discussed above, Cantor relates to the identification and sequencing of target nucleotide sequences in a biological sample. Ex. 1031, 1–4. As noted by Patent Owner, Cantor’s solid supports and methods answer the question of whether a biological molecule of interest is present in a sample nucleic acid, which is achieved

⁵ Ex. 1038, Chee, U.S. No. 2007/0231824 A1, published Oct. 4, 2007 (“Chee-824”).

through bulk analysis. Prelim. Resp. 4–6, 42–51 (citing Ex. 2002 ¶¶ 16–20, 31–43). Each of Cantor’s solid supports are designed to identify target nucleotide sequences within the biological sample. Ex. 2002 ¶¶ 29–43. While Cantor’s beads may be arranged in an X,Y array, the placement of the beads on the substrate is not disclosed as random. Ex. 1031, 17–18; Ex. 2002 ¶ 171. That is, as Patent Owner argues, “Cantor *never* teaches or suggests that the beads and their corresponding identification sequences (if present) are either placed at a known location or placed randomly, with locations determined prior to use so that the identification sequence can be *traced back* to a unique location on the substrate.” Prelim. Resp. 59 (citing Ex. 2002 ¶ 168).

Petitioner, however, suggests that a POSA would have been motivated to arrange Cantor’s beads randomly on a substrate “to simplify and expedite the array generation and fabrication process.” Pet. 35 (citing Ex. 1103 ¶ 145). A POSA could then have used Cantor’s “identification sequence” in “any of a number of known decoding procedures” to determine the unique location of the bead on the substrate. *Id.* (citing Ex. 1038, 42, 46; Ex. 1103 ¶¶ 325–326).

Here, Petitioner directs our attention to decoding procedures disclosed in other prior art references. Pet. 33–36, 39–40. For example, Petitioner relies heavily on the arrays disclosed in Chee-824. *See, e.g.*, Pet. 35 (“a POSA would have found it obvious to use the decoding by sequencing procedure disclosed in Chee-824.”). As Patent Owner notes, however, the array in Chee-824 differs from the arrays disclosed in Cantor in that Chee-824 relates to DNA microarray sensors that use *in situ* on-substrate imaging.

Prelim. Resp. 73 (citing Ex. 2002 ¶ 183). Array sensors such as DNA microarrays

generate a signal (such as fluorescence) directly on the array itself (i.e., *in situ*) when a target nucleic acid molecule hybridizes to a probe on the array. In that context, the identity of the probe at each location on the array is known or determined prior to use. This is so the signal generated *in situ* can provide the identity of the target nucleic acid molecule that hybridizes.

Ex. 2002 ¶ 175; *see also id.* at ¶¶ 176, 177 (describing how DNA microarrays work). “But Cantor is not a DNA microarray, and it does not use *in situ* detection of hybridization in this manner.” *Id.* at ¶ 178. Thus,

Petitioner’s obviousness case requires the POSA to modify Cantor to trace back its identification sequences to locations on a substrate (by selective loading of capture probes to locations on the array and/or randomly loading the capture probes and then decoding). EX2002, ¶151. As described above in §VII.B, Cantor does not teach or suggest doing so. It would be unnecessary and contradictory to Cantor’s objective of “efficiently preparing” copies of nucleic-acid molecules of interest for bulk analysis. EX2002, ¶173. Likewise, Cantor does not teach or suggest its identification sequences (for assembling large nucleotide sequences from smaller sequence “reads” by identifying overlapping sequences) could provide spatial information. *Id.*, 25, 53-55 (Example 1); EX2002, ¶45.

Prelim. Resp. 69–70.

What is missing from Petitioner’s stated motivation for modifying the array of Cantor is a reason why a POSA would seek to correlate the identification sequence with a location on the array at all. Prelim. Resp. 72. Indeed, the location of a bead on the substrate is not pertinent to the analysis disclosed in Cantor. Ex. 2002 ¶ 172; *see also id.* at ¶ 31 (Cantor “does not relate to the [spatial] analysis of tissue samples . . .”).

“[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Here, Cantor fails to teach or suggest capture probes distributed randomly on a substrate comprising a nucleic acid sequence that identifies a unique location on the substrate as required by the challenged claims, and Petitioner fails to adequately articulate why a person of ordinary skill in the art would have modified Cantor to make the recited capture probes.

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. Accordingly, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing on its challenge that any of claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 would have been obvious over Cantor.

D. Obviousness of Claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 over Cantor and Armani, and knowledge of a POSA

Petitioner asserts that claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 would have been obvious over Cantor, Armani, and knowledge of a POSA. Pet. 43–49. Consistent with Ground 1, Petitioner asserts that the challenged claims would have been obvious over Cantor and further relies on Armani to “provide[] additional information rendering obvious disposing the tissue section on the array as recited by Claim 16 and the tissue section being a fresh-frozen tissue section as required by Claim 24.” Pet. 43. 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 the 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.

Pet. 45–46. Petitioner contends that a person of ordinary skill in the art would have combined Armani’s method with “Cantor’s bead array with the plurality of beads disposed in wells” in order “to detect nucleic acids from a tissue sample, while specifically using the identification sequences to identify the location at which beads were provided.” *Id.* at 47–49.

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. As summarized above, Armani’s methods do not involve using capture probes. Rather, Armani discloses a 2D-PCR method for mapping tissue sections to a multi-well array device. Ex. 1022, 3527; Ex. 2002 ¶¶ 94–100. Thus, the combination of Cantor and Armani likewise fails to teach or suggest capture probes distributed randomly on a substrate comprising a nucleic acid sequence that identifies a unique location on the substrate as required by the challenged claims. And, as in Ground 1, Petitioner fails to adequately articulate why a person of ordinary skill in the art would have modified Cantor to make an array requiring the decoding of Cantor’s “identification sequences” in order to determine the location of capture probes. Rather, we are persuaded by Patent Owner’s conclusion that

Armani’s methods rely on forcing portions of a tissue sample into discrete wells forming individual samples, performing individual well-by-well PCR reactions on the individual samples in the wells, and then imaging them in place. Armani does not need to

use a coding identifier because Armani's method preserves the physical location of the individual samples during imaging.

Prelim. Resp. 76–77 (internal citations omitted).

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, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 would have been obvious over Cantor and Armani.

E. Anticipation of Claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 by Frisen

Petitioner asserts that claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 are anticipated by Frisen. Pet. 50–76. Frisen has an effective filing date of April 13, 2011. Ex. 1020, code (30). Petitioner contends that Frisen qualifies as prior art to the '030 patent because the challenged claims are not entitled to a priority date earlier than February 14, 2019. Pet. 51.

For the reasons set forth below, we find that the '030 patent is entitled to its earliest claim priority date of April 5, 2010. Frisen therefore does not qualify as prior art to the '030 patent. Accordingly, we determine that Petitioner has not demonstrated a reasonable likelihood that claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 are anticipated by Frisen.

1. Petitioner's Contentions

The '030 patent issued from application No. 18/074,992 ("992 Application"), filed on Dec. 5, 2022, which is a continuation of application No. 17/850,538, filed on June 27, 2022 (which issued as Patent No. 11,519,022), which is a continuation of application No. 17/480,914, filed on Sept. 21, 2021 (which issued as Patent No. 11,371,086), which is a continuation of application No. 17/321,090, filed on May 14, 2021 (which issued as Patent No. 11,156,603), which is a continuation of application No.

17/145,210, filed on Jan. 8, 2021 (which issued as Patent No. 11,067,567), which is a continuation of application No. 16/669,246, filed on Oct. 30, 2019 (which issued as Patent No. 10,982,268), which is a continuation of application No. 16/437,637, filed on June 11, 2019 (which issued as Patent No. 10,494,667), which is a continuation of application No. 16/430,015, filed on June 3, 2019, which is a continuation of application No. 16/414,213, filed on May 16, 2019 (which issued as Patent No. 10,787,701), which is a continuation of application No. 16/402,098, filed on May 2, 2019 (which issued as Patent No. 10,472,669), which is a continuation of application No. 16/276,235, filed on Feb. 14, 2019 (which issued as Patent No. 10,480,022), which is a continuation of application No. 15/187,661, filed on June 20, 2016 (which issued as Patent No. 10,308,982), which is a continuation of application No. 13/080,616, filed on Apr. 5, 2011 (which issued as Patent No. 9,371,598), which claims priority to provisional application No. 61/321,124, filed on Apr. 5, 2010. Ex. 1005, codes (21), (22), (63), (60). For ease of reference, we reproduce below Petitioner's table summarizing the priority data of the '030 patent.

 '030 Patent Priority Documents	Filing Date	Exhibit
17/850,538 (the "'538 Application")	June 27, 2022	EX1049
17/480,914 (the "'914 Application")	September 21, 2021	EX1050
17/321,090 (the "'090 Application")	May 14, 2021	EX1051
17/145,210 (the "'210 Application")	January 8, 2021	EX1052
16/669,246 (the "'246 Application")	October 30, 2019	EX1053
16/437,637 (the "'637 Application")	June 11, 2019	EX1054
16/430,015 (the "'015 Application")	June 3, 2019	EX1055
16/414,213 (the "'213 Application")	May 16, 2019	EX1056
16/402,098 (the "'098 Application")	May 2, 2019	EX1057
16/276,235 (the "'235 Application")	February 14, 2019	EX1010
15/187,661 (the "'661 Application")	June 20, 2016	EX1011
13/080,616 (the "'616 Application")	April 5, 2011	EX1012
61/321,124 (the "'124 Provisional")	April 5, 2010	EX1009

Pet. 50.

Petitioner contends that the '661 Application does not provide written description support for the challenged claims as certain passages in the '124 Provisional were omitted from the '661 and '616 Applications. Pet. 51–52. Petitioner contends that, in order to gain the benefit of priority to the '124 Provisional, “there has to be a continuous chain of copending applications each of which satisfies the requirements of §112 with respect to the subject matter claimed,” and that the “break in the priority chain precludes [Patent

Owner] from relying on any date earlier than February 14, 2019, the filing date of the '235 Application.” *Id.* at 51 (quoting *Holmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012)).

Petitioner contends that there are two key elements of independent claims 1 and 16 that allegedly lack written-description support, specifically, that there is no disclosure of

(1) the plurality of beads/capture probes being attached to a substrate nor (2) beads that (i) have a capture probe with a nucleic acid sequence that identifies a unique location on the substrate and (ii) are randomly distributed on the substrate.

Pet. 52 (citing Ex. 1103 ¶¶ 201–232).

Petitioner further contends that

A POSA reviewing the '661 Application would not have understood it to demonstrate that the inventor possessed arrays that included substrate with a plurality of probe-functionalized beads attached thereto. Instead, a POSA would have understood the disclosures to have been limited to the delivery of reagents, including binding agents and encoded probes, to a tissue sample already affixed to the solid support. EX1103, ¶204.

Pet. 55.

2. *Patent Owner's Contentions*

Patent Owner responds that the claims of the '030 patent are entitled to the priority date of the '124 Provisional's filing date of April 5, 2010. Prelim. Resp. 19–36. First, Patent Owner notes that “Petitioner does not and cannot dispute that each application in the '030 patent's priority chain included a ‘specific reference’ to the earlier-filed application under §§119(e) and 120,” and specifically the '124 Provisional. Prelim. Resp. 22 (citing Pet. 50–52).

Second, Patent Owner notes “[e]ach intervening application and the ’992 [Application] expressly and unambiguously incorporated by reference the disclosure of the ’124 provisional. *Id.* at 23 (citing Ex. 1011, 2 (’661 application incorporating the ’124 provisional by reference); Ex. 1010, 6 (’235 application incorporating the ’124 provisional by reference); Ex. 1057, 15 (’098 application incorporating the ’124 provisional by reference); Ex. 1056, 16 (’213 application incorporating the ’124 provisional by reference); Ex. 1055, 21 (’015 application incorporating the ’124 provisional by reference); Ex. 1054, 15 (’637 application incorporating the ’124 provisional by reference); Ex. 1053, 15 (’246 application incorporating the ’124 provisional by reference); Ex. 1052, 16 (’210 application incorporating the ’124 provisional by reference); Ex. 1051, 19 (’090 application incorporating the ’124 provisional by reference); Ex. 1050, 14 (’914 application incorporating the ’124 provisional by reference); Ex. 1049, 14 (’538 application incorporating the ’124 provisional by reference); 2013, 14 (’992 application incorporating the ’124 provisional by reference)).⁶ In view of the above, Patent Owner contends that

the disclosure of the ’124 provisional was “as much a part of the [each] application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.” MPEP §2163.07(b).

Prelim. Resp. 23–24. Thus, according to Patent Owner,

Because the ’124 provisional was incorporated by reference into the specification of the ’992 application and all intervening applications, if the claim elements have written-description

⁶ We also note the substitute specification submitted contemporaneously as part of the ’235 application, which literally incorporated the relevant text from the ’124 provisional into the body of the ’235 application specification. Ex. 1010, 69, 106–118.

support in the '124 provisional, then they also have written-description support in the '992 application and all intervening applications.

Id. at 24.

Next, Patent Owner contends that “[t]he '124 provisional provides written-description support under §112 for each challenged claim element and Petitioner’s priority challenge fails.” *Id.* Specifically, Patent Owner contends that the '124 provisional supports delivering a tissue sample to a previously generated array of bead-affixed capture probes attached to a substrate. *Id.* at 24–25 (citing Pet. 53). More specifically, Patent Owner contends that

Paragraphs 17 and 18 [of the '124 provisional] explain that, in one embodiment of the invention, binding agents (e.g., capture probes) are “immobilized directly or indirectly to the **substrate** surface.” EX1009, ¶¶17–18; EX1005, 22:29-49; EX2002, ¶114. 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 onto beads that are **then** placed on the substrate surface, for example in wells or channels. EX2002, ¶114; *see also* EX1009, ¶17; EX1005, 22:29-37. These passages describe an array as depicted in Petitioner’s “Figure A” because, once constructed, that array would then be contacted with a tissue sample 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 pre-generated arrays—with beads immobilized directly or indirectly onto a “substrate surface.” EX2002, ¶116. One passage does so in the context of peptide binding agents; another does so in the context of chemical binding agents. EX1009, ¶¶21-22; EX1005, 23:1-22; EX2002, ¶116.

Prelim. Resp. 26–27.

Next, Patent Owner contends that the '124 provisional supports “beads that have a capture probe with a nucleic acid sequence that identifies a unique location on the substrate.” *Id.* at 30–33. Specifically, Patent Owner notes that the

the '124 provisional discloses that its “unique coding scheme” uses “both molecule-specific binding agents and coding identifiers to provide a practical and cost-effective determination of information on multiple biological molecules, including specific positional information of such molecules in a biological sample, e.g., a tissue section.” EX1009, ¶7; EX1005, 20:60-21:14; EX2002, ¶124. The unique encoding scheme allows “multiple molecules and their respective multiple locations to be identified in a single system.” *Id.* And here the presence or absence and specific positional information of the biological molecules is based on detection of both the binding agent, the coding identifier, and the knowledge of the location of the binding agents (and thus coding identifier) on the substrate. EX1009, ¶¶7, 18; EX2002, ¶¶125-126.

Prelim. Resp. 30. Furthermore, Patent Owner contends that “[t]he '124 provisional provides explicit disclosure of an embodiment in which the “binding agents are nucleic acids,” and “the nucleic acids may be immobilized directly or indirectly onto beads.” *Id.* at 30–31 (citing Ex. 1009 ¶ 18; Ex. 1005 22:38–49; Ex. 2002 ¶ 127).

Next, Patent Owner contends that the '124 provisional supports beads “randomly distributed on the substrate.” *Id.* at 34–36. Specifically, Patent Owner contends that

the '124 provisional teaches pre-generated bead arrays in which binding agents and coding identifiers (e.g., capture probes) are deposited onto substrate at “discrete, independent measureable” [sic] locations. EX1009, ¶47; EX1005, 24:20-43; EX2002, ¶137. It also teaches that their location “is known or determined prior to use of the substrate surface in the assay system.” EX1009, ¶¶17-18; EX1005, 22:29-49; EX2002, ¶137.

Prelim. Resp. 35. Here, Patent Owner contends that a person of ordinary skill in the art would have understood “determined prior to use” to mean that beads are randomly distributed on the array and their location later decoded, prior to use of the array. *Id.* at 36 (citing Ex. 2002 ¶¶ 139–141); *see also*, Ex. 1009 ¶ 12 (The '124 provisional discloses that “the assay system can utilize an encoding scheme that comprises a 2-dimensional grid format based on the discrete positioning of the binding agents in the substrate surfaces. In another example, the spatial patterns may be based on more randomized cell locations . . .”).

Finally, Patent Owner concludes that “Frisen is not prior art,” asserting that “Frisen’s earliest possible priority date is April 13, 2011” and that “this date is after the Challenged Claims priority date of April 5, 2010,” the filing date of the '124 provisional application. *Id.* at 19. Finally, Patent Owner urges the Board to deny institution on Ground 3 “[b]ecause Frisen is not prior art and Petitioner cannot cure this this defect [in the Petition] at trial.” *Id.* at 36.

3. *Discussion*

Petitioner challenges whether certain elements of independent claims 1 and 16 are supported by the '124 provisional and/or whether the '030 patent's priority chain is intact. Pet. 50–61. Having considered the parties' positions and evidence of record, however, we agree with Patent Owner's written description analysis, summarized above, and find (1) that the '124 Provisional provides adequate written description support for each of the challenged claim elements, including through incorporation by reference; (2) that the '030 patent's priority chain is intact; and (3) that the '030 patent is therefore entitled to the priority date of April 5, 2010. Consequently, Frisen is not prior art to the challenged claims.

III. CONCLUSION

Petitioner has not established a reasonable likelihood of prevailing in demonstrating that claims 1, 3, 6, 10, 11, 16, 18, 21, 24–26, and 30 are unpatentable over prior art set forth in the asserted grounds.

IV. ORDER

In consideration of the foregoing, it is hereby:

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

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Patent 11,761,030 B2

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