

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 and Real-Party-In-Interest.

IPR2025-00192
Patent No. 11,549,138

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,549,138**

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EX1003	U.S. Patent No. 11,001,879 issued to Chee
EX1004	U.S. Patent No. 11,549,138 issued to Chee
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EX1006	10x Genomics' Complaint for Patent Infringement, Case 1:23-cv-01375, Doc. 1, filed December 1, 2023
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EX1013	Nick J. Proudfoot, <i>et al.</i> , <i>Integrating mRNA Processing with Transcription</i> , Cell, Vol. 108, 501-512, February 22, 2002
EX1014	Uwe Kuhn <i>et al.</i> , <i>Poly(A) Tail Length Is Controlled by the Nuclear Poly(A)-binding Protein Regulating the Interaction between Poly(A) Polymerase and the Cleavage and Poladenylation Specificity Factor</i> , The Journal of Biologic Chemistry VOL. 284, NO. 34, pp 22803-22814, August 21, 2009
EX1015	James Eberwine <i>et al.</i> , <i>Complementary DNA Synthesis in Situ: Methods and Applications</i> , Methods in Enzymology, VOL. 216, 1992

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EX1017	Anna Ligasová and Karel Koberna, <i>In situ reverse transcription: the magic of strength and anonymity</i> , Nucleic Acids Research, 2010, Vol. 38, No. 16
EX1018	Victor Trevino <i>et al.</i> , <i>DNA Microarrays: a Powerful Genomic Tool for Biomedical and Clinical Research</i> , Mol Med 13 (9-10) 527-541, September-Doctor 2007
EX1019	Stahl <i>et al.</i> , "Visualization and analysis of gene expression in tissue selections [sic: sections] by spatial transcriptomics," <i>Science</i> 353(6294):78-82 (July 1, 2016)
EX1020	WO 2012/140224 A1 to Frisen
EX1021	WO 2010/088517 A1 to Emmert-Buck, Armani <i>et al.</i>
EX1022	Michael Armani <i>et al.</i> , <i>2D-PCR: a method of mapping DNA in tissue sections</i> , Lab Chip, 2009, 9(24), 3526-3534; NIH Public Access Author Manuscript
EX1023	Lambda Moses and Lior Pachter, <i>Museum of spatial transcriptomics</i> , Nature Methods, VOL 19, May 2022 [534-546]
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EX1025	JP2007-14297 to Okano
EX1026	EP 2 130 913 A1 to Okano
EX1027	Franklin M. Harold, <i>Molecules into Cells: Specifying Spatial Architecture</i> , Microbiology and Molecular Biology Reviews, Dec. 2005, p. 544-564
EX1028	Vanessa M. Brown <i>et al.</i> , <i>Multiplex Three-Dimensional Brain Gene Expression Mapping in a Mouse Model of Parkinson's Disease</i> , Genome Research, 12:868-884, 2002

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EX1029	Michael L. Metzker, <i>Sequencing technologies-the next generation</i> , Nature Reviews Genetics, Volume 11, January 2010
EX1030	Poornima Parameswaran, <i>et al.</i> , <i>A pyrosequencing-tailored nucleotide barcode design unveils opportunities for largescale sample multiplexing</i> , Nucleic Acids Research, 2007, Vol. 35, No. 19
EX1031	WO 2009/091934 A1 Cantor
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EX1033	WO 2008/075086 A1 Southern <i>et al.</i>
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EX1036	Norman P. Gerry, <i>et al.</i> , <i>Universal DNA Microarray Method for Multiplex Detection of Low Abundance Point Mutations</i> , J. Mol. Biol. (1999) 292, 251-262
EX1037	U.S. Patent No. 8,835,358 issued to Fodor
EX1038	U.S. No. 2007/0231824 A1 to Chee
EX1039	Jian-Bing Fan, <i>et al.</i> , <i>Illumina Universal Bead Arrays</i> , Methods in Enzymology, VOL. 410, 2006
EX1040	10X Genomics' Petition for IPR Review of Nanostring Technologies' Patent No. 11,377,689 (IPR2023-01298)
EX1041	July 24, 2024 Email from Counsel for Patent Owner to Counsel for Petitioner
EX1042	July 16, 2024 Email from Counsel for Patent Owner to Counsel for Petitioner
EX1043	Scheduling Order, Doc #25, C.A. 23-cv-1375 (D.Del.)

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EX1044	Leslie P. Gartner, Ph.D. and James L. Hiatt Ph.D., <i>Color Textbook of Histology</i> , Third Edition, Saunders Elsevier
EX1045	WO 2014/060483 A1 ("Frisen")
EX1046	Marshall S. Scicchitano <i>et al.</i> , <i>Preliminary Comparison of Quantity, Quality, and Microarray Performance of RNA Extracted From Formalin-fixed, Paraffin-embedded, and Unfixed Frozen Tissue Samples</i> , 2006, J. Histochemistry & Cytochemistry 54(11), 1229-1237.
EX1047	Stephen M. Hewitt, MD <i>et al.</i> , <i>Tissue Handling and Specimen Preparation in Surgical Pathology</i> , Arch. Pathol. Lab. Med. (2008) 132, 1929-1935.
EX1048	US6,133,436 issued to Köster
EX1049	17/850,538 (the "'538 Application")
EX1050	17/480,914 (the "'914 Application")
EX1051	17/321,090 (the "'090 Application")
EX1052	17/145,210 (the "'210 Application")
EX1053	16/669,246 (the "'246 Application")
EX1054	16/437,637 (the "'637 Application")
EX1055	16/430,015 (the "'015 Application")
EX1056	16/414,213 (the "'213 Application")
EX1057	16/402,098 (the "'098 Application")
EX1058	Reserved
EX1059	16/988,284 (the "'284 Application")
EX1060	17/030,230 (the "'230 Application")

EX NO.	<u>PETITIONER'S EXHIBIT LIST</u>
EX1061	Exemplary Infringement Claim Chart-U.S. Patent No. 11,549,138 Case 1:23-cv-01375, Doc. 1-11, filed December 1, 2023 (EX N)
EX1062	Exemplary Infringement Claim Chart-U.S. Patent No. 11,761,030, Case 1:23-cv-01375, Doc. 1-11, filed December 1, 2023 (EX O)
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EX1101	Curriculum Vitae of Joseph D. Puglisi, Ph.D.
EX1102	Reserved
EX1103	Declaration of Joseph D. Puglisi, Ph.D. for IPR2025-00192 & IPR2025-00193

LISTING OF CHALLENGED CLAIMS

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

each of the plurality of capture probes comprises: (i) a target-binding domain, (ii) 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, and (iii) a primer binding site;

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

each of the plurality of capture probes are immobilized on the substrate in a random pattern.

5. The composition of claim 1, wherein the array is deposited on a slide or flow-cell.

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

the tissue section is disposed on the array;

each of the plurality of capture probes comprises: (i) a target-binding domain (ii) 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, and (iii) a primer binding site;

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

each of the plurality of capture probes are immobilized on the substrate in a random pattern.

20. The composition of claim 17, wherein the tissue section is a formalin-fixed paraffin-embedded tissue section or a fresh frozen tissue section.

23. The composition of claim 17, wherein the array is deposited on a slide or flow-cell.

28. The composition of claim 17, wherein the nucleic acid comprises RNA or DNA.

29. The composition of claim 28, wherein the RNA is mRNA.

Curio Bioscience, Inc. (“Petitioner”) requests *inter partes* review and cancellation of claims 1, 5, 17, 20, 23, 28, and 29 of U.S. Patent No. 11,549,138 (“Chee-138”), entitled “Spatially Encoded Biological Assays.” Chee-138 is owned by Prognosys, and was exclusively licensed to real-party-in-interest 10x Genomics (“10x”) in November 2018.¹

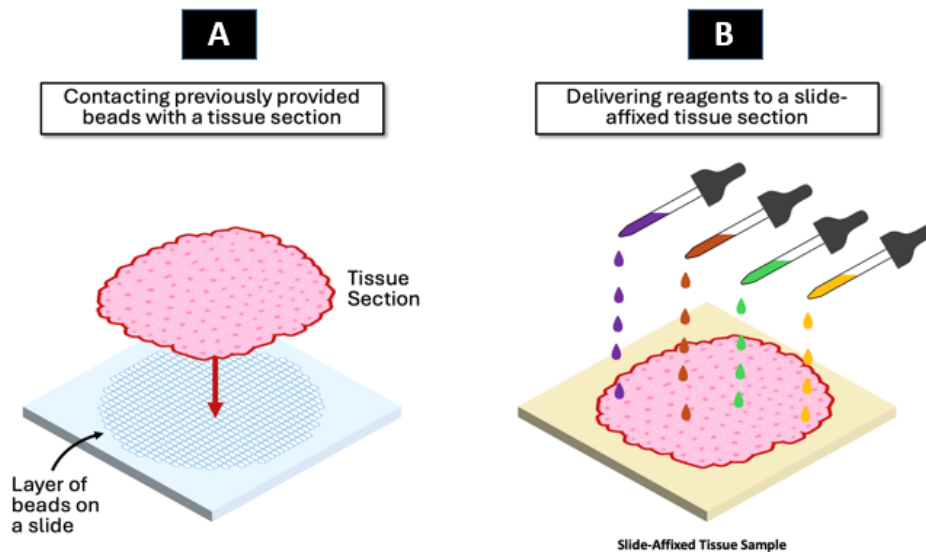
I. INTRODUCTION

The claims of Chee-138 recite “[a] composition comprising an array comprising a substrate and a plurality of capture probes,” which describes conventional nucleic acid array technology that has long been known in the art. EX1004, cl. 1. In co-pending litigation, PO reads the claims of Chee-138 to cover such devices when used in analysis of the spatial organization of nucleic acids in a tissue sample placed on top of the array, and using the array to tag captured mRNA with “spatial barcodes.” *See* EX1061.

Such devices and methods are not described by Chee-138 or its priority documents. Rather, Chee-138’s specification focuses on the patterned delivery of probes to a slide-affixed tissue sample using allegedly novel “reagent delivery systems” such as inkjet printing or photolithography, techniques Chee-138 calls “integral to the assay system of the invention.” EX1004, 16:3-21. The stark contrast

¹ Patent Owner (“PO”) collectively refers to 10x and Prognosys. 10x and Prognosys refer to the separate actions of each.

between the approach and devices PO now claims (Figure A) and the approach actually described in the specification (Figure B) is illustrated below.



This disconnect exists because 10x drafted the Chee-138 well after the priority date to cover implementations of technology it acquired from Spatial Transcriptomics AB (“ST”). ST is a company 10x acquired in late 2018, around the same time it licensed Chee-138 from Prognosys. In proceedings not involving Prognosys, 10x has stated:

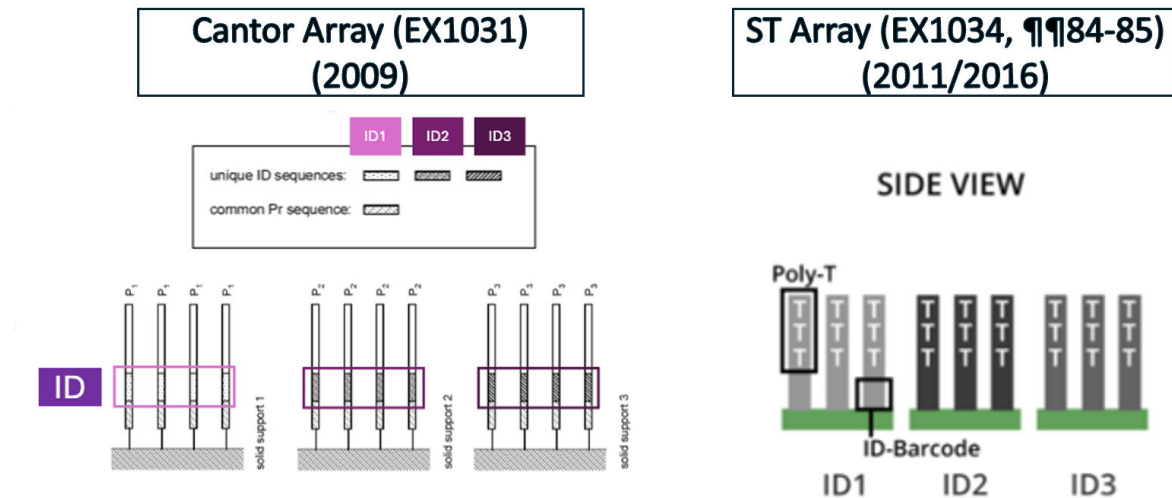
As early as 2011, Stahl et al. *developed a pioneering spatially barcoded array paradigm* for determining the locations of target mRNAs in a biological sample. *The scientists disclosed this foundational technology in a patent application filed in 2011* (WO 2012/140224; [EX1020, to Frisen]) and subsequently published it in a 2016 article [EX1019].

EX1034, ¶82. 10x's claim that Stahl/Frisen's "spatially barcoded array" structures—filed over one year after what PO contends is Chee-138's priority date (April 2010)—was "foundational" and "pioneering" is a telling sign that Chee-138 does not support claims to spatially barcoded arrays for nucleic acid analysis.

The written description requirement exists precisely "to prevent an applicant from later asserting that he invented that which he did not, [which] is particularly important when, as here, claims are added later during prosecution in response to development by others." *Quake v. Lo*, 928 F.3d 1365, 1373 (Fed. Cir. 2019) (internal quotation omitted). In this case, the lack of support for the claims in Chee-138's priority documents means that it is not entitled to a priority date before Frisen (EX1045). Accordingly, Chee-138 is anticipated by Frisen (EX1045).

To be sure, before Chee-138's earliest priority date, there was nothing new about either its claims or the later-filed yet still somehow "pioneering" and "foundational" ST array designs it purports to cover. By 2009, noted geneticist Charles Cantor had already published nucleic acid bead arrays in which each bead comprises (i) a probe sequence that binds a target nucleic acid in a tissue sample and (ii) an identification sequence (ID) (or "barcode") that is unique for each bead. Because each bead necessarily occupies a different spatial location on a given array, each barcode necessarily corresponds to a particular location in the array. As illustrated below, Cantor's 2009 array consists of the exact same

[solid support (e.g., bead)]—[barcode]—[probe] structure as the subsequently-disclosed ST embodiment—which is claimed but not disclosed in Chee-138. EX1103, ¶116.



As explained further below, and in the accompanying declaration of Joseph Puglisi, Ph.D., the Board should institute IPR and cancel the challenged claims.

II. GROUNDS FOR STANDING

Petitioner certifies that the '138 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging its claims on the grounds identified in this petition.

III. MANDATORY NOTICES

A. Real Party-In-Interest

Petitioner Curio Bioscience, Inc. is the real party-in-interest with respect to this petition for *inter partes* review.

B. Related Matters

On December 1, 2023, Prognosys and 10x Genomics filed a lawsuit against Petitioner in the District of Delaware. *10x Genomics, Inc. and Prognosys Biosciences Inc. v. Curio Bioscience, Inc.*, No. 23-cv-01375-MN (D. Del.) alleging infringement of US Patent Nos. 10,480,022; 10,662,468; 11,001,879; 11,549,138; and 11,761,030.

On September 11, 2024, Petitioner filed *inter partes* review petition IPR2024-01289 challenging claims 1-7, 11-15, 17, 19, and 27-29 of US Patent No. 10,480,022.

On November 15, 2024, Petitioner filed *inter partes* review petition IPR2025-00193 challenging claims 1, 3, 6, 10-11, 16, 18, 21, 24-26, and 30 of U.S. Patent No. 11,761,030.

Chee-138 issued from application No. 17/825,718 filed on May 26, 2022, which is a continuation of application No. 17/030,230, filed on September 23, 2020, now Pat. No. 11,384,386, which is a continuation of application No. 16/988,284, filed on August 7, 2020, now Pat. No. 10,961,566, which is a continuation of application No. 16/414,213, filed on May 16, 2019, now Pat. No. 10,787,701, which is a continuation of application No. 16/402,098, filed on May 2, 2019, now Pat. No. 10,472,669, which is a continuation of application No. 16/276,235, filed on February 14, 2019, now Pat. No. 10,480,022, which is a continuation of application No.

15/187,661, filed on June 20, 2016, now Pat. No. 10,308,982, which is a continuation of application No. 13/080,616, filed on April 5, 2011, now Pat. No. 9,371,598. Chee-138 also claims priority to provisional application No. 61/321,124 filed on April 5, 2010.

C. Lead and Back-up Counsel and Service Information

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D. Additional Service Information

Please address all correspondence to the lead and back-up counsel as shown above. Petitioner consents to electronic service at: CurioIPRs@irell.com.

IV. GROUNDS FOR THE CHALLENGES

Petitioner challenges the claims of Chee-138 on grounds tabulated below. Grounds 1 and 2 are based on references that are prior art even if Chee-138 is entitled to the filing dates of its priority applications.

Ground	Challenged Claims	Basis
1	1, 5, 17, 20, 23, 28, and 29	Obviousness (pre-AIA §103) over Cantor in view of the knowledge of a POSA
2	1, 5, 17, 20, 23, 28, and 29	Obviousness (pre-AIA §103) over Cantor in view of Armani and the knowledge of a POSA
3	1, 5, 17, 20, 23, 28, and 29	Anticipation (AIA §102) by Frisen

V. THE '138 PATENT

According to its face, Chee-138 issued from Application No. 17/825,719, which was filed on May 26, 2022. EX1004, Code (22). The '138 Patent claims priority to “Provisional application No. 61/321,124, filed on Apr. 5, 2010.” *Id.*, Code (60).

The **ABSTRACT** of the '138 Patent states that “[t]he present invention provides assays and assay systems for use in spatially encoded biological assays,” and that the assay system of the invention is “capable of high levels of multiplexing where reagents are provided to a biological sample in defined spatial patterns; instrumentation capable of controlled delivery of reagents according to the spatial patterns; and a decoding scheme providing a readout that is digital in nature.” *Id.*, Abstract.

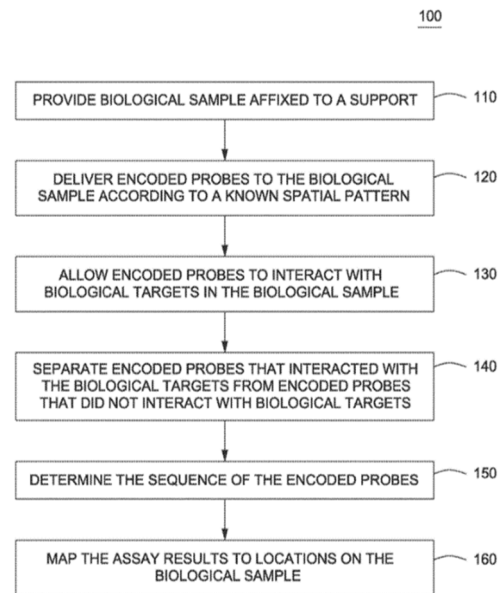


FIG. 1

To the extent any inventive subject matter is disclosed in Chee-138, it is the fluid delivery systems for spatial patterning of reagents that the specification repeatedly emphasizes as “the invention.” For example, in the section headed “The Invention in General,” the inventor wrote: “The assay systems of *the invention* provide spatially encoded, multiplexed assays comprising 1) an assay capable of high levels of multiplexing with an efficient spatial encoding scheme; 2) *instrumentation capable of delivering reagents according to a spatial pattern*; and 3) decoding determined by a readout that is digital in nature.” EX1004, 8:49-56. It continues: “The assay system further provides instrumentation *with an ability to deliver reagents in a spatially-defined pattern. This instrumentation*, together

[]with software, reagents, and protocols, *provides a key component of the highly innovative assay system of the invention.*” *Id.*, 8:63-67.

When Chee-138 discusses nucleic acid binding arrays, its disclosures are unrelated to the subject matter that it now seeks to claim. Instead, it discusses them as conventional genotyping techniques; not as tools for performing “the invention.” *See id.*, 24:57-64 (“Genotyping may be performed using any technique known to those skilled in the art.... Some examples of suitable techniques involve...nucleic acid arrays, bead arrays....”). Moreover, when nucleic acid arrays are discussed in the (exclusively prophetic) examples, they are not used as examples of “the invention”; rather, “[a] microarray is used as *a proxy for a tissue section.*” *Id.*, 30:46. The examples do **not** describe any array or probe structure as inventive, consistent with Chee-138’s repeated characterization of “the invention” as methods for delivering reagents onto a substrate-affixed biological sample (as illustrated in Figure B, above).

VI. CITED PRIOR ART

A. Cantor

Cantor, WO 2009/091934, is a WIPO application that was published on July 23, 2009. EX1031; EX1103, ¶¶107-109.

B. Armani

Armani et al., “2D-PCR: a method of mapping DNA in tissue sections,” is an article that was published in *Lab on a Chip* on October 12, 2009. EX1022; EX1103, ¶110.

C. Frisen

Frisen et al., WO 2014/060483 A1 is a WIPO application that was published on April 24, 2014. EX1045, Field (43); EX1103, ¶¶111-116.

VII. LEVEL OF ORDINARY SKILL IN THE ART

As Dr. Puglisi explains, a POSA in the field of Chee-138 in February 2010:

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.

EX1103, ¶¶30-34. As of the February 2019 priority date applied in Ground 3, “a POSA would have at least the foregoing level of skill and education, plus the

additional knowledge acquired and documented in the literature in the intervening years.” *Id.*, 34.

VIII. BACKGROUND KNOWLEDGE OF A POSA

A. Molecular Biology

The specification of the '138 Patent refers to the analysis and detection of “biological molecules,” and in particular nucleic acids. The '138 Patent’s “**BACKGROUND OF THE INVENTION**” admits that prior art “gene expression and protein analysis have been useful tools in understanding mechanisms of biology,” and that “[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.” EX1004, 1:41-50. The concept of “gene expression” refers to the process by which a gene encoded by DNA gets turned on in a cell to make RNA and proteins. EX1103, ¶¶36-43.

B. Cells and Tissues

Tissues are groups of cells that function together as a unit. Important to many aspects of biological research, tissues can be in a normal, healthy state, or in a disease state, and a POSA would have been familiar with many techniques for isolating and preparing tissue samples for further investigation. EX1103, ¶¶45-51.

C. Spatial Analysis

Chee-138 admits that “conventional methods” were used in the prior art to “reveal[] spatial patterns of gene expression and have helped shed light on the molecular basis of development and disease.” EX1004, 1:46-50.

As Dr. Puglisi explains, by April 2010 biologists found important information not only in the identity and quantitation of the genes expressed in a biological system, but also in the location at which particular genes are expressed (or not expressed). Accordingly, scientists had long been devising ways to analyze the spatial relationships of biological molecules, developing numerous tools and techniques to answer questions such as “whether there is...a spatial relationship between the position of genes and the location of their products in cell space.” EX1027, 552; EX1103, ¶¶52-57.

1. Detection of Nucleic Acids

Many nucleic acid technologies historically used fluorescence and other labelling and imaging techniques to detect the presence or absence of a target nucleic acid sequence. For example, nucleic acids are readily labeled with fluorescent dyes to form labelled probes, and when such probes are hybridized with a target, will cause the target-probe complex to be fluorescent upon exposure to an appropriate light source, allowing detection with simple imaging or spectroscopy methods. EX1103, ¶¶59-60.

Sequencing generally refers to techniques used to determine the order of nucleotide bases present in the DNA or RNA of a biological sample. Such techniques include high-throughput “Next Generation Sequencing” (NGS) as well as traditional Sanger sequencing. Some applications of these techniques included the use of “custom-designed oligonucleotide microarrays...for targeting regions of interest.” EX1029, 41. Such techniques may be applied in conjunction with NGS to sequence nucleic acids of interest captured using microarrays. *Id.*, 41; EX1103, ¶¶61-62.

2. Nucleic Acid Arrays

Nucleic acid arrays are a class of technologies in which DNA or other nucleic acid sequences are provided on a solid support. Because “[i]t is well known that complementary single-stranded sequences of nucleic acids form double stranded hybrids,” nucleic acid arrays leverage this property by presenting “thousands of single-stranded sequences that are complementary to target sequences,” and hybridization is then detected by fluorescence or sequencing. EX1018, 528. EX1103, ¶¶63-64.

Around the priority date, there were two main classes of solid supports on which the hybridization probes, sometimes called capture probes, were typically affixed: glass slides, similar to microscope slides, and beads. EX1018, 528. In bead arrays, the beads would then be deposited on a support, and the position of each bead

and the sequence it carried would be determined by a process called “decoding.” *Id.* EX1103, ¶65.

Well before 2010, a POSA would have been familiar with a variety of techniques for “decoding” bead arrays to determine the identity and location of each bead in an array. For example, in a 2007 publication, the Dr. Chee explained that “after the array is made, a correlation of the location of an individual site in the array with the bead or bioactive agent at that particular site can be made.” EX1038, [0013]. Known processes for such decoding included “positional decoding” methods in which the beads carrying known probes were selectively placed at particular locations. *Id.*, [0043]. Other known techniques involved analyzing “identification sequences” affixed to the beads. *Id.*, [0042]. This facilitated the use of “decoding by sequencing” methods to map the location of particular beads in the array, and which “allow[] decoding to be accomplished independent of the” capture agent on the molecule. *Id.*, [0141]. EX1103, ¶¶66-71.

3. Sequence Barcoding

Multiplexing, which allows higher throughput analysis of many samples in parallel, was a key development for nucleic acid sequence analysis before the priority date. As such, a POSA would have been familiar with the concept of barcoding, including using nucleic acid sequences as barcodes to identify and differentiate between different nucleic acid molecules or sets of molecules. *See, e.g.,*

EX1037, 3:55-64. Consistent with this knowledge, it is notable that in a prior proceeding involving EX1037, 10x asserted that the concept of nucleic acid barcoding “is as old as the scientific method and is familiar to every student in any introductory science class.” EX1035, 4-5. As such, 10x asserted that the use of barcodes or tags in “the particular technological environment of DNA (and other nucleic acids) by adding ‘attaching,’ ‘amplifying,’ and ‘detecting steps and other similarly generic techniques were *well-known and conventional before 2009.*” *Id.* EX1103, ¶¶72-73.

Examples of nucleic acid barcoding approaches specifically for correlating particular spatial locations in arrays (such as X,Y coordinates) with particular nucleic acid sequences (barcodes) were disclosed in numerous references before the priority date. For example, Barany describes a barcoding scheme for microarrays, which is used to direct target nucleic acids “to specific zip-code addresses attached covalently to a three-dimensional gel-matrix array.” EX1036, 251. For example, by using tetramer (4 nucleotide) bar codes, an array may be designed that uniquely barcodes up to 256 (4^4) separate locations according to, for example, a grid pattern. EX1103, ¶¶74-75.

	2nd two bases																			
1st two bases	TT	TC	TG	TA	CT	CC	CG	CA	GT	GC	GG	GA	AT	AC	AG	AA				
TT												TTGA 6			TTAG 8					
TC			TCTG 1		30'	TCCC 3			TCGT 5										6'	
TG		TGTC 2		36'			TGCG 4							TGAT 7		11'				
TA					18'		TACA 36			33'										
CT	32'		CTTG 9					CTCA 11	CTGT 13										8'	
CC				CCTA 33					29'					CCAT 15						
CG		CGTT 10		12'				4'							28'				CGAA 16	
CA		34'			25'		CACG 12			CAGC 14		1'				9'				
GT					GTCT 19	24'				GTGC 22			31'							
GC	GCTT 17		14'												22'			GCAA 23		
GG		20'		GGTA 18	35'							3'		GGAC 24						
GA			GATG 34			GACC 20		2'	GAGT 21											
AT						ATCG 28	7'			15'				ATAC 31						
AC		21'			ACCT 27					ACGG 29	5'					13'				
AG			AGTG 25			AGCC 35			27'			AGGA 30			19'					
AA		AATC 26					10'			17'						AAAG 32				

Figure 2. Design of tetramers for use in zip-code arrays. The checkerboard pattern shows all 256 possible tetramers. A given square represents the two bases on the left followed by the two bases on the top of the checkerboard. To be included, each tetramer must differ from all others by at least two bases, and be non-complementary. The chosen tetramers are shown in the white boxes, while their complements are listed as (number)'. Thus, as an example, the complementary sequences GACC (20) and GGTC (20') are mutually exclusive in this scheme. In addition, tetramers that are palindromic, e.g. TCGA (off-diagonal hatched boxes) or repetitive, e.g. CACA (hatched boxes on diagonal from upper left to lower right) have been eliminated. All other sequences which differ from the 36 tetramers by only one base are shaded in light gray. Four potential tetramers were not chosen as they are either all A·T or G·C bases (open boxes).

Similarly, Chee-824 discloses barcoded bead arrays in which “a spatial or positional coding system is done.” EX1032, 28:6-7; *see also* EX1038, [00146] (“In this way, beads are tagged with fluorescent labels, i.e., barcodes of sorts, their location or identity deciphered and recorded.”). EX1103, ¶¶76-78.

D. Overview of Spatial Analysis Technologies

By 2009, a POSA would have been familiar with 2D-PCR techniques in which “[a] 2d map of [a gene] was created from a tissue section and shown to correlate

with the spatial area of the sample.” EX1022 (Armani), 3526 (Abstract). These techniques were anticipated to “be easily adapted to assess the status of multiple genes within tissue sections, yielding a molecular map that directly correlates with the histology of the sample,” thus “provid[ing] investigators with a new tool to interrogate the molecular heterogeneity of tissue specimens.” *Id.* For example, Armani observed 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.*, 3526. Thus, Armani noted a desire and motivation in the art to study nucleic acids in a manner that maintained their spatial organization. EX1103, ¶¶79-84.

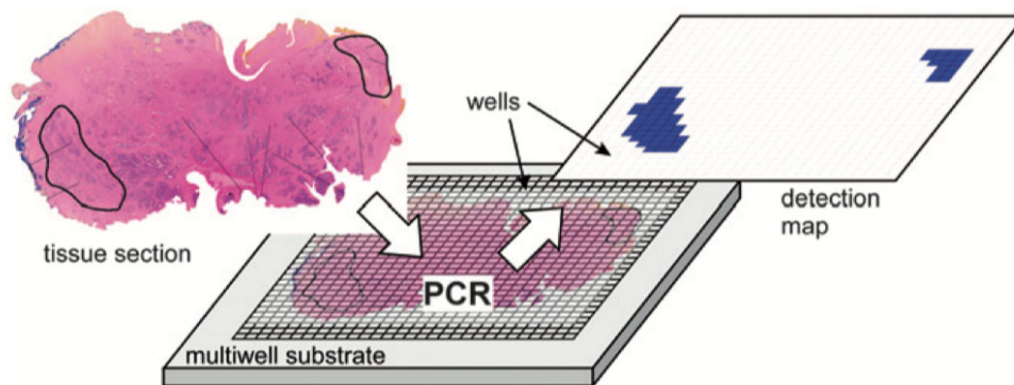


Fig. 1 2D-PCR is achieved by transferring a tissue section vertically into a multi-well array device, isolating tissue subregions. The DNA is extracted and then amplified by the polymerase chain reaction. A detection map is created by imaging the amplified DNA, for example using a DNA-intercalating dye.

Another related set of technologies involved the spatial analysis of gene expression using arrays of capture agents, including poly-T capture agents and gene-specific capture agents, to immobilize mRNA in two-dimensional space and detect its presence using fluorescent or other labeled probes, including after reverse-transcription processes. EX1103, ¶¶86-91.

Shirai discloses an example of such techniques. For example, Shirai explains that it “provides a method and/or means for collecting and analyzing an individual cell in a tissue, and at the same time, quantitatively monitoring the expression levels of various genes *while keeping two-dimensional information in the tissue.*” EX1024, Abstract. In Example 4, Shirai describes providing a plurality of beads: “beads smaller than cells are arranged on a surface.” EX1024, 27:5-6. These beads comprise a plurality of binding agents: “[o]n the beads surface, poly-T probes are immobilized.” *Id.*, 27:6-7. The poly-T probes immobilized on the beads’ surface are configured to interact with at least one mRNA present in a tissue sample: “On the resultant structure,” that is, an array of poly-T coated beads, “a tissue slice is mounted” and the cells are permeabilized or lysed to release their mRNA, which is then reverse transcribed into complementary cDNA molecules. *Id.*, 27:5-19. EX1103, ¶¶92-95. Shirai then discloses detecting gene expression using fluorescent probes to generate a spatial map. EX1024, 10:46-55; EX1025; EX1103, ¶¶96-102.

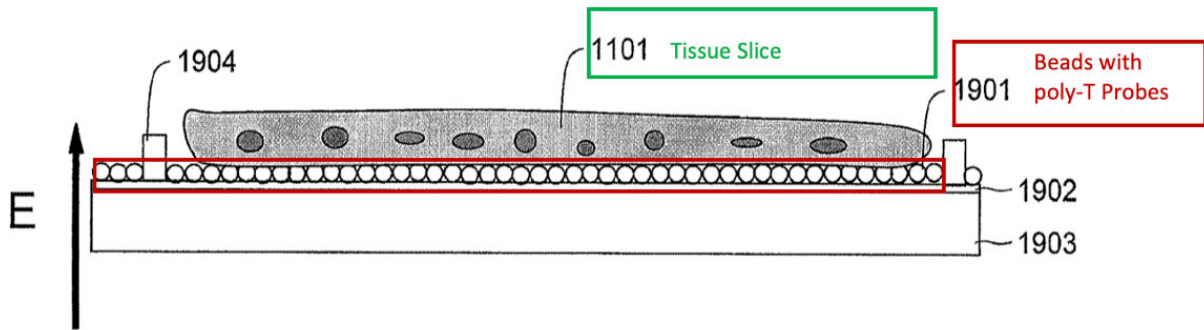


FIG. 19

Similarly, Southern discloses the detection of target nucleic acids on arrays so that “[t]he spatial arrangement of the samples is maintained” and the location of “results of the analysis [may] be matched to individual samples.” EX1033, Abstract. “One analytical procedure that can be used with” Southern’s arrays “involves capture of mRNA by hybridisation to an immobilised capture DNA, followed by reverse transcription of the mRNA using the immobilised DNA as a primer.” *Id.*, 9:17-25. In this procedure, Southern discloses creating a complementary cDNA by extending the probe, using the captured mRNA as a template for *in situ* reverse transcription. Southern discloses using optical means, such as fluorescence, as the method for detecting the spatial location of an interaction between its binding agent and a target nucleic acid. EX1030, 27:12-28. In addition to detection by fluorescence, Southern continues by noting that “single molecule sequencing” is also a suitable readout. *Id.*, 39:25-28. EX1103, ¶¶103-104.

Approaching the priority date, a POSA would have found using sequencing-based techniques as a readout for nucleic acid assays as an alternative for fluorescence-based detection methods to have been an obvious and natural substitution. First, sequencing methods provide a direct readout of the nucleic acid identity, without the use of probe hybridization, imaging, or microscopy to indirectly confirm the identity of a target sequence. Second, using the analogy presented by 10x in prior litigation, labelling target nucleic acids with fluorescence would have been akin to a “form of labeling such as placing one in a green cup and one in a blue cup,” whereas nucleic acid barcodes simply apply the concept of “serial numbers” to nucleic acids. EX1035, 4-5. Such approaches are illustrated in Cantor and Frisen, as discussed in the Grounds below. EX1103, ¶¶105-106.

IX. CLAIM CONSTRUCTION

The Petition applies the understanding of the claim terms applied by PO to assert infringement against Curio. PO has asserted that no claim terms require construction. EX1041-1042.

In the District Court litigation, the parties dispute whether a poly-T sequence on a capture probe constitutes a “target-binding domain.” PO contends that this limitation is satisfied in Curio’s accused products by the interaction of poly-T probes and the poly-A tails present on typical mRNA molecules. Curio disputes that such interactions constitute the “target-binding” required by the claims. However, the

Board need not address this dispute because the prior art identified in each ground discloses gene-specific probes, in addition to probes that satisfy the broader implicit interpretation advanced by PO.

X. THE BOARD SHOULD CANCEL THE CHALLENGED CLAIMS

A. Ground 1: Obvious over Cantor in view of the Knowledge of a POSA

1. Claim 1

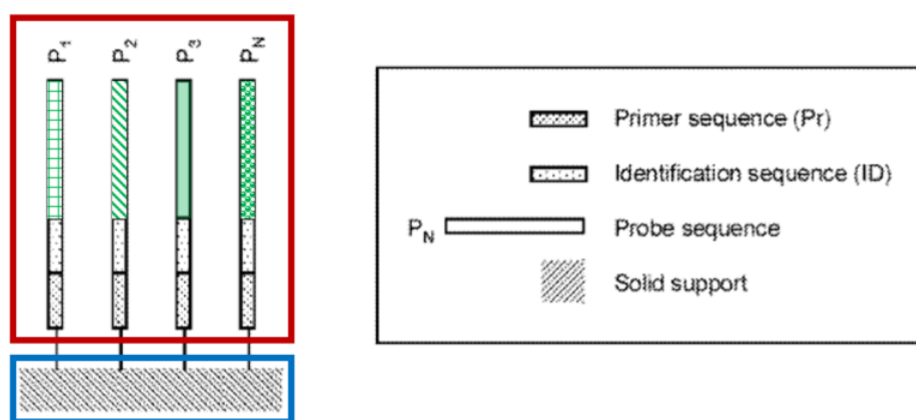
As described below, Cantor discloses each limitation of Claim 1.

(a) “A composition comprising...”

Cantor discloses “[a] composition comprising an array comprising a substrate and a plurality of capture probes.” Thus, to extent the preamble is limiting, it is disclosed by Cantor.

Cantor discloses arrays comprising a substrate with a plurality of beads that each include a capture probe. In detail, Cantor discloses “[i]mproved solid supports and methods for analyzing target nucleotide sequences....” EX1031, 1. A specific example of Cantor’s disclosure “provides *a substrate* comprising *a collection of beads* oriented in *an array*.” *Id.*, 4. Each bead “is in association with single-stranded nucleic acid.” *Id.* The bead-associated nucleic acids, which constitute the claimed capture probes, include “a probe sequence,” which “hybridizes to” (*i.e.*, captures) “a sample nucleic acid when the probe sequence is complementary to a nucleotide sequence in the sample nucleic acid.” *Id.*; EX1103, ¶303.

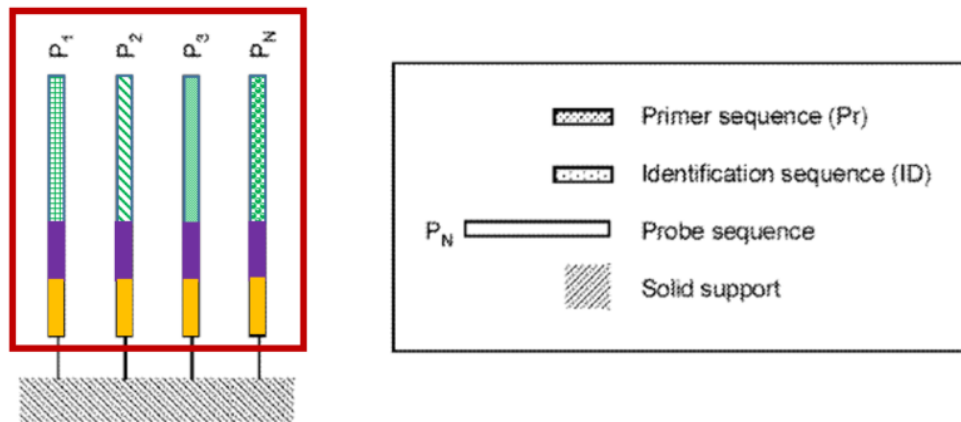
Figure 1 (annotated below) depicts examples of the claimed “**capture probes**.” Each of the capture probes include a probe sequence, which is a **target nucleic acid binding domain** that is configured to interact with a target nucleic acid. Figure 1 also shows a **solid support**, which in the specific example above is a bead attached to a substrate. EX1031, 4; EX1103, ¶304.



- (b) each of the plurality of capture probes comprises: (i) a target-binding domain, (ii) 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, and (iii) a primer binding site; the target-binding domain of each of the plurality of capture probes comprises a nucleic acid sequence that is complementary to at least a portion of the nucleic acid that binds to the target-binding domain”

The claims require the capture probes to have (i) a target-binding domain, (ii) a nucleic acid sequence that identifies a unique location on the substrate, and (iii) a primer binding site.

Cantor discloses this configuration. As explained in greater detail below, in Figure 1 (annotated below), each single-stranded nucleic acid (i.e., **capture probe**) in Cantor's arrays comprises (1) **a primer binding site**, (2) **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 (3) **a target nucleic acid binding domain**, wherein the target-binding domain of each of the plurality of capture probes comprises a nucleic acid sequence that is complementary to at least a portion of the nucleic acid that binds to the target-binding domain. EX1103, ¶306.

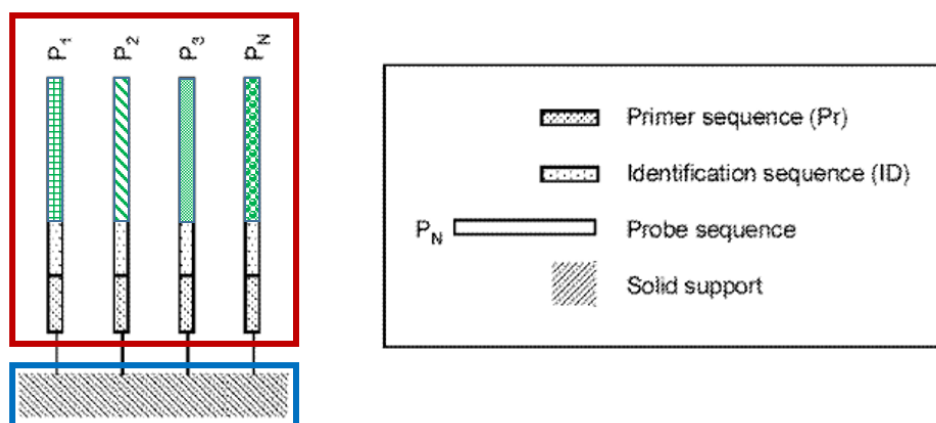


- (i) “each of the capture probes...comprises:... (i) a target-binding domain,... the target-binding domain of each of the plurality of capture probes comprises a nucleic acid sequence that is complementary to at least a portion of the nucleic acid that binds to the target-binding domain”

Cantor discloses that each of the capture probes has a target-binding domain comprising a nucleic acid sequence that is complementary to at least a portion of the nucleic acid that binds to the target-binding domain.

Cantor is directed to “[i]mproved solid supports and methods for analyzing target nucleotide sequences.... Certain improvements are directed to 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.” EX1031, 1. In particular, Cantor discloses that the capture probes (*i.e.*, single-stranded nucleic acids) contain a sequence that is “complementary to or substantially complementary to a sample nucleic acid nucleotide subsequence and allows [the] solid phase nucleic acid to hybridize to [the] sample nucleic acid. Such a subsequence (e.g., illustrated in Figures 1A-1C) is referred to herein as a ‘probe’ sequence.” *Id.*, 13. EX1103, ¶307.

This “**probe sequence**” (*i.e.*, **target-binding domain**) is shown below in Figure 1A. This sequence is the third sequence of the **capture probe** from the **solid support** surface, as depicted below. EX1103, ¶308.

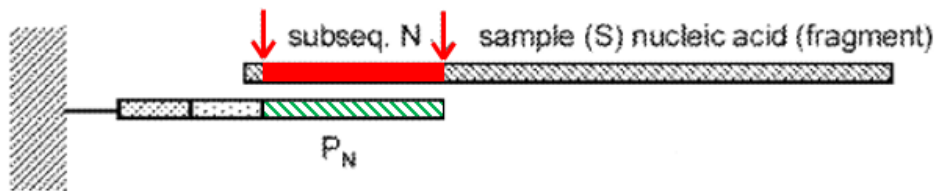


Cantor discloses that the target-binding domain is “a nucleic acid sequence that is complementary to at least a portion of the nucleic acid that binds to the target-binding domain.”

For example, Cantor’s “probe sequences” bind to target nucleic acids (including those from a sample such as a tissue section) because they are “complementary to subsequences in the sample nucleic acid (e.g., probe sequence species P₁, P₂, P₃,...P_n are complementary to sample nucleic acid subsequences 1, 2, 3,...N, respectively).” EX1031, 16. Cantor explains: “*A probe nucleotide sequence is of a length sufficient to specifically hybridize to a sample nucleic acid nucleotide sequence.*” *Id.*, 14. EX1103, ¶309.

This is further confirmed in Figure 2, which depicts the target-binding domain hybridized to the target nucleic acid. Cantor explains that in Figure 2 “[s]ample nucleic acid molecule (S) may include a **nucleotide sequence (i.e., subseq.N)** that hybridizes to a **complementary probe sequence (P_N)** of the solid phase nucleic

acid.” EX1031, 24. Cantor does not describe any other part of the single-stranded nucleic acid hybridizing (*i.e.*, binding) to the target nucleic acid. EX1103, ¶309.

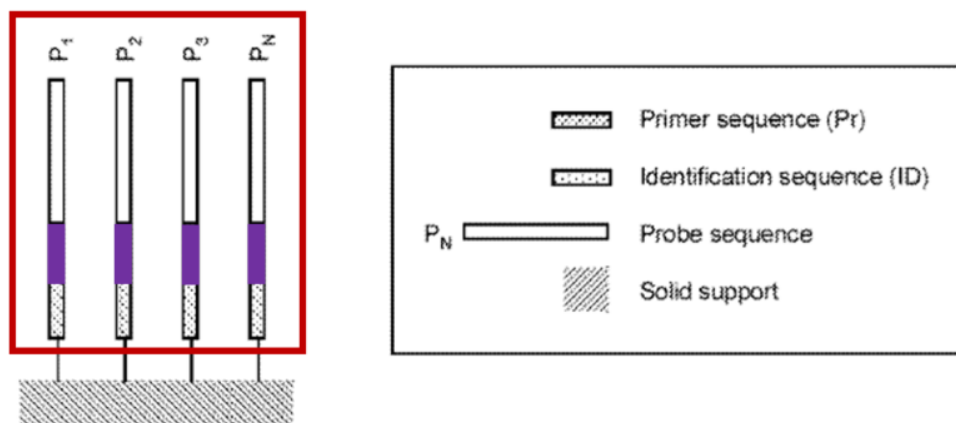


- (ii) “each of the capture probes of the plurality of capture probes comprises:... (ii) a nucleic acid sequence that identifies a unique location on the substrate and is not configured to hybridize to a nucleic acid that binds to the target-binding domain”

Each of the capture probes in Cantor’s arrays (e.g., the single-stranded nucleic acids depicted in Fig. 1) also includes 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-binding domain.

Cantor discloses that in its arrays, “each of the solid supports in the collection share a unique identifier sequence different than the identifier sequence of [the] solid phase nucleic acid of the other solid supports.” EX1031, 2. In other words, each solid support (e.g., bead) is coded with a unique nucleic acid “identifier sequence” that differs from the “identifier sequence” coding of every other bead. This **identifier sequence** is depicted on the **capture probes** shown in Figure 1 below. Since Figure 1 depicts a single solid support, and each capture probe on a given solid support

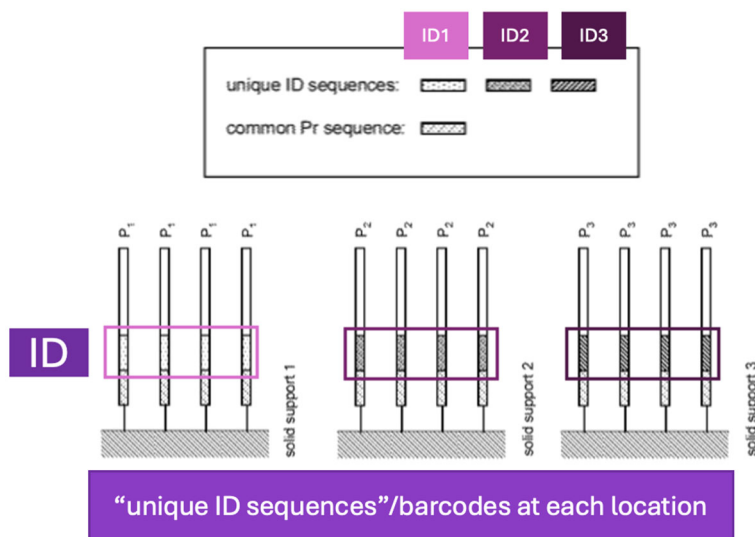
shares a common identifier sequence, each identifier sequence is the same. EX1103, ¶310.



Cantor also explains that the disclosed “[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,” such as beads, “in one dimension and Y number of sample locations or solid supports,” such as beads, “in a perpendicular dimension.” EX1031, 17. EX1103, ¶311.

Thus, a POSA would understand that Cantor discloses a bead array in 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. Indeed, this is shown in Cantor’s Figure 1C, which depicts separate solid supports, such as beads, each having “unique ID sequences” that are correlated to the specific solid supports

“solid support [e.g., bead] 1,” “solid support [e.g., bead] 2,” and “solid support [e.g., bead] 3.” EX1103, ¶¶312-313.

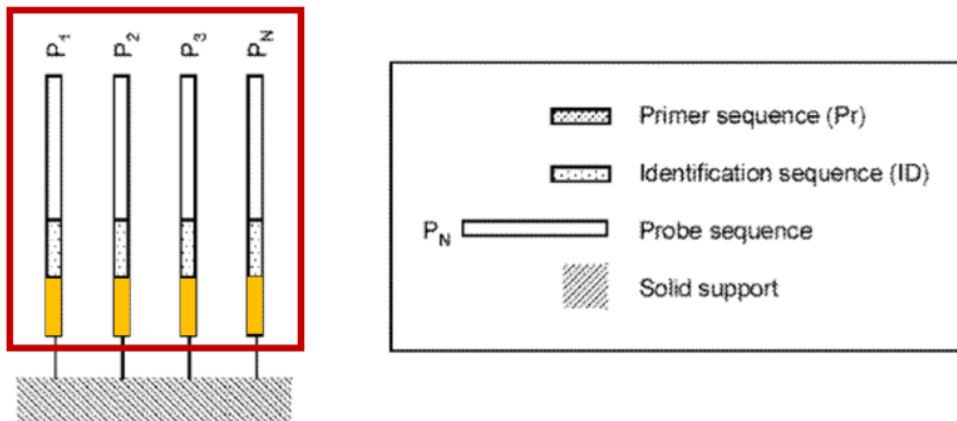


Thus, a POSA would understand that the “identification sequence” described in Cantor is a “nucleic acid sequence that identifies a unique location on the substrate.” For example, in the figure annotated above, a POSA would understand that ID1 identifies the unique location “solid support [e.g., bead] 1,” ID2 identifies the unique location “solid support [e.g., bead] 2,” and ID3 identifies the unique location “solid support [e.g., bead] 3.” EX1103, ¶314.

Cantor also discloses that the “nucleic acid sequence that identifies a unique location on the substrate” “is not configured to hybridize to a nucleic acid that binds to the target-binding domain.” Rather as previously shown in Figure 2, the target-binding domain is configured to bind to the target nucleic acid. See Section X.A.1(b)(i) above. EX1103, ¶315.

(iii) “each of the capture probes of the plurality of capture probes comprises:... (iii) a primer binding site”

Cantor discloses that the single-stranded nucleic acid can “include[] a primer sequence (Pr), which is also referred to [in Cantor] as a ‘primer *hybridization* sequence.’” EX1031, 15. This is because “[p]rimer sequence (Pr) *can hybridize [i.e., bind] to a complementary nucleotide sequence in a primer nucleic acid.*” *Id.* Exemplary **primer sequences** (*i.e.*, **primer binding sites**) on **capture probes** are shown in Figure 1 below. EX1103, ¶316.



(c) “each of the plurality of capture probes are immobilized on the substrate in a random pattern”

Cantor in view of the knowledge of a POSA renders this limitation obvious. Cantor describes associating its beads with a substrate to form an array. As just one example, Cantor explains that “the invention in part provides a substrate comprising a collection of beads oriented in an array.” EX1031, 4. “*The array can be arranged on any substrate* suitable for sequence analysis or manufacture processes described

herein.” EX1031, 17-18. Cantor discloses the claimed “immobilizing” by disclosing orienting the beads on, and in contact with, the substrate. In certain embodiments, Cantor’s substrate may have “wells or pits” which “may contain one or more” beads. EX1103, ¶¶317-318.

An exemplary embodiment is described in Cantor’s published claim 48:

48. A substrate comprising a collection of beads oriented in an array, wherein:
each bead is in association with single-stranded nucleic acid;
the solid phase nucleic acid comprises an identifier sequence and a probe sequence;
the probe sequence hybridizes to sample nucleic acid when the probe sequence is complementary to a nucleotide sequence in the sample nucleic acid;
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; and
the solid phase nucleic acid of each of the solid supports in the collection share a unique identifier sequence different than the identifier sequence of solid phase nucleic acid of the other solid supports.

In addition to the physical immobilization methods disclosed above, a POSA would also immediately understand, including from references incorporated by reference by Cantor, that Cantor discloses chemically immobilizing its beads to the substrate through various methods known in the art. *See, e.g.*, EX1048, 2:56-57 (incorporated by reference into Cantor) (“FIG. 1 is a schematic showing the covalent attachment of a bead to a solid support and DNA to the bead.”); EX1031, 12 (discussing methods known in the art for binding beads to a solid support). EX1103, ¶¶319-320.

It also would have been immediately apparent that when attaching the probes to the substrate, there were only a limited number of ways to “arrange” (i.e.,

“position”) the capture probes on the substrate: (i) selective loading of capture probes to particular locations on the array and/or (ii) randomly loading the capture probes and then decoding the array prior to use. EX1103, ¶¶321, ¶¶66-71.

Cantor discloses that its “identifier sequence is about 5[-]50 nucleotides in length.” EX1031, 15. In a selective loading procedure, a POSA would have found it obvious to provide beads having, for example, 5-nucleotide identifier sequences that correspond to particular locations in Cantor’s (X, Y) array. 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 work of the named inventor and others. *See* EX1032 (Chee-584), 7:30-33 (beads are spatially arranged in “a regular pattern of sites such that the sites may be addressed in the X-Y coordinate plane.”); EX1038 (Chee-824), [0044] (“Once the identity of the bioactive agent and its location in the array has been fixed, the array is exposed to samples containing target analytes.”); EX1036, 251 (Barany 1999) (describing 4 nucleotide “zip-code” sequences to define spatial locations on an array in a “checkerboard” (X, Y) array pattern). EX1103, ¶¶322.

As an example, the below illustration shows a 16 bead array with unique 5-nucleotide identifier sequences at each (X,Y) location. X coordinates are numbered 1-4, and Y coordinates are lettered A-D. EX1103, ¶¶323.

	1	2	3	4
A	AGTGA	TGTGC	TCAAA	AGCTA
B	GTACG	TATCC	GCTTG	CTCGA
C	CCTTC	TTCGT	CTACC	TGGGC
D	TGAAT	CCTTA	CATTG	GATTA

In a selective loading technique, to correlate position A1 with the identification sequence AGTGA, a POSA would have found it obvious to deposit a bead that was manufactured to include sequence AGTGA at the A1 coordinate in the array according to methods known in the art. *See* EX1038, [0043] (describing “positional decoding” by “targeting the placement of the beads” to predetermined locations on the array). A POSA would have found it obvious to target the placement of the other barcoded beads to the other locations according to similar methods. EX1103, ¶323.

While the example above only uses 16 total positions, the use of 5 nucleotide barcodes allows uniquely addressing 1,024 (4^5) positions on an array, and each additional nucleotide added to the barcode length would have been known to exponentially increase the number of unique barcodes and thus the number of beads that can be uniquely addressed and loaded on an array. EX1103, ¶¶75, 324. For example, the use of 10-nucleotide barcodes would allow for over 1 million ($>4^{10}$)

uniquely barcoded beads. Thus, a POSA would recognize that selectively loading the beads in a defined pattern becomes more difficult as more beads are added to the array. *Id.*, ¶325.

As an alternative, 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 site on the array with the bead or candidate agent at that particular site can be made.” EX1038, [0042]. A POSA would have been motivated to use such a random loading procedure to simplify and expedite the array generation and fabrication process. EX1103, ¶325.

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, ¶¶325-326.

Thus, a POSA would have found it obvious to fabricate Cantor's arrays by randomly distributing the plurality of beads/capture probes on the substrate in Cantor. EX1103, ¶327.

(d) Conclusion as to Claim 1

Cantor in view of the knowledge of a POSA renders Claim 1 obvious.

2. Claim 5

Cantor discloses and/or renders obvious "wherein the array is deposited on a slide or flow-cell."

In particular, Cantor states "[t]he array can be arranged on any substrate suitable for sequence analysis or manufacture processes described herein. Examples of substrates include without limitation flat substrates, filter substrates, wafer substrates, etched substrates, substrates having multiple wells or pits..., substrates having one or more channels, substrates having one or more electrodes, and the like, and combinations thereof." EX1048, 17-18. Cantor also discloses that these "[s]ubstrates can comprise or consist essentially of a suitable material for conducting sequence analysis or manufacture processes described herein, including without limitation, fiber (e.g., fiber filters), glass (e.g., glass surfaces, fiber optic surfaces), metal (e.g., steel, gold, silver, aluminum, silicon and copper; metal coating), plastic (e.g., polyethylene, polypropylene, polyamide, polyvinylidenedifluoride), silicon and the like." EX1031, 18; *see also id.*, 53 ("Synthesized oligonucleotides

containing probe, primer and identification sequences are linked to solid support (beads, *slides*, chips, and the like[]).”). Thus, a POSA would understand Cantor to disclose depositing the array on a slide. *See, e.g.*, EX1004, 30:49-50 (“Synthetic oligonucleotide templates are attached to a glass slide via a 5' amino modification.”). EX1103, ¶330.

Additionally, a POSA would consider the plain and ordinary meaning of “slide” to include all flat substrates, filter substrates, wafer substrates, etched substrates, substrates having multiple wells or pits, and substrates having one or more channels. Thus, Cantor discloses substrates that are either a “slide” or “flow cell,” and it would be obvious to a POSA to use any one of these substrates with Cantor’s disclosed array. EX1103, ¶331.

3. Claim 17

As described below, Cantor in view of the knowledge of a POSA renders obvious Claim 17.

(a) “A composition comprising (i) an array comprising a substrate and a plurality of capture probes, and (ii) a tissue section”

As described above in Section X.A.1(a), Cantor discloses “[a] composition comprising (i) an array comprising a substrate and a plurality of capture probes.” As described below, Cantor in view of the knowledge of a POSA renders obvious the combination of (i) an array and (ii) a tissue section.

In particular, Cantor explains that its capture probes interact with a “sample nucleic acid” by hybridization. EX1031, 2. (“[T]he solid support and sample nucleic acid are contacted in the mixture under conditions that allow hybridization of the solid phase nucleic acid,” i.e., the probe, “to the sample nucleic acid.”). Cantor explains that this sample may be “a solid material *such as a tissue...or a biopsy.*” *Id.*, 6. A POSA would have immediately appreciated that a biopsy is a type of tissue section. *See, e.g.*, EX1004, 12:9-11 (“Exemplary biological samples include *tissue sections (e.g., including* whole animal sectioning and *tissue biopsies)*, cell populations on slides or culture dishes, and the like.”). EX1103, ¶¶334-335.

(b) “the tissue section is disposed on the array”

Cantor in view of the knowledge of a POSA renders obvious “the tissue section is disposed on the array.” Cantor explains that its sample may be “a solid material such as a tissue...or a biopsy,” EX1031, 6, and the literature evidenced multiple reasons why a POSA would have been motivated to perform array-based nucleic acid analysis on a tissue sample (such as an intact tissue section or a biopsy sample), including because the analysis of such samples would provide information, such as spatial information, that could not be obtained through the analysis of, for example, a tissue homogenate:

Variations 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. However, to study the molecular basis of normal and pathological conditions, many researchers identify genes of interest from tissue specimens by examining cell homogenates (all the cells in the sample mixed together). Since tissue comprises a complex milieu of diverse cell populations that define the local microenvironments, combining the multiple cell populations into one measurement masks a tremendous amount of information. Therefore, to achieve a more complete view, DNA variability within a tissue sample needs to be correlated with the type of cell from which it originates (for example, stroma vs. epithelium), the physical location within the tissue section, and/or histopathological features (for example, a specific disease lesion).

EX1022 (Armani), 3526.

When handling cells, which constitute a large percentage of specimens, there are instances in which it is problematic to convert the cell component being measured to a solution state. Since balance of the whole is achieved through mutual interaction between a cell and adjacent cell groups in multi-cellular organisms, pulverizing cell groups will result in a uniform state, causing localized information for each cell to be lost. Further, even within individual cells, mRNA, which is an expressed gene, is localized. Proteins, which are the final product, are also localized within the cell in accordance with their function. These local mRNA and proteins change in accordance with a cell's state of activity, in other words the level of communication between a cell

and the adjacent cell group, and the environment in which the cell is placed. Therefore, if an attempt is made to obtain information useful for medically-directed drug discovery, and to describe biological functions more accurately, the mRNA and proteins localized between or inside cells must be quantitatively detected in a state in which local space information is retained.

EX1026 (Okano), [0008]. Thus, a POSA would have been motivated to contact Cantor's with a tissue section, yielding the claimed combination. EX1103, ¶336.

Furthermore, Cantor explains that its capture probes interact with the target nucleic acid by contacting the nucleic acids with the array to allow for hybridization between the capture probes and the nucleic acids. EX1031, 2 (“[T]he solid support and sample nucleic acid are contacted in the mixture under conditions that allow hybridization of the solid phase nucleic acid,” i.e., the probe, “to the sample nucleic acid.”). Thus, a POSA would have recognized that Cantor teaches that the tissue section would need to be contacted with (i.e., disposed on) the array. EX1103, ¶337.

Cantor further explains in its Example 1, “Sequence analysis methodology,” that “[s]ample nucleic acid may be prepared by any means commonly known in the art, including but not limited to cell lysis procedures using chemical, physical or electrolytic lysis methods.” EX1031, 53-54. A POSA would have been familiar with, and would have been motivated to apply such techniques to intact tissue or biopsy samples such that the tissue or biopsy sample disposed on the array is then treated

such that the capture probes can hybridize to the nucleic acids in the tissue sample.
EX1103, ¶338.

Indeed, these techniques were frequently applied in the art. For example, Southern similarly discloses the spatial analysis of nucleic acid molecules by contacting tissue-derived nucleic acid molecules with a binding agent affixed to a solid support. EX1033, 16:28-30;7:3-7. Southern discloses that, “[i]n some methods, *samples are applied directly to the support to generate a spatial arrangement of samples*, as illustrated in Fig. 1. Thus, *when the samples are biological samples comprising cells, the step a) of applying the samples to a support may comprise: (i) applying cells to the support; then (ii) releasing material from the cells.*” *Id.*, 2:17-27. A POSA would recognize that “releasing material from the cells” is synonymous with lysing the cells, as disclosed by Cantor. EX1103, ¶339.

A POSA would similarly have been familiar with methods for releasing and capturing locally target nucleic acid from cells in a tissue sample disposed on an array, including a bead array. *See* EX1021-1022 (Armani) (physical pressing and chemical lysis of tissue samples to release target nucleic acid); EX1024 (Shirai) (use of electrophoretic force to lyse cells in tissue sample to locally release target nucleic acid for capture on probes attached to beads); EX1025 (Yasuda) (same); EX1026 (Okano) (same). Thus, a POSA would have been further motivated to dispose the

tissue section of the array disclosed in Cantor and lyse the cells such that the probes can interact with the target nucleic acids within the tissue sample. EX1103, ¶339.

- (c) **“each of the plurality of capture probes comprises: (i) a target-binding domain (ii) a nucleic acid sequence that identifies a unique location on the substrate..., and (iii) a primer binding site....”**

Cantor discloses this limitation. Section X.A.1(b) above. EX1103, ¶340.

- (d) **“each of the plurality of capture probes are immobilized on the substrate in a random pattern”**

As described above in Section X.A.1(c), Cantor in view of the knowledge of a POSA renders obvious “each of the plurality of capture probes are immobilized on the substrate in a random pattern.” EX1103, ¶341.

4. Claim 20

Cantor in view of the knowledge of a POSA renders obvious “wherein the tissue section is a formalin-fixed paraffin-embedded tissue section or a fresh frozen tissue section.”

Cantor discloses that its target/sample nucleic acid may be “a solid material *such as a tissue...or a biopsy.*” EX1031, 6. Furthermore, Cantor explains in its Example 1, “Sequence analysis methodology,” that the “[s]ample nucleic acid may be prepared by any means commonly known in the art.” *Id.*, 53-54. As Dr. Puglisi explains, there were only a few methods of preparing a tissue sample known in the art prior to 2010, including formalin fixation followed by paraffin embedding and

freezing a fresh tissue section to create a fresh frozen tissue sample. EX1103, ¶¶50, 343. Given the limited number of options, it would have been obvious to a POSA to try depositing a fresh-frozen tissue sample on the array disclosed in Cantor, particularly in light of Cantor's disclosure to utilize a solid material such as a tissue or biopsy as a source of sample nucleic acid. EX1103, ¶343.

Moreover, a POSA would have been motivated to use a fresh-frozen tissue sample with the array disclosed in Cantor for multiple reasons. First, in 2010, fresh-freezing tissue samples was a common method for preserving tissue samples in a laboratory and clinical setting. Given the prominence of fresh-frozen tissue samples in the field, a POSA would have been motivated to try using a fresh frozen tissue sample with Cantor's array. Second, because fresh frozen tissue samples were known to have better RNA/nucleic acid quality than formalin-fixed paraffin embedded tissues, *see* EX1046, 1229; EX1047, 1933, a POSA would have been motivated to use fresh-frozen samples because their high quality, highly intact nucleic acid content made them highly suitable for use with arrays designed to detect RNA/nucleic acids, like Cantor's. EX1103, ¶¶50, 344.

5. Claim 23

Cantor discloses "wherein the array is deposited on a slide or flow-cell." See Section X.A.2 above. EX1103, ¶346.

6. Claims 28-29

Cantor discloses “wherein the target nucleic acid comprises DNA or RNA,” and specifically “wherein the RNA is mRNA.” For example, Cantor discloses that “[a] sample nucleic in certain embodiments can comprise or consist essentially of DNA...*RNA (e.g., message RNA (mRNA), short inhibitory RNA (siRNA), ribosomal RNA (rRNA), tRNA and the like), and/or DNA or RNA analogs.*” EX1031, 6; EX1103, ¶¶348, 350.

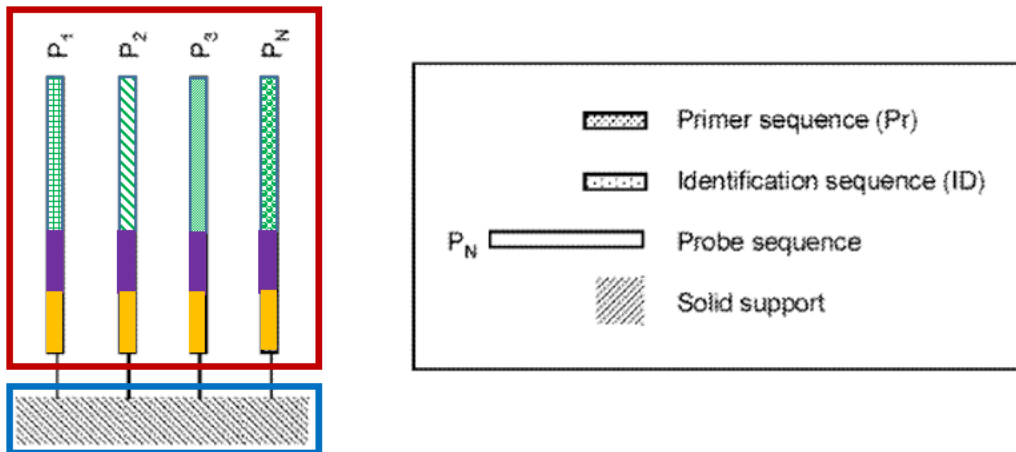
B. Ground 2: Obviousness over Cantor in view of Armani and Knowledge of a POSA.

The analysis from Ground 1 above, which outlines why the Challenged Claims are obvious over Cantor in view of the knowledge of a POSA, is herein incorporated by reference. Armani provides additional information rendering obvious disposing the tissue section on the array as recited by Claim 17, as well as additional information rendering obvious the tissue section being a fresh frozen tissue section as required by Claim 24. However, because Claim 17 recites the same features as Claim 1 with the additional requirement of “(ii) a tissue section, wherein: the tissue section is disposed on the array,” Claim 1 is obvious over Cantor in view of Armani and Knowledge of a POSA for the same reasons as Claim 17. Thus, all challenged claims are rendered obvious by this ground.

1. Claim 17

Cantor in view of Armani and the knowledge of a POSA further renders obvious the composition of claim 17 wherein “the tissue section is disposed on the array.”

Cantor describes a device for detecting nucleic acids using nucleic acid arrays that capture, extend, amplify, and detect target nucleic acids with sequencing. In other words, Cantor discloses providing a substrate with a plurality of **beads (i.e., solid supports)** with the claimed “**capture probes**” in the form of nucleic acid constructs that include a “**probe sequence**” that is configured to hybridize with a target nucleic acid, as well as a “**coding identifier**” or “**identification sequence**” that may be used to identify a unique location on the substrate. Cantor’s Figure 1A, annotated below, shows an example of its **solid support, such as a bead surface**, with a plurality of “**capture probes**,” each having the same “**primer sequence**” and “**identification sequence**” and different “**probe sequences**.” EX1103, ¶354.



Cantor further explains that its “array can be arranged on any substrate suitable for sequence analysis or manufacture processes described herein,” including “substrates having multiple wells or pits,” with varying volumes ranging from the microliter to picoliter scale. EX1031, 17-18. Cantor explains that “[w]ells or pits of multiple well and pit substrates may contain one or more solid support units (e.g., each unit being a single bead or particle.” *Id.*, 18. Thus, Cantor discloses providing a plurality of beads containing the claimed binding agents by arranging the beads in a multiple well plate. This arrangement of binding agents in wells would have motivated a POSA to combine the teachings of Cantor with the teachings of Armani, as discussed next. EX1103, ¶355.

Armani discloses methods for the analysis of nucleic acids in a tissue section. In Armani’s method, (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. This is depicted in Armani’s Figure 2. EX1103, ¶356.

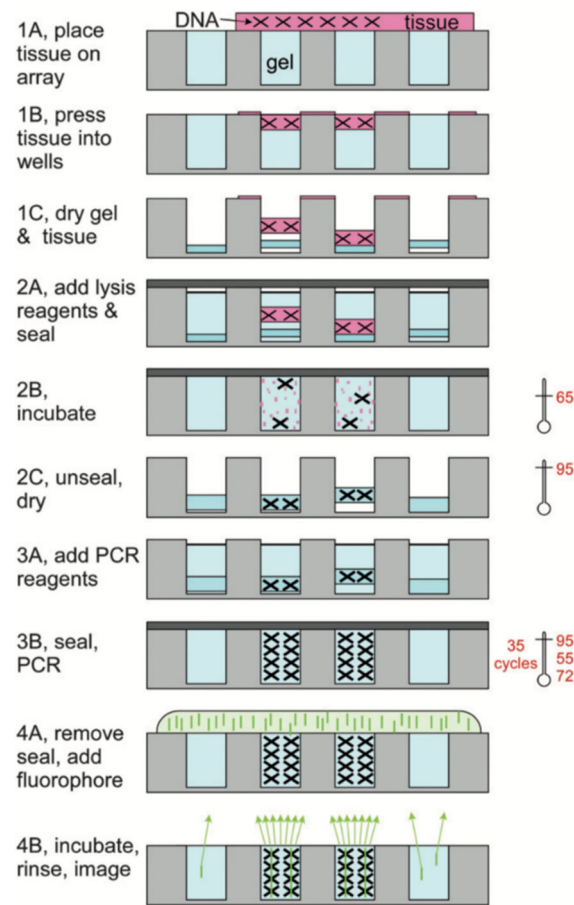


Fig. 2 Experimental protocol used to demonstrate the 2D-PCR concept. Tissue is transferred into wells, isolated, and lysed to extract the genomic DNA (represented by “x”s). PCR is performed to amplify the target DNA, and the targets are visualized with fluorescent dye (indicated by vertical lines “|”).

A POSA would have found it obvious to combine the teachings of Cantor and Armani by providing Cantor’s bead array with the plurality of beads disposed in wells, contacting that array with a tissue slice as disclosed by Armani, and then pressing the tissue sample into the wells and lysing the tissue as described by Armani. EX1022, 3531 (describing “loading the tissue vertically, pressing it directly into the array of wells to isolate tissue subregions while preserving the overall 2D spatial relationship.... This tissue loading technique also has the advantage of

beginning with traditional histological sectioning and transfer steps, which are familiar to investigators and clinicians who may wish to adopt this technique for research or diagnosis.”). EX1103, ¶357.

A POSA reviewing Cantor and Armani would have been motivated to combine their teachings for several reasons. Cantor’s protocols facilitate the capture, amplification, and detection of mRNA by sequencing, which Armani indicates was a desirable application for spatial analysis. By using sequencing as a detection technique, rather than direct visualization (e.g., fluorescence), the combination would allow the detection of even low abundance mRNAs. *See* EX1022, 3532 (“We are currently working on mapping RNA from tissue, since current visualization techniques for RNA cannot reliably detect below a few dozen copies per cell in situ.”). EX1003, ¶358.

Moreover, the use of Cantor’s methods to generate cDNA libraries of target nucleic acids coded with location information (via Cantors’ identification sequences) would simplify Armani’s detection procedure by eliminating at least the steps of unsealing the array, adding a fluorophore, incubating, rinsing, and imaging in Armani’s steps 4A-4B. Instead, using sequencing as a detection method would allow a POSA to simply pool the contents of all wells together in a multiplexed sequencing procedure, where the data can then be deconvoluted and spatially

mapped based on the read out of location-correlated identification sequences. EX1103, ¶358.

Furthermore, a POSA would have reasonably expected success in combining the teachings of Cantor and Armani. Indeed, the combination would have involved using Cantor's device and methods in the manner they are disclosed—to detect nucleic acids from a tissue sample, while specifically using the identification sequences to identify the location at which beads were provided. Armani further provides additional specific implementations of how to prepare successfully and process effectively a nucleic acid tissue sample for localized detection, methods not claimed in Claim 17, but the practice of which confirms the obviousness of the claimed arrangement to a POSA. EX1003, ¶359.

2. Claim 20

Claim 20 recites “wherein the tissue section is a formalin-fixed paraffin-embedded tissue section or a fresh frozen tissue section.”

Cantor explains that its target/sample nucleic acid may be “a solid material *such as a tissue...or a biopsy*.” EX1031, 6. Furthermore, Cantor explains in its Example 1, “Sequence analysis methodology,” that “[s]ample nucleic acid may be prepared by any means commonly known in the art.” *Id.*, 53-54. EX1103, ¶361.

Armani describes an apparatus for the analysis of nucleic acids in a frozen tissue section. In particular, Armani discloses placing a fresh-frozen tissue section

on a multi-well array as shown below to detect the presence of a target nucleic acid at various location throughout the tissue sample. EX1022, 3528 (explaining “[t]wo types of tissue were used in these studies: frozen tissue samples from a human prostate...hyperplasia and breast tissue,” which “were snap frozen”); *id.* (“Tissue sections were transferred to the multi-well device immediately after sectioning while still frozen[.]”). After “the tissue section is transferred onto the surface of the multi-well array (step 1A),” (1) the tissue section is “pressed onto the surface (1B),” (2) “[t]he contents of the well are dehydrated to enable the addition of lysis reagents (1C); (3) “the tissue is lysed to release genomic DNA into solution”; (4) the “DNA is amplified” using PCR; and (5) “the DNA is imaged” using fluorescent detection techniques, as shown below. *Id.*, 3527; EX1103, ¶362.

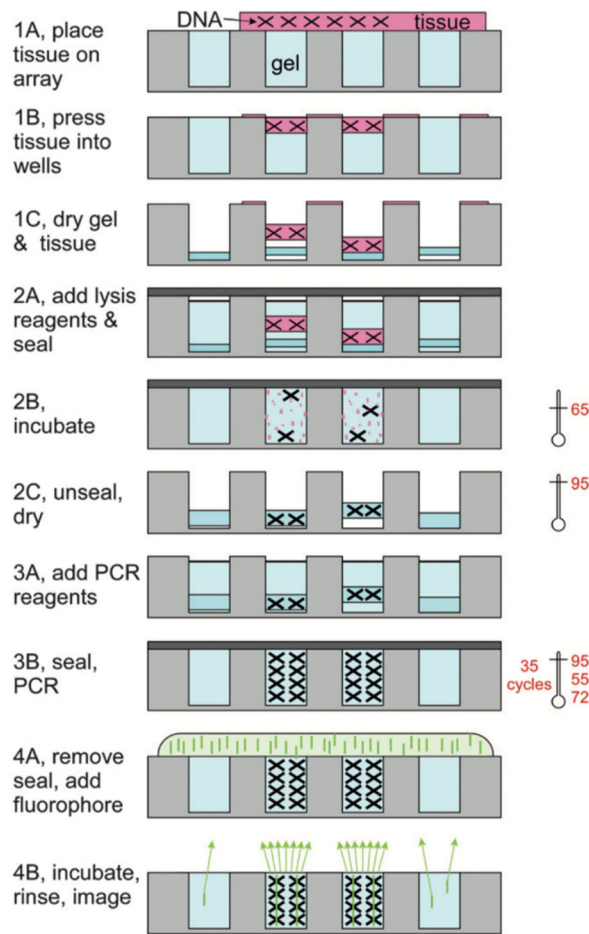


Fig. 2 Experimental protocol used to demonstrate the 2D-PCR concept. Tissue is transferred into wells, isolated, and lysed to extract the genomic DNA (represented by “x”s). PCR is performed to amplify the target DNA, and the targets are visualized with fluorescent dye (indicated by vertical lines “|”).

A POSA would have found it obvious to combine the teachings of Cantor and Armani by providing Cantor’s bead array with the plurality of beads disposed in wells, disposing a frozen-tissue slice on the array as disclosed by Armani, and then pressing the tissue sample into the wells and lysing the tissue as described by Armani. EX1022, 3531 (describing “loading the tissue vertically, pressing it directly into the array of wells to isolate tissue subregions while preserving the overall 2D

spatial relationship.... This tissue loading technique also has the advantage of beginning with traditional histological sectioning and transfer steps, which are familiar to investigators and clinicians who may wish to adopt this technique for research or diagnosis.”). EX1103, ¶363.

A POSA reviewing Cantor and Armani would have been motivated to combine their teachings and would have expected success in combining their teachings for the reasons outlined above in Section X.B.1. *See also* EX1103, ¶¶364-365.

C. Ground 3: Anticipation by Frisen

1. Priority Date

The priority applications leading to Chee-138 are tabulated below:

’138 Patent Priority Documents	Filing Date	Exhibit
17/030,230 (the “’230 Application”)	September 23, 2020	EX1060
16/988,284 (the “’284 Application”)	August 7, 2020	EX1059
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

The challenged claims of the '138 Patent are not entitled to a priority date earlier than February 14, 2019, the filing date of the '235 Application because the claimed invention is not disclosed “in the manner provided by §112(a)” in the earlier '661 Application, '616 Application, and '124 Provision (hereinafter “the Priority Applications”). 35 U.S.C. §§119(e), 120. As explained below, the Priority Application do not support the challenged claims, and since “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,” this break in the priority chain precludes PO from relying on any date earlier than February 14, 2019, the filing date of the '235 Application.² *Holmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012) (quotation omitted). EX1103, ¶367.

The '661 Application fails to disclose the subject matter recited in the claims of the '138 patent. The application preceding the '661 Application—the '616 Application—shares the same specification as the '661 Application, and thus fails to provide adequate description of the subject matter recited in the challenged claims for the same reasons. Finally, the passages of the '124 Provisional that were omitted

² Curio does not concede support in the '235 Application, or any subsequent application, for the challenged claims.

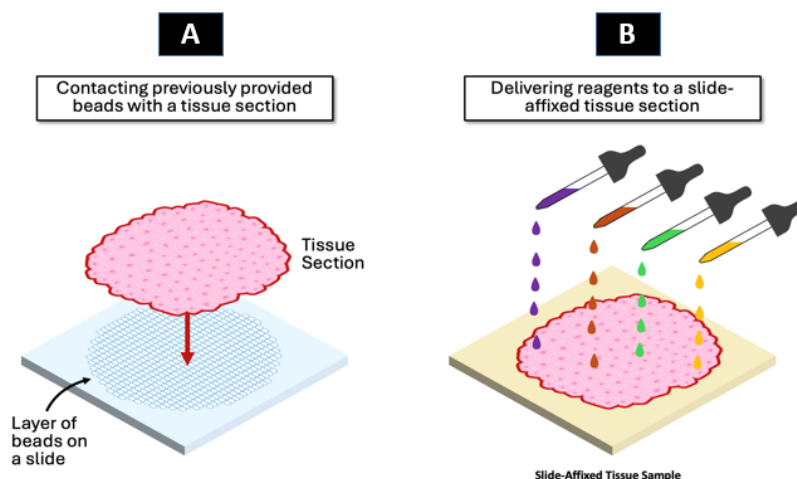
from the '661 and '616 Applications also fail to describe the subject matter of the challenged claims. EX1103, ¶368.

As set forth below, the Priority Applications at most contain ambiguous disclosures of isolated aspects of the claims, with no explanation of how those disclosures are linked to other aspects of the specification. Because “[a] patent owner cannot show written description support by picking and choosing claim elements from different embodiments that are never linked together in the specification,” Chee-138 is not entitled to the filing dates of the Priority Applications. *Flash-Control, LLC v. Intel Corp.*, No. 2020-2141, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021); *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (“pointing to an ‘amalgam of disclosures’ from which an artisan could have created the claimed invention does not satisfy this requirement.”).

At least one key element of independent claims 1 and 17 is not disclosed by the Priority Documents. Specifically, there is no disclosure of “[a] composition comprising an array comprising a substrate and a plurality of capture probes, wherein...each of the plurality of capture probes are immobilized on the substrate in a random pattern.” The challenged dependent claims do not further limit claims 1 and 17 in a manner that cures this deficiency.

The Priority Documents also fail to support “the tissue section is disposed on the array” limitation of claim 17.

The claims as drafted and as read by Patent Owner to assert infringement require an array of capture probes attached to a substrate, as shown in Figure A below. Claim 17 as read by Patent Owner to assert infringement further recites disposing a tissue on top of such an array, as depicted in Figure A below. But the '661 Application focuses exclusively on providing a tissue sample affixed to a solid support, and then delivering reagents, such as binding agents, to the top of the support-affixed tissue sample according to a spatial pattern, as depicted in Figure B below.



In fact, the specification emphasizes that the novelty of the “invention” lies in the delivery instrumentation used in the system of Figure B. EX1004, 8:63-67 (“The assay system further provides instrumentation with an ability to deliver reagents in a spatially-defined pattern. This instrumentation, together with software, reagents and protocols, provides a key component of the highly innovative assay system of

the invention....”); 18:3-4 (“In a preferred aspect of the invention, the reagent delivery instrumentation is based on inkjet printing technology.”). The claims of the ’138 patent do not cover the allegedly “highly innovative assay system of the invention” as depicted in Figure B. EX1103, ¶369.

As Dr. Puglisi explains, the differences between these methodologies are not trivial. For example, consistent with the ’661 Application’s focus on fluid handling techniques for delivery of probes, it repeatedly describes the delivery of probes to tissue in solution. As a result, Chee-138 repeatedly emphasizes a step of “washing” or separating encoded probes that did not bind to a target away from the sample, which is important for eliminating “noise” from the sequencing readout. EX1011, Figs. 1-2, [0028]. By contrast, the claims purport to encompass providing an array, in which solid phase probes are immobilized on a substrate, and to which a tissue sample is subsequently delivered. Such techniques require fabrication technologies and chemistries to create beads or other surfaces with the nucleic acids (such as probes) affixed to the desired locations. Here, a step of separating or washing encoded probes that did not bind to a target would not make sense in the context of these bead chemistries, because the probes are covalently bound to a substrate such as a slide or beads. EX1103, ¶370.

Moreover, the ’138 Patent criticizes Armani, which provides a variation of the Figure A approach, stating that its reliance on the transfer of tissue into wells,

“prevents random access to tissue samples and prevents high levels of multiplexing.”
See EX1004, 1:65-2:4. To the extent that the disclosures of the ’138 Patent (but not its claims) purport to address these alleged deficiencies, it is through the delivery of reagents from above the tissue sample. EX1004, 16:19-21 (“Integral to the assay system of the invention is instrumentation that allows for spatial patterning of reagents *onto* the biological sample.”). EX1103, ¶371.

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 capture probes 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, ¶372.

The ’661 Application’s Specification and Drawings are replete with statements confirming that its “invention” requires (i) providing a sample affixed to a support before (ii) delivering probes to the sample. These include:

- **SUMMARY OF THE INVENTION:** “The assay system comprises an assay capable of high levels of multiplexing where encoded probes *are provided to a biological sample in a defined spatial patterns....*” EX1011, [0007]. The other embodiments disclosed in this section

similarly involve “providing a sample affixed to a support” and “delivering encoded probes.” *E.g., id.*, [00015]. EX1103, ¶¶373-375.

- **FIGURES:** The figures require (i) providing biological samples affixed to a support, and (ii) delivering encoded probes to the biological sample. EX1011, Figs. 1-2. EX1103, ¶¶376-379.
- **“The Invention in General”:** “The assay system further provides *instrumentation with an ability to deliver reagents in a spatially-defined pattern. This instrumentation*, together with software, reagents and protocols, *provides a key component* of the highly innovative assay system *of the invention....*” EX1011, [00023]-[00024]; EX1103, ¶381.
- **“Assays”:** “The assay portion of the assay systems of *the present invention* comprise the following general steps: *delivering probes and encoding agents*” to samples, where “[t]he samples of the present invention include virtually any biological sample or samples *that can be affixed to a support* or provided essentially in a two dimensional manner....” EX1011, [00035]; EX1103, ¶383.

Further confirming that the ’661 Application discloses only the delivery of reagents, including probes, to a sample affixed to a solid support, the Specification further notes that “instrumentation capable of delivering reagents according to a

spatial pattern” “onto the biological sample” is “*integral to the assay system of the invention.*” EX1011, [00055]. Such techniques are disclosed to include, for example, ink jet printing and photolithographic processes. *Id.*, [00056], [00064]-[00065]; *see also Id.*, [00054] (“The reagent delivery system *of the invention* includes instrumentation that allows the *delivery* of reagents to discrete portions of the biological sample.”). EX1103, ¶¶384-385

A POSA would not have understood these disclosures, which necessarily involve delivering reagents, including capture probes (i.e., target binding nucleic acids) on top of a substrate-affixed tissue sample, to demonstrate possession an array of immobilized capture probes, as claimed. EX1100, ¶¶264, 266-267; EX1103, ¶386. *See also Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) (finding failure of written description for claims directed to furniture with controls off the console where “the original disclosure clearly identifies the console as the only possible location for the controls”); *Rivera v. Int’l Trade Comm’n*, 857 F.3d 1315, 1321 (Fed. Cir. 2017) (The “question is whether a pod adaptor assembly intended to allow compatibility between distinct brewing systems, also supports an undisclosed configuration that eliminates a fundamental component of one of those systems (i.e., the ‘pod’) through integration. It does not.”); *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1378 (Fed. Cir. 2009) (The “specification describes

only medical valves with spikes... [A POSA] would not understand the inventor...to have invented a spikeless medical valve”).

2. Claim 1

As described below, Frisen anticipates claim 1.

(a) “A composition comprising...”

Frisen discloses “[a] composition comprising an array comprising a substrate and a plurality of capture probes.” Thus, to extent the preamble is limiting, it is anticipated by Claim 14 of Frisen. EX1103, ¶391.

Frisen’s published Claims 1, 13 and 14 recite:

1. A method for localized or spatial detection and/or analysis of RNA in a tissue sample or a portion thereof, comprising:

(a) 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;*

(b) contacting said substrate with a tissue sample and allowing RNA of the tissue sample to hybridise to the capture probes;....

13. The method of any one of claims 1 to 13, wherein the capture probes further comprise a positional domain which is 5' relative to the capture domain, wherein said positional domain comprises a sequence that corresponds to the position of the capture probe on the object substrate, preferably wherein the positional domain of each species of capture probe comprises a unique barcode sequence.

14. The method of any one of claims 1 to 13, wherein the capture probes further comprise a universal domain which is 5' relative to the capture domain or, if present the positional domain, wherein said universal domain comprises:

- (i) an amplification domain, for amplifying the generated DNA molecules;....

EX1045, 117, 120.

Of particular relevance here is the limitation of Frisen's Claim 1 requiring "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." A POSA would recognize that this limitation discloses an array comprised of *a substrate* with *a plurality of capture probes* being immobilized directly or indirectly thereon. Indeed, Frisen refers to a substrate as an array. *See* EX1045, 2 ("The invention also provides an object substrate, such as a chip or slide (e.g. an array)."). EX1103, ¶394.

- (b) **"each of the plurality of capture probes comprises: (i) a target-binding domain, (ii) a nucleic acid sequence that identifies a unique location on the substrate..., and (iii) a primer binding site...."**

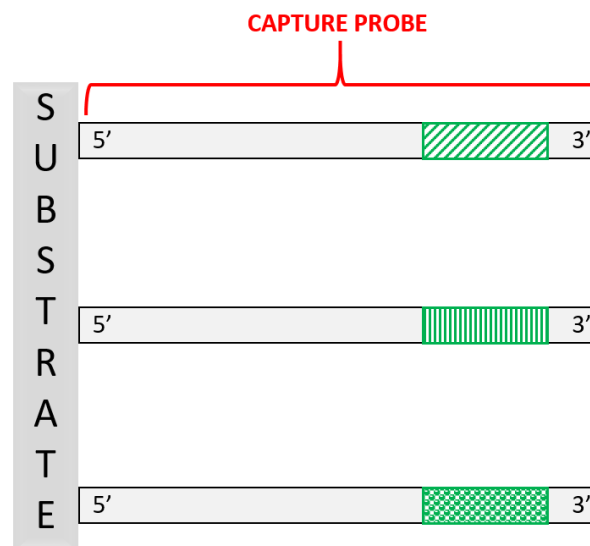
As described below, Frisen discloses this limitation.

- (i) **"each of the plurality of capture probes comprises: (i) a target-binding domain,...the target-binding domain of each of the plurality of capture probes comprises a nucleic acid sequence that is complementary to at least a**

**portion of the nucleic acid that binds to the
target-binding domain”**

Claim 1 of Frisen requires “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.”

A POSA would recognize that Frisen’s Claim 1 describes capture probes attached to a substrate by their 5’ ends such that their 3’ ends are free. Thus, a POSA would understand Frisen to disclose a substrate with a plurality of **capture probes** with **target-binding domains**, wherein the **capture probes** are attached to the substrate by their 5’ ends, as shown below. EX1103, ¶397.



Additionally, Frisen’s “capture domain comprises a nucleotide sequence that is capable of hybridizing to nucleic acid, e.g. RNA (preferably mRNA) present in

the cells of the tissue sample contacted with the array.” EX1045, 24-25. Moreover, “the capture domain may be selected or designed to bind (or put more generally may be capable of binding) selectively or specifically to the particular nucleic acid, e.g. RNA, it is desired to detect or analyse.” *Id.*, 25.

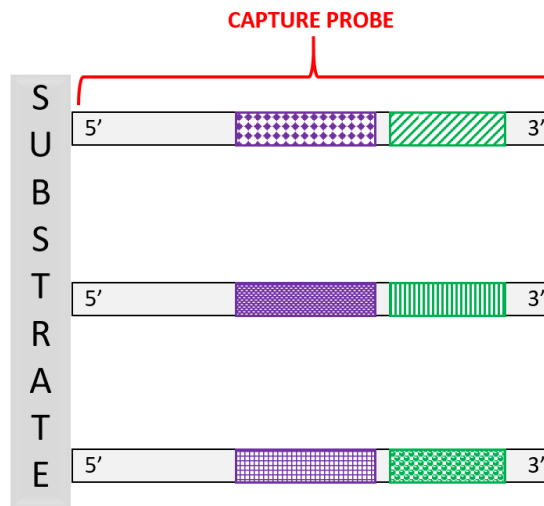
For example, Frisen discloses that the capture domain may be designed for the “selective capture of mRNA,” as opposed to other classes of nucleic acids (e.g., DNA, rRNA, tRNA), using poly-T capture domains. *Id.* As another example, Frisen discloses that “[t]he capture domain may be capable of binding selectively to a desired subtype or subset of nucleic acid, e.g. RNA, for example a particular type of RNA such mRNA or rRNA etc. as listed above, or to a particular subset of a given type of RNA, for example, a particular mRNA species e.g. corresponding to a particular gene or group of genes. Such a capture probe may be selected or designed based on sequence of the RNA it is desired to capture. Thus it may be a sequence-specific capture probe, specific for a particular RNA target or group of targets (target group etc).” *Id.* at 26.

Thus, a POSA would understand that the capture domain (i.e., target nucleic acid-binding domain) of each of the plurality of capture probes described in Claim 1 of Frisen comprises a nucleic acid sequence that is complementary to at least a portion of the target nucleic acid that binds to the target-binding domain. EX1103, ¶399.

- (ii) **“each of the plurality of capture probes comprises:...(ii) 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”**

Claim 13 of Frisen depends from Claim 1 and recites “wherein the capture probes further comprise a positional domain which is 5' relative to the capture domain, wherein said positional domain comprises a sequence that corresponds to the position of the capture probe on the object substrate, preferably wherein the positional domain of each species of capture probe comprises a unique barcode sequence.” *See also id.*, 26 (“The positional domain (feature identification domain or tag) of the capture probe, if present, is located directly or indirectly upstream, i.e. closer to the 5' end of the capture probe nucleic acid molecule, of the capture domain.”).

Because Claim 13 incorporates each limitation of Claim 1, Claim 13 of Frisen discloses an embodiment in which the substrate and **capture probes** of Claim 1 are further defined to have capture probes with “a **positional domain** which is 5' relative to the **capture domain**, wherein said **positional domain** comprises a sequence that corresponds to the position of the **capture probe** on the object substrate, preferably wherein the **positional domain** of each species of **capture probe** comprises a unique barcode sequence,” as shown below. EX1103, ¶401.



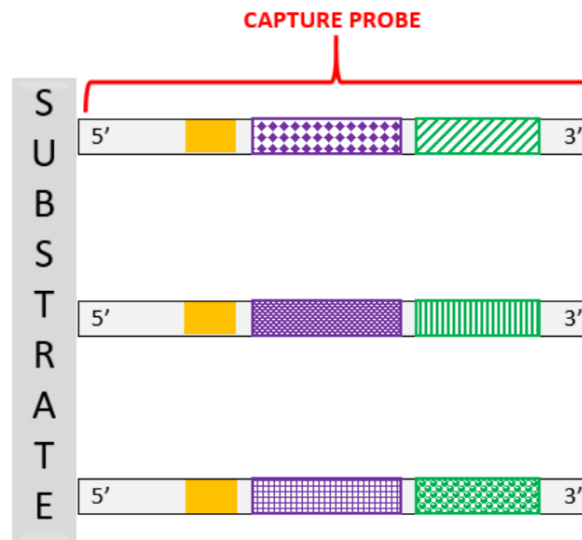
Frisen explains that “[t]he positional domain (or tag),” when present in the disclosed capture probes, “comprises the sequence which is unique to each feature or a group of directly or indirectly adjacent features, and acts as a positional or spatial marker (the identification tag). In this way, each 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.*, 28.

Frisen also explains that while “[a]ny suitable sequence may be used as the positional domain in the capture probes of the invention,” “the 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. For example, the positional domain should be designed such that nucleic acid molecules in the tissue sample do not hybridize specifically to the positional domain.” *Id.*, 29-30.

Thus, Frisen discloses that “each of the capture probes of the plurality of capture probes comprises...(ii) 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.” EX1103, ¶404.

(iii) “each of the plurality of capture probes comprises...(iii) a primer binding site”

Claim 14 of Frisen, which depends from Claim 13, further requires “wherein the **capture probes** further comprise a universal domain which is 5' relative to the **capture domain** or, if present the **positional domain**, wherein said universal domain comprises: (i) **an amplification domain**, for amplifying the generated DNA molecules,” as shown below. EX1103, ¶405.



When describing the amplification domain in detail, Frisen explains that “it may be advantageous to amplify the nucleic acid, e.g. cDNA molecules, for example

after they have been released (e.g. removed or cleaved) from the substrate. It will be appreciated, however, that the initial cycle of amplification, or indeed any or all further cycles of amplification may also take place in situ on the substrate. *The amplification domain comprises a distinct sequence to which an amplification primer may hybridize.*” EX1045, 32; EX1103, ¶406.

Thus, the “amplification domain” disclosed by Frisen is a “primer binding site” and “each of the plurality of capture probes comprises...(iii) a primer binding site.” EX1103, ¶407.

**(c) “each of the plurality of capture probes are
immobilized on the substrate in a random pattern”**

Frisen discloses “each of the plurality of capture probes are immobilized on the substrate in a random pattern.” For example, Frisen states that “the probes may be immobilized on beads, e.g. plastic microbeads, which can be used to immobilize the probes on the substrate” using “methods known in the art.” EX1045, 20. A POSA would appreciate from this disclosure that as known in the art the capture probes could either be (1) linked randomly to the substrate, such as described in Chee-874, or (2) linked in a predetermined manner, such as described in Chee-584. EX1038, [0013]; EX1032, 28:6-19. Thus, a POSA would immediately envisage the plurality of capture probes being positioned on the substrate in a random pattern. EX1103, ¶408.

3. Claim 5

Frisen discloses “wherein the array is deposited on a slide or flow-cell.” In particular, Claim 1 of Frisen requires “an *object substrate* on which at least one species of capture probe, comprising a capture domain, is directly or indirectly immobilized.” Frisen explains that “[t]he ‘object substrate’ or ‘substrate’ of the invention may be any solid substrate on which nucleic acid molecules can be immobilized directly or indirectly, e.g. *a slide* or chip.” EX1045, 17; *see also id.*, 1 (“The methods of the invention allow the nucleic acid molecules (e.g. RNA molecules) in the tissue sample, particularly mRNA, to be captured on an object substrate (e.g. a slide or chip, which may be an array).”). Thus, a POSA would recognize that Frisen discloses “wherein the array is deposited on a slide or flow-cell.” EX1103, ¶¶410-11.

4. Claim 17

As described below, Frisen anticipates Claim 17.

- (a) **“A composition comprising (i) an array comprising a substrate and a plurality of capture probes, and (ii) a tissue section”**

Frisen discloses “[a] composition comprising (i) an array comprising a substrate and a plurality of capture probes, and (ii) a tissue section.”

As described above in Section X.C.2(a) and herein incorporated by reference, Frisen discloses “[a] composition comprising (i) an array comprising a substrate and

a plurality of capture probes.” Claim 1 of Frisen also discloses combining such an array with a tissue section.

A method for localized or spatial detection and/or analysis of RNA in a tissue sample or a portion thereof, comprising:

(a) 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;

(b) *contacting said substrate with a tissue sample* and allowing RNA of the tissue sample to hybridise to the capture probes;....

Moreover, a POSA would understand that a tissue sample is synonymous with a tissue section. *See also* EX1045, 6 (“In its simplest form, the invention may be illustrated by the following summary. The invention requires reverse transcription (RT) primers to be immobilised 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.”). EX1103, ¶416.

(b) “the tissue section is disposed on the array

Frisen discloses “the tissue section is disposed on the array.” For example, Claim 1 of Frisen requires “contacting said substrate [i.e., array] with a tissue sample.” Frisen also explains that “[i]n its simplest form, the invention may be illustrated by the following summary. The invention requires reverse transcription (RT) primers to be immobilised 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.” EX1045, 6; EX1103, ¶¶417-418.

(c) each of the plurality of capture probes comprises:....

Frisen discloses this limitation. See Section X.C.2(b) above. EX1103, ¶419.

(d) “each of the plurality of capture probes are immobilized on the substrate in a random pattern”

As described above in Section X.C.2(c), Frisen discloses “each of the plurality of capture probes are immobilized on the substrate in a random pattern.” EX1103, ¶420.

5. Claim 20

Frisen discloses “wherein the tissue section is a formalin-fixed paraffin-embedded tissue section or a fresh frozen tissue section.” For example, Frisen discloses a few types of tissue samples that may be used with the disclosed array, including formalin-fixed paraffin-embedded (“FFPE”) tissue sections and fresh frozen tissue sections. EX1045, 42 (“[I]n one embodiment of the invention, the tissue sample, i.e. the section of the tissue sample contacted with the substrate, e.g. array, is prepared using FFPE or other methods of fixing and embedding. In other words the sample may be fixed, e.g. fixed and embedded. In an alternative embodiment of the invention the tissue sample is prepared by deep-freezing. In

another embodiment a touch imprint of a tissue may be used, according to procedures known in the art. In other embodiments an unfixed sample may be used.”); *Id.*, 41 (“As a first representative example of a tissue sample for use in the invention, the tissue may prepared by deep freezing at temperature suitable to maintain or preserve the integrity (i.e. the physical characteristics) of the tissue structure....”); *Id.* (“In a second representative example, the tissue may be prepared using standard methods of formalin-fixation and paraffin-embedding (FFPE), which are well-established in the art.”). Thus, a POSA would immediately envisage that the tissue section used with the disclosed array is a formalin-fixed paraffin-embedded tissue section or a fresh frozen tissue section. EX1103, ¶¶422-423.

6. Claim 23

Frisen discloses “wherein the array is deposited on a slide or flow-cell.” See Section X.C.3 above. EX1103, ¶425.

7. Claims 28-29

Frisen discloses “wherein the nucleic acid comprises RNA or DNA” and “wherein the RNA is mRNA.” For example, Frisen explains that the disclosed “capture domain comprises a nucleotide sequence that is capable of hybridizing to nucleic acid, e.g. RNA (preferably mRNA) present in the cells of the tissue sample contacted with the array.” EX1045, 24-25. EX1103, ¶¶426-430.

XI. SECONDARY CONSIDERATIONS

Petitioner is not aware of any secondary considerations of non-obviousness, and reserves the right to respond to any such issues raised by PO.

XII. NO BASIS FOR DISCRETIONARY DENIAL

A. 314(a) Does Not Warrant Denial

As explained below, factors 1-4 and 6 of *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 6 (PTAB March 20, 2020) strongly favor institution, and factor 5 does not weigh against institution:

1. Likelihood of a stay – Petitioner intends to move for a stay promptly after filing this Petition. Here, each of the factors the Court will consider favors a stay: the parallel litigation is still in early stage, and discovery is still ongoing, *see* EX1043; a stay would simplify the issues in question because all of the asserted claims of Chee-138 are being challenged in this Petition, and thus the invalidity issues in the district court would be narrowed by the estoppel provisions of § 315(e)(2); and there is no evidence of prejudice to Patent Owner, which did not seek a preliminary injunction.

2. Proximity of the court's trial date to a final written decision – Trial is scheduled for May 2026. If instituted, the Board's FWD would be expected in May 2026. *See* EX1040, 77 (10x (as Petitioner) asserting that "*Fintiv* simply does not

apply” in IPR proceeding where FWD would post-date trial, which was scheduled “approximately two months *before* a Final Written Decision would be reached”).

3. Investment in the parallel proceeding by the court and the parties – As noted above, the parallel litigation is in its early stages, investment by the parties and the court has been limited. Claim construction will not be fully briefed until after the Board’s anticipated decision to institute. EX1043.

4. Overlap between issues raised in the Petition and in the parallel proceeding – The most efficient course is for the Board to address the issues before it, and the district court to address only the issues that remain.

5. Whether the petitioner and the defendant in the parallel proceeding are the same party – The parties are the same in this IPR and in the parallel district court proceeding.

6. Other circumstances that impact the Board’s exercise of discretion, including the merits – This Petition presents a compelling merits case that all challenged claims are unpatentable, and therefore favors institution. *See Fintiv*, Paper 11 at 14-15.

In view of the above factors, this Petition should not be denied under §314(a).

B. 325(d) Does Not Warrant Denial

This Petition is not based on “the same or substantially the same arguments previously presented to the Office.” *Advanced Bionics, LLC v. MED-EL*

Elektromedizinische Gerate GmbH, IPR2019-01469, Paper 6 at 7. *See* Section V.

Thus, denial under 325(d) is inappropriate.

Grounds 1-2: A patent related to Cantor, U.S. Patent No. 10,144,966, was cited in an IDS by applicant during prosecution. However, the '966 Patent was just one of over 1,300 references cited by the applicant in IDSs during prosecution, and the '966 Patent was not the basis for any rejections by the Examiner during the prosecution. Where, as here, a reference was “not extensively evaluated during examination and [were] not the basis for a rejection,” and the Petition “present[s] a sufficient showing that the Examiner overlooked disclosures” that invalidate the claims, “the Office erred in a manner material to [] patentability.” *Apple Inc. v. Telefonaktiebolaget LM Ericsson*, IPR2022-00457, Paper No. 7 at 8 (P.T.A.B. Sept. 21, 2022).

Ground 3: The prosecution history does not indicate that the Examiner critically evaluated Chee-138's claims for section 112 support in the priority documents or otherwise meaningfully evaluated the claims against Frisen. Thus, the Office materially erred, because had the Examiner analyzed the lack of support for the claims in the priority documents, they would have then appreciated the relevance of Frisen as anticipatory prior art.

Moreover, the Office did not have the benefit of the detailed expert evidence submitted with this Petition, which shows why the claims are not supported and how

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Cantor, Frisen, and Armani confirm their unpatentability. *See* EX1103; *see also* *Mylan Pharmaceuticals Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 21 at 20 (PTAB May 12, 2020).

XIII. CONCLUSION

Petitioner respectfully submits that the Board should institute IPR and cancel the challenged claims.

Dated: November 15, 2024

Respectfully submitted,

/Andrew E. Krause/

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CERTIFICATE OF WORD COUNT

I hereby certify, pursuant to 37 C.F.R. section 42.24, that the foregoing Petition contains 13,476 words, excluding the words in the table of contents, table of authorities, exhibit list, this certificate of word count, and certificate of service. The word count is based on the word count of the Microsoft Word program used to prepare the Petition.

/Susan M. Langworthy/
Susan M. Langworthy

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for *Inter Partes* Review of U.S. Patent No. 11,549,138 and Exhibits are being served via Express Mail on November 15, 2024, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the patent prosecution counsel of record for the Patent Owner:

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Courtesy copies were also sent via ShareSite to Patent Owner's counsel of record in the related district court litigation at the following addresses:

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