

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIO-RAD LABORATORIES, INC.,
Petitioner,

v.

CALIFORNIA INSTITUTE OF TECHNOLOGY,
Patent Owner

Case No. IPR2024-01451

U.S. Patent No. 11,827,921 B2

PATENT OWNER'S PRELIMINARY RESPONSE

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

	<u>Page</u>
TABLE OF AUTHORITIES	iii
EXHIBIT LIST	vi
I. INTRODUCTION	1
II. BACKGROUND	3
A. Technology	3
B. The ’921 Patent and the Challenged Claims	6
C. The ’921 Patent’s Prosecution History	10
D. The Ground References.....	12
1. Larson.....	12
2. Saxonov.....	18
E. Related Proceedings	25
III. PERSON OF ORDINARY SKILL IN THE ART	27
IV. CLAIM CONSTRUCTION	27
V. THE BOARD SHOULD DENY INSTITUTION.....	29
A. Saxonov Is Not Prior Art.....	29
1. Petitioner’s Position on the ’921 Patent and Saxonov.....	30
2. By Assuming the ’921 Patent Is Entitled to Its Earliest- Claimed Priority Date, Petitioner Has Failed to Shift the Burden to Patent Owner to Prove this Entitlement.....	30
3. It Was Petitioner’s Burden to Show the Relied-Upon Subject Matter from Saxonov Was Carried Over from the Saxonov Provisional	33
4. Petitioner Failed to Meet Its Burden of Showing the Relied-Upon Material Was Carried Over	37
5. The Relied-Upon Subject Matter of Saxonov Was Not Carried Over from the Saxonov Provisional.....	39
B. The Challenged Claims Are Novel and Patentable over the Ground References	43

1.	Ground 1, Claims 1-10, 13-19: Anticipation by Larson.....	43
2.	Ground 3 (Claims 1-10 and 12-19): Obviousness in view of Larson and Saxonov.	49
a.	Larson Eliminates the “Multiple Occupancy” Situations to Which Petitioner Points	50
b.	Larson does not teach or suggest analyzing multiple targets in a single droplet	51
3.	Ground 4 (Claim 11): Obviousness In View of Larson, Saxonov, and Silverbrook.....	62
C.	The Board Should Deny Under §314(a) and <i>Fintiv</i>	63
1.	Factor 1: Likelihood of a Stay	63
2.	Factor 2: Proximity of Trial Date to a Final Written Decision	64
3.	Factor 3: Investment in the Parallel Litigation	65
4.	Factor 4: Overlap of Issues	66
5.	Factor 5: Whether Petitioner Is the Defendant in the Parallel Litigation.....	68
6.	Factor 6: Other Circumstances, Including the Merits.....	69
VI.	CONCLUSION.....	70

TABLE OF AUTHORITIES

<u>Cases</u>	<u>Page(s)</u>
<i>Apple Inc. v. Fintiv, Inc.</i> IPR2020-00019, Paper 15 (PTAB May 13, 2020)	3, 63, 64, 65, 67, 68, 69, 70
<i>Apple Inc. v. Telefonaktiebolaget LM Ericsson</i> IPR2022-00348, Paper 9 (PTAB Sept. 21, 2022).....	30, 33, 36
<i>Ariosa Diagnostics, Inc. v. Illumina, Inc</i> IPR2014-01093, Paper 69 (PTAB Jan. 7, 2016)	31, 32
<i>Carrier Fire & Security Ams. Corp. v. Sentrilock, LLC</i> IPR2021-00665, Paper 12 (PTAB Sept. 16, 2021).....	63
<i>In re: ChromaCode Litig.</i> No. 5:23-cv-04823 (N.D. Cal.).....	25
<i>ChromaCode, Inc. v. Bio-Rad Labs., Inc.</i> No. 5:23-cv-06360 (N.D. Cal.).....	25
<i>Commscope Techs. LLC v. Dali Wireless, Inc.</i> IPR2022-01293, Paper 18 (PTAB Mar. 9, 2023)	67, 68
<i>Commscope Techs. LLC v. Dali Wireless, Inc.</i> IPR2022-01242, Paper 23 (PTAB Feb. 27, 2023).....	69, 70
<i>Ex Parte Robert A. Mann</i> 2016 WL 7487271 (PTAB Dec. 21, 2016).....	35, 42
<i>Forescout Techs., Inc., v. Fortinet, Inc.</i> IPR2021-01328, Paper 12 (PTAB Jan. 27, 2021)	34, 35, 36, 42
<i>In re Giacomini</i> 612 F.3d 1380 (Fed. Cir. 2010)	34, 36, 42
<i>Google LLC v. Ikorongo Tech. LLC</i> IPR2021-00058, Paper 14 (PTAB May 10, 2021)	34, 36, 39
<i>Great West Casualty Company et. al. v. Intellectual Ventures II LLC</i> IPR2015-01706, Paper 69 (PTAB Feb. 14, 2020).....	28

<i>Illumina, Inc. v. Ravgen</i> IPR2021-01271, Paper 12 (PTAB Jan. 26, 2022)	38
<i>Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.</i> 821 F.3d 1359 (Fed. Cir. 2016)	31, 33, 38
<i>Intex Recreation Corp. v. Bestway (USA), Inc.</i> 2020 WL 3421699 (PTAB June 22, 2020).....	28, 29
<i>Lyft, Inc. v. Ikorongo Tech. LLC</i> IPR2021-00423, Paper 10 (PTAB July 26, 2021).....	37, 38, 39
<i>Mastercard, Inc. v. OV Loop, Inc.</i> IPR2023-01289, Paper 15 (PTAB Mar. 20, 2024)	38
<i>OpenSky Indus., LLC v. VLSI Tech. LLC</i> IPR2021-01064, Paper 102 (PTAB Oct. 4, 2022).....	69
<i>Plas-Pak Industries, Inc. v. Sulzer Mixpac AG</i> 600 Fed.Appx. 755 (Fed. Cir. 2015).....	54, 61
<i>Precision Planting LLC v. Maschio Gaspardo S.p.A.</i> IPR2024-00008, Paper 12 (PTAB Mar. 26, 2024)	64
<i>Sand Revolution II, LLC v. Cont’l Intermodal Group – Trucking LLC</i> IPR2019-01393, Paper 24 (PTAB June 16, 2020)	65
<i>Schlumberger Tech. Corp. v. Dynaenergetics Europe GmbH</i> PGR2021-00089, Paper 13 (PTAB Dec. 14, 2021).....	33, 34, 35
<i>Sotera Wireless, Inc. v. Masimo Corp.</i> IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020)	63, 67, 68
<i>T-Mobile USA, Inc. v. Cobblestone Wireless, LLC</i> IPR2024-00136, Paper 18 (PTAB June 5, 2024)	66
<i>T-Mobile USA, Inc. v. Wireless Alliance, LLC</i> IPR2024-00607, Paper 16 (PTAB Sept. 10, 2024).....	66, 68
<i>Zomm, LLC v. Apple Inc.</i> 391 F. Supp. 3d 946 (N.D. Cal. 2019).....	64

Codes, Statutes

35 U.S.C. § 102(e) 2, 12, 30, 42

35 U.S.C. § 312(a)(3).....33

37 C.F.R. § 42.22(a)(2) 34

37 C.F.R. § 42.104(b) 33

EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Kevin Struhl, Ph.D.
2002	<i>Curriculum Vitae</i> of Kevin Struhl, Ph.D.
2003	File history of U.S. Patent No. 11,827,921
2004	U.S. Provisional Application No. 61/507,082
2005	Patent Scheduling Order dated March 8, 2024, Dkt No. 47, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , Case No. 5:23-cv-06360, N.D. Cal.
2006	Petitioner's Amended Invalidity Contentions, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , Case No. 5:23-cv-06360, N.D. Cal.
2007	Comparison of Saxonov and Saxonov Provisional
2008	Appendix M to Bio-Rad's Amended Invalidity Contentions
2009	Appendix I to Bio-Rad's Amended Invalidity Contentions
2010	Docket, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , Case No. 5:23-cv-06360, N.D. Cal.
2011	Plaintiff's Opening Claim Construction Brief, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , Case No. 5:23-cv-06360, N.D. Cal.
2012	Reply Claim Construction Brief, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , Case No. 5:23-cv-06360, N.D. Cal.
2013	Notice Setting Claim Construction Hearing, Dkt. 83, <i>Chromacode Litig.</i> , Case No. 5:23-cv-04823, N.D. Cal.
2014	Joint Case Management Statement, Dkt. 80, <i>Chromacode Litig.</i> , Case No. 5:23-cv-04823, N.D. Cal.
2015	Minute Entry for Case Management Conference held on November 6, 2024, Dkt. 88, <i>Chromacode Litig.</i> , Case No. 5:23-cv-04823, N.D. Cal.

I. INTRODUCTION

The Board should not institute IPR of claims 1-19 of U.S. Patent No. 11,827,921 (EX1001) because Petitioner has not met its burden of showing it has a reasonable likelihood of prevailing on any claim.

After years of significant investment in research and development, inventors from Patent Owner California Institute of Technology (“PO” or “Caltech”) conceived of a long-sought and powerful technology for unambiguously distinguishing multiple analytes (e.g., genetic sequences) in any combination of presence or absence within a biological sample. The ’921 Patent, entitled “Signal Encoding and Decoding in Multiplexed Biochemical Assays,” is one of several Caltech patents that protect embodiments of this innovative technology. Petitioner Bio-Rad Laboratories, Inc. asserts the ’921 Patent is anticipated by or unpatentable over U.S. Publication No. 2011/0250597 (EX1017, “Larson”), alone or in view of U.S. Publication No. 2013/0040841 (EX1004, “Saxonov”) and/or U.S. Publication No. 2011/0312704 (EX1009, “Silverbrook”). However, each of Petitioner’s alleged invalidity grounds fails for multiple reasons.

First, Petitioner fails to show a reasonable likelihood of demonstrating that the challenged claims are anticipated by Larson, or obvious over Larson alone or in view of Saxonov and/or Silverbrook. As explained below, Larson is deficient in multiple regards. Despite—or perhaps because of—Larson’s deficiencies,

Petitioner attempts to revise and reinterpret Larson in a manner which is inconsistent with Larson's own teachings. And, while Petitioner tries combining Larson with Saxonov to obtain the '921 Patent claims, both references expressly teach away from Petitioner's proposals, and Petitioner's proffered rationale for combining the references with one another fails.

Second, for the grounds which rely upon Saxonov in combination with Larson to allegedly render the claims obvious, Petitioner fails to establish Saxonov qualifies as prior art under 35 U.S.C. §102(e), or any other code section. Although Saxonov nominally claims priority to two provisional applications filed in July 2011 (EX1007, EX2004), Petitioner has not shown that either provisional application contains all the subject matter on which each of Petitioner's grounds relies. Not only has Petitioner failed to carry its burden to make the required showing, but the only provisional application of Saxonov upon which Petitioner relies also does not disclose this subject matter. Instead, this subject matter, upon which certain of Petitioner's grounds rely, was only first added into Saxonov's *non-provisional* application, which was not filed until July 12, 2012—*after* the '921 Patent's priority date of February 3, 2012. Petitioner's grounds that rely on subject matter found exclusively in Saxonov's non-provisional application are fatally flawed.

In view of the Petition's substantial deficiencies, Petitioner has failed to demonstrate a reasonable likelihood of prevailing on any claim. The Petition should be denied. Alternatively, the Board should exercise its discretion to deny institution because the *Fintiv* factors as a whole weigh in favor of denial.

II. BACKGROUND

A. Technology

A variety of techniques have been developed to detect a target polynucleotide analyte, such as a particular genetic sequence, within a biological sample. EX2001, ¶28. Caltech's innovations described and claimed in the '921 Patent and its priority applications addressed a long-standing problem in the field: namely, as the number of analytes in a biological sample increases, it quickly becomes more complicated to identify the analytes. EX2001, ¶29. The term "multiplexing" refers to a broad class of techniques for detecting multiple analytes in a biological sample. *Id.* Early assays used polymerase chain reaction (PCR) to amplify (create copies of) each of the target polynucleotide analytes, and often involved gel electrophoresis to separate the various PCR products that distinguished the analytes. *Id.*

A subsequent multiplex PCR approach uses "probes" to bind to target analytes and fluoresce with different colorimetric labels (fluorophores) corresponding to the different analytes, with results being detected with

appropriate optical channels configured to detect specific wavelength(s) of light, *i.e.*, colors produced by the probes when the probes bind or “hybridize” to complimentary genetic sequences in the target analytes, such that each optical channel corresponds to a probe color (wavelength). EX2001, ¶30. For example, a probe is designed to be complementary to a particular genetic sequence, and the probe and sequence bind via “hybridization.” *Id.* The fluorophore emits light only if the probe has bound its target within the sample. *Id.* For example, a probe with a blue fluorophore binds analyte A and its light is observed in a blue channel; and a probe with a red fluorophore binds analyte B and its light is observed in a red channel. *Id.*, ¶31. Of course, increasing the numbers of probe types (each with distinct fluorophore color) and channels (one per color) increases the number of detectable analytes. *Id.* However, scaling up to detect more analytes in the same sample has the limitation of the number of distinct colorimetric probes and optical channels that could be assayed simultaneously. *Id.*

Some multiplexing techniques use probes with colorimetric labels (fluorophores) of the same color. EX2001, ¶32. Here, color alone does not distinguish the analytes from one another: light in the channel means an analyte is present, but does not identify *which* analyte is present. *Id.* Some techniques (*e.g.*, Larson) tried to avoid this problem by (i) highly diluting the sample, (ii) physically dividing the diluted sample into droplets, (iii) observing the intensity of light from

each droplet, and (iv) drawing conclusions about the analytes based on that intensity. *Id.* For example, probes with the same color could be designed to fluoresce at different intensities, to identify the analyte using the intensity. *Id.*

When a dilute sample is divided into droplets, different droplets may contain different numbers of unique analyte molecules. EX2001, ¶33. The “Poisson distribution” describes the statistics of how many analyte molecules the droplets contain. *Id.* In the “limiting dilution” regime, the majority of droplets contain zero analyte molecules, fewer droplets contain exactly one analyte molecule, even fewer contain exactly two analyte molecules, still fewer contain exactly three analyte molecules, and so on. *Id.* At terminal dilution, the sample is sufficiently diluted that the Poisson distribution basically guarantees that almost all droplets are either empty or contain only a single analyte molecule, with droplets rarely containing multiple analyte molecules. *Id.* At terminal dilution, to best avoid droplets containing multiple analyte molecules, most droplets are empty, which wastes material and time. *Id.*

The '921 Patent refers to analytes that are indistinguishable from one another in a given assay as being “degenerate.” EX1001, 16:47-50. At the time the '921 Patent and its priority applications were filed, a significant need remained for inexpensive, material-efficient, and time-efficient multiplexing that could non-degenerately identify a higher number of targets within a given sample, without the

need to add another optical channel corresponding to each additional analyte. *Id.*, 1:35-47, 8:45-62; EX2001, ¶34.

B. The '921 Patent and the Challenged Claims

To address the above-described needs, Caltech inventors conceived of a solution—described and claimed in the '921 Patent and its priority applications—that enables non-degenerate detection of more polynucleotide analytes in a single sample solution volume, in any combination of presence or absence, than the number of wavelength components used to detect them. The application that issued as the '921 Patent was filed on May 1, 2020 as a continuation of application no. 15/914,356, filed March 7, 2018, which was a continuation of application no. 14/451,876, filed August 5, 2014 as a continuation of application no. 13/756,760, filed February 1, 2013. EX1001, §§(22), (63). The '921 Patent claims priority to provisional application nos. 61/594,480, filed February 3, 2012, and 61/703,093, filed September 19, 2012. EX1001, §(60); EX2001, ¶35.

The Caltech inventors recognized that in traditional multi-channel methods such as those described above, “the number of detectable analytes is equal to the number of spectrally resolvable fluorophores. Therefore the number of analytes may only be increased by increasing the number of spectrally resolvable fluorophores.” EX1001, 12:39-45. To overcome this limitation, the inventors developed a technique to non-degenerately identify analytes in a sample, using

fewer fluorophores than the number of analytes (in contrast to prior multi-channel techniques). EX1001, 8:45-66. Instead, “each analyte to be detected is encoded as a value in each of two components of a signal (e.g., intensity and wavelength)[,]” these components are cumulatively measured for the sample, and the “presence or absence of an analyte may then be determined based on the values used to encode the presence of the analyte (i.e., those values in the coding scheme).” *Id.*, 8:66-9:5, 9:41-47; EX2001, ¶36.

Table 3 of the '921 Patent, below, describes an example in which seven analytes (A-G), plus a control, are encoded using combinations of four fluorophores (fewer fluorophores than analytes):

TABLE 3

Encoding of eight analytes (including control) with four colors and up to four colors per analyte.				
	Blue	Green	Yellow	Red
Ctrl. (p)	1	0	0	0
A	1	0	0	1
B	1	0	1	0
C	1	1	0	0
D	1	0	1	1
E	1	1	0	1

TABLE 3-continued

Encoding of eight analytes (including control) with four colors and up to four colors per analyte.				
	Blue	Green	Yellow	Red
F	1	1	1	0
G	1	1	1	1

EX1001, 13:55-14:9; EX2001, ¶37.

As the '921 Patent explains,

The presence of the control and analyte A is indicated by a result of 2001. The presence of the control and analyte G is indicated by a result of 2111. These results express the cumulative intensity of the signal in each color. For example, the result 2111 has a 2X signal intensity in the blue channel, while the result 1000 has only a 1 X signal intensity in the blue channel. EX1001, 14:14-21; EX2001, ¶38.

While these example results are for a single analyte, the '921 Patent also explains how the inventive coding method may be used to detect *combinations* of different analytes in a single sample volume. For example, the following excerpt from Table 4 demonstrates that the cumulative signal intensity from the combination of analytes A-F in a single sample volume is different, and

measurably distinguishable from, that from the combination of analytes A-G in a single sample volume:

7	3	3	3	pABCDEF
8	4	4	4	pABCDEFG

EX1001, 15:60-61; EX2001, ¶39.

The Caltech inventors recognized that sometimes a result may be degenerate “because it can indicate more than one possibility in terms of the presence or absence of an analyte. For example, with reference to Table 4, result 5233 is degenerate because it can be decoded as either pADFG or pBDEG.” EX1001, 16:47-52; EX2001, ¶40. The Caltech inventors solved this problem by reducing or eliminating degeneracy from the coding scheme, “thereby increasing the confidence with which an analyte is detected.” EX1001, 16:57-59; EX2001, ¶40. The '921 Patent describes different ways to eliminate degeneracy such that every possible combination of analytes has a unique cumulative intensity. EX1001, 22:11-23:56; EX2001, ¶¶40-41. The '921 Patent claims are directed to the Caltech inventors' innovations providing assays kits that are capable of unambiguously detecting the presence or absence of each of said at least M analytes, in any combination of presence or absence, in a single sample volume, based on detection of said F wavelength components, when M is greater than F. EX1001, 67:9-20, 68:19-38; EX2001, ¶42.

C. The '921 Patent's Prosecution History

Initially, Examiner Negin rejected the claims as being obvious over Nature Biotechnology, volume 19, 2001, pages 631-835 ("Han") in view of secondary references, or indefinite. EX2003, 4372-4381. Examiner Negin also issued a double patenting rejection over U.S. 8,838,394, U.S. 10,068,051, and U.S. 10,770,170, all of which are the '921 Patent's parents. *Id.*, 4381-4385. Following PO's response including amendments and arguments, Examiner Negin issued a Final Office Action maintaining the obviousness and double-patenting rejections. *Id.*, 4423-4432, 4450-4464. PO replied with arguments and a terminal disclaimer, and amended the independent assay claim as follows, into its now-granted form¹:

21. **(Currently Amended)** An assay that is capable of unambiguously detecting the presence or absence of each of at least M analytes,

¹ PO made analogous amendment to the independent kit claim (now granted as claim 14) to recite "the kit does not require the use of mass spectrometry or immobilization of said M analytes[.]" EX2003, 4469.

wherein each of said at least² M analytes is encoded as a value of one component of a fluorescent signal, thereby generating a coding scheme,

wherein said fluorescent signal comprises F wavelength components, and

wherein said assay is capable of unambiguously detecting the presence or absence of each of said at least M analytes, in any combination of presence or absence, in a single sample volume ~~without immobilization, separation, mass spectrometry, or melting curve analysis,~~ based on detection of said F wavelength components, when M is greater than F,

wherein the assay does not require the use of mass spectrometry or immobilization of said at least M analytes, and

wherein the analytes are amplified in the single sample volume.

EX2003, 4466-4467, 4483.

PO filed an IDS citing Saxonov, which Examiner Negin initialed to indicate that he considered Saxonov. EX2003, 225, 4400.

² Double-underlines indicate PO's amendments "to improve the form" after the notice of allowance issued. EX2003, 4528-4529.

Examiner Negin then allowed the application, stating “[t]he claims recite an empirical assay for detecting the presence and absence of M analytes with F wavelength components wherein M is greater than F without using mass spectrometry or immobilization.” EX2003, 4525-4526; EX2001, ¶43.

Examiner Negin also examined Saxonov around the same time as the '921 Patent's family. *See generally* EX2003; EX1004.

D. The Ground References

Petitioner's grounds all rely on Larson as the primary reference. Petition, 21 *et seq.* As described below in §V.B., Petitioner fails to establish the claims are anticipated by, or unpatentable over, Larson, whether alone or in combination with Saxonov and/or Silverbrook. Moreover, as described in §V.A., Petitioner does not (and cannot) establish Saxonov as §102(e) prior art against the '921 Patent for Grounds 3 and 4 set forth in the Petition.

1. Larson

U.S. Patent Application Publication No. US 2011/0250597 to Larson et al. (“Larson”) was filed on February 11, 2011, and issued on October 13, 2011. EX1017, §§(22), (43); EX2001, ¶44.

Larson discloses “droplet based digital PCR and methods for analyzing a target nucleic acid using the same.” EX1017, Abstract. Larson states:

Methods of the invention involve novel strategies for performing multiple different amplification reactions on the same sample simultaneously to quantify the abundance of multiple different DNA targets, commonly known to those familiar with the art as “multiplexing”. Methods of the invention for multiplexing dPCR assays promise greater plexity—the number of simultaneous reactions—than possible with existing qPCR or dPCR techniques. EX1017, ¶45.

Larson states it is “based on the singular nature of amplifications at terminal or limiting dilution that arises because most often only a single target allele is ever present in any one droplet even when multiple primers/probes targeting different alleles are present.” *Id.*, ¶¶45, 98, 99. That is, that the sample is sufficiently diluted that a single analyte is located within a droplet. EX2001, ¶45.

Larson describes terminal dilution as “the vast majority of reactions contain either one or zero target DNA molecules for practical intents and purposes,” and limiting dilution as “some reactions contain zero DNA molecules, some reactions contain one molecule, and frequently some other reactions contain multiple molecules, following the Poisson distribution.” EX1017, ¶6; EX2001, ¶46. Larson asserts various advantages of having one allele per droplet. *See, e.g., id.*, ¶¶99-100; EX2001, ¶47.

Larson discloses digital PCR (dPCR) assays for detecting different numbers of analytes; illustratively, FIG. 15 discloses a “9-plex dPCR assay for spinal muscular atrophy with only two fluorophores, showing the process of optimizing droplet intensities.” EX1017, ¶35, FIG. 15; EX2001, ¶48.

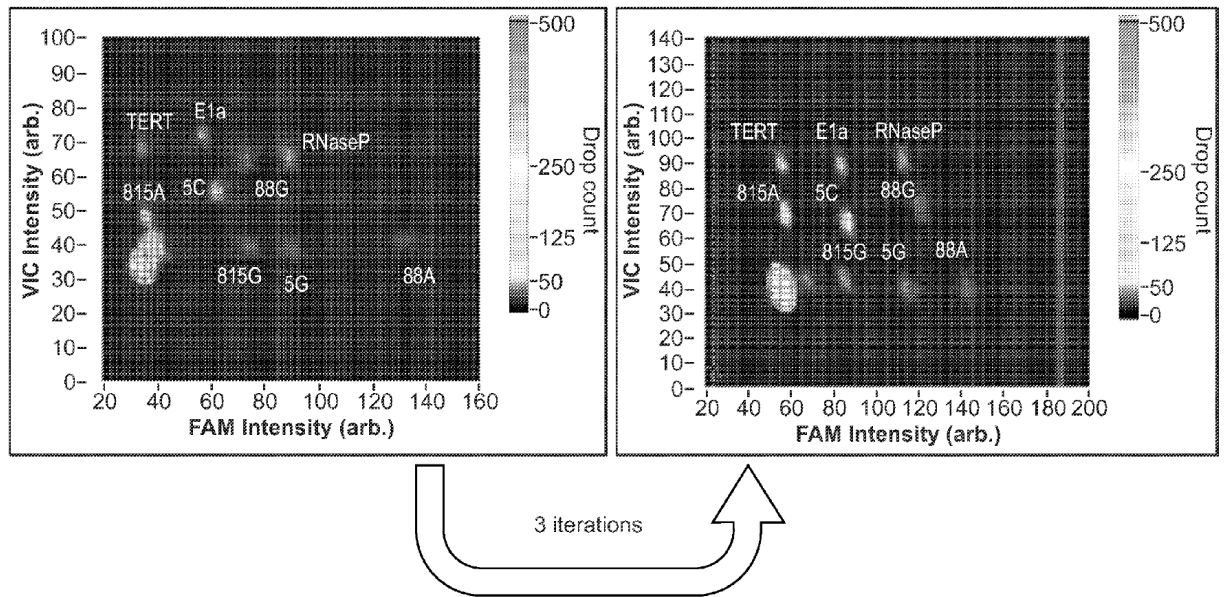


FIG. 15

Larson's FIG. 15 shows only single-analyte clusters (respectively TERT, 815A, E1a, 5C, 815G, RNaseP, 88G, 5G, 88A). EX1017, ¶35, FIG. 15; EX2001, ¶49.

Other graphs in Larson similarly appear to show measurements from only single-analyte droplets/clusters, and conspicuously omit measurements from multi-analyte droplets/clusters. EX2001, ¶49, *citing* EX1017, FIGS. 5B, 5C, 6B, 7C, 8D, 9D, 14a, 18A, 19A, 20A, 21B, 21E, 21H.

Larson teaches “[h]igher degrees of multiplexing would require greater dilution,” because of possible unintended “cross-reactivity” between analytes in a droplet. EX1017, ¶129; EX2001, ¶50. Accordingly, Larson expressly and fundamentally relies on *increasing* sample dilution as the number of analytes increases, to reduce the probability that one probe overlaps any of the other probes – that is, to reduce the probability that any droplet contains two or more analytes. EX2001, ¶¶50-55.

To the extent any droplets nonetheless contain more than one analyte, Larson expressly teaches *excluding* such droplets from analysis. EX2001, ¶56. More specifically, Larson states “[m]ethods of the invention are able to detect which droplets contain a *heterogeneous population* of molecules and are able to *exclude* those droplets from the analysis.” EX1017, ¶172; EX2001, ¶56. Larson describes a *heterogeneous* population of molecules: “[d]roplets that produce two signals are classified as droplets that contain a heterogeneous population of molecules.” EX1017, ¶173; EX2001, ¶57. A POSA considering Larson as a whole would have readily understood that droplets containing a heterogeneous population of molecules produce two signals because they contain two different analytes, each analyte producing a different signal. EX2001, ¶¶57-59.

In contrast to heterogeneous populations that produce two signals, Larson describes a *homogeneous* population: “[d]roplets that produce only a *single* signal

are classified as droplets that contain a homogeneous population of target.”

EX1017, ¶172; EX2001, ¶60. A POSA considering Larson as a whole would have readily understood that droplets containing a homogeneous population of molecules produce *one signal* because they contain only a single analyte, producing a single signal. EX2001, ¶¶60-61.

Larson describes *how* to exclude “[d]roplets that produce two signals” from analysis in a section entitled “Droplet Sorting.” EX2001, ¶¶62-64. According to Larson, “[b]ased upon the detected signal at the detection module, droplets containing a heterogeneous population of molecules are sorted away from droplets that contain a homogeneous population of molecules.” EX1017, ¶181; EX2001, ¶63. From Larson’s full teachings, a POSA readily would have understood that Larson teaches *detecting* and *sorting* droplets based on the detected number of signals from those droplets: *two signals* from droplets containing a *heterogeneous* population of molecules, and *one signal* from droplets containing a *homogeneous* population of molecules; and *excluding* the droplets with *two signals*. EX2001, ¶¶62-64.

Larson’s reasons for excluding “multiple occupancy” droplets relate to complexities associated with “multiple occupancy:”

With multiple occupancy arises the complexity of
simultaneous assays competing within the same reaction

droplet, and also complexity of assigning the resulting fluorescence intensity that involves a combination of fluorescence from two different reaction products that may or may not be equal to the sum of the two fluorescence intensities of the individual reaction products. However, methods of the invention can accommodate these complications arising from multiple occupancy.

EX1017, ¶141; EX2001, ¶65.

A POSA readily would have understood, considering the above excerpt from Larson's ¶141 in view of Larson as a whole, that "multiple occupancy" droplets contain a "heterogeneous population of molecules." EX2001, ¶66. Moreover, they readily would have understood Larson's statement "methods of the invention can accommodate these complications arising from multiple occupancy" means *first*, increasing sample dilution as the number of analytes increases, reducing the probability that one probe overlaps any other probes – that is, to reduce the probability that any droplet contains two or more analytes. EX2001, ¶¶45-55, 67; and *second*, detecting, sorting away, and excluding droplets containing heterogeneous populations of molecules based how many signals (one or two) the droplets produce. EX2001, ¶¶56-67.

Larson is replete with examples of how to identify a *single* analyte, repeats this as a key inventive concept, and indeed a POSA reasonably would have considered identifying a *single* analyte within a droplet to be Larson's principle of operation. EX2001, ¶68, *citing* EX1017 abstract, ¶¶7, 8, 11, 13, 18-20, 45, 46, 49, 68, 99-101, 107, and claims 1, 3, 10, 11, and 15.

2. Saxonov

Saxonov was filed July 12, 2012 and claims priority to U.S. Provisional Patent App. Nos. 61/507,082, filed July 12, 2011, and 61/510,013, filed July 20, 2011 ("Saxonov Provisional"). EX1004, §§(22), (60); EX2001, ¶69.

Saxonov discloses "performing a digital assay with multiplexed detection of two or more distinct targets in the same optical channel." EX1004, Abstract.

Regarding "digital assays," Saxonov explains:

Digital assays generally rely on the ability to detect the presence or activity of individual copies of an analyte in a sample. In an exemplary digital assay, a sample is separated into a set of partitions, generally of equal volume, with each containing, on average, less than about one copy of the analyte. If the copies of the analyte are distributed randomly among the partitions, some partitions should contain no copies, others only one copy, and, if the number of partitions is large enough, still others should contain two copies, three copies, and even

higher numbers of copies. The probability of finding exactly 0, 1, 2, 3, or more copies in a partition, based on a given average concentration of analyte in the partitions, is described by a Poisson distribution.

EX1004, ¶3; EX2001, ¶70.

Here, Saxonov teaches that in a standard digital assay, most droplets (partitions) are empty, fewer droplets contain exactly one analyte, even fewer contain exactly two analytes, and even fewer contain exactly three analytes; this is consistent with the limiting dilution regime discussed above in §II.A. EX2001, ¶71.

According to Saxonov, “[d]igital assays frequently rely on amplification of a nucleic acid target in partitions to enable detection of a single copy of an analyte,” and such “[a]mplification may be conducted via the polymerase chain reaction (PCR).” EX1004, ¶5; EX2001, ¶72. Saxonov states “[a]mplification of the target can be detected optically from a fluorescent probe included in the reaction,” and “the probe can include a dye that provides a fluorescence signal indicating whether or not the target has been amplified.” EX1004, ¶5; EX2001, ¶72.

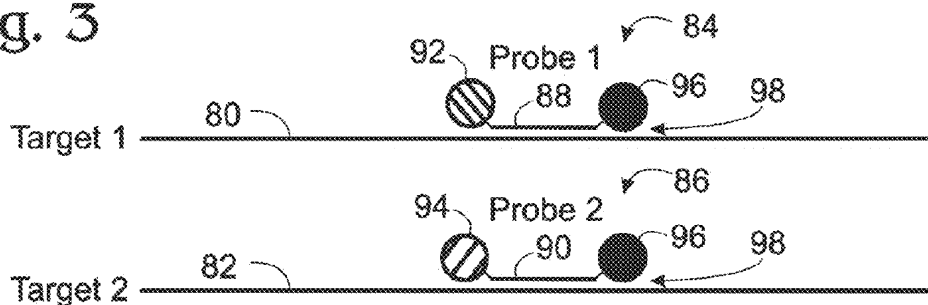
Like others, Saxonov tried to multiplex: “[a] new approach is needed to increase the multiplex levels of digital assays.” EX1004, ¶7, EX2001, ¶73.

Saxonov identified various shortcomings in then-known multiplexing techniques,

such as “instruments with more optical channels, to detect emission from more dyes, are more expensive than those with fewer channels,” and “increasing the number of distinguishable dyes is expensive and becomes impractical beyond a certain number.” EX1004, ¶6, EX2001, ¶73.

Saxonov tried solving this problem using a “common or shared channel (‘the same optical channel’)” to detect signals from “reporters for two or more distinct targets.” EX1004, ¶19; EX2001, ¶74. For example, in FIG. 3, Saxonov illustrates target sequences 80, 82; probes 84, 86 with oligonucleotides 88, 90; and fluorophores 92, 94; when oligonucleotide 88 hybridizes to sequence 80 or oligonucleotide 90 hybridizes to sequence 82, the respective fluorophores separate from quenchers 96 and fluoresce. EX1004, ¶¶48-52, FIG. 3; EX2001, ¶74.

Fig. 3



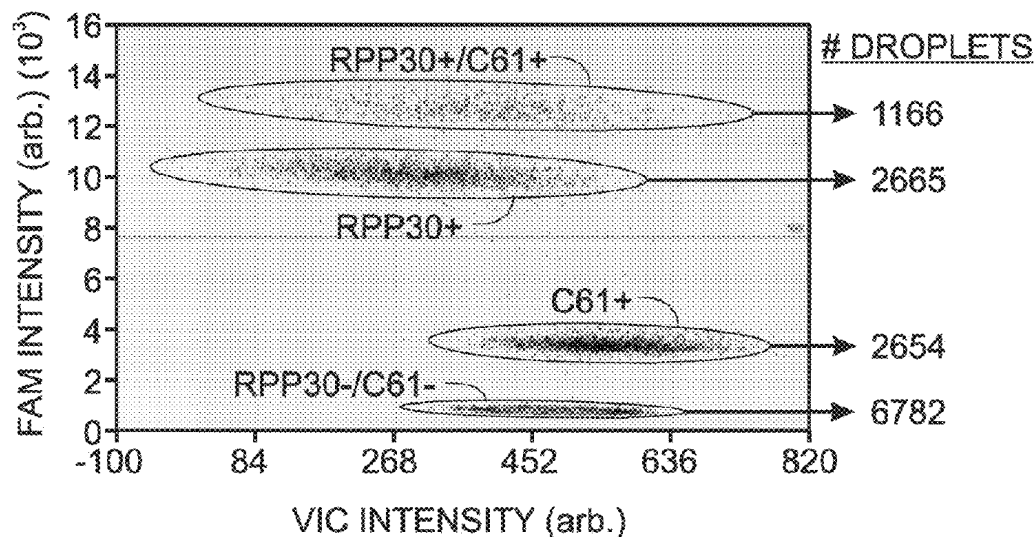
Saxonov describes different ways to distinguish fluorophores’ signals based on intensity, including that “one probe may be labeled with a different number of fluorophores than the other probe,” or “there may be less of one probe than the other in the sample,” or “the fluorophores themselves might be different, with one

more or less intrinsically fluorescent than the other.” EX1004, ¶51; EX2001, ¶75.

According to Saxonov, the partition “may be classified as being positive or negative for each of the reactions/targets contributing to the signal.” EX1004, ¶41; EX2001, ¶75.

Saxonov's FIG. 5 illustrates clusters for a two-analyte system (assaying the C61 and RPP30 genes) in a common channel (the channel for FAM, a fluorophore type). EX1004, ¶¶51, 60, 63, FIG. 5; EX2001, ¶77.

Fig. 5



In FIG. 5, the RPP30-/C61- cluster of 6782 droplets “corresponds to droplets that are negative for RPP30 and C61 (i.e., droplets that did not include either gene).” EX1004, ¶64, EX2001, ¶78. The C61+ cluster of 2654 droplets “corresponds to droplets that are positive for C61 and negative for RPP30 (i.e., droplets that included the C61 gene but did not include the RPP30 gene).”

EX1004, ¶65; EX2001, ¶78. The RPP30+ cluster of 2665 droplets “corresponds to droplets that are positive for RPP30 and negative for C61 (i.e., droplets that included the RPP30 gene but did not include the C61 gene).” EX1004, ¶66; EX2001, ¶78. The RPP30+/C61+ cluster of 1166 droplets “corresponds to droplets that are positive for both RPP30 and C61 (i.e., droplets that included both genes).” EX1004, ¶67; EX2001, ¶78.

FIG. 5 is consistent with Saxonov's digital assay description above and with the “limiting dilution” regime (*supra* §II.A.): 6782 droplets were empty (the majority); $2654+2665=5319$ droplets contained a single analyte (fewer than the number of empty droplets); and 1166 droplets contained both analytes (fewer than the number containing a single analyte). EX2001, ¶79-80.

Saxonov's FIG. 5 is fairly simple because there are only two analytes and four populations or clusters. EX2001, ¶81. According to Saxonov, “data including all permutations of positives will generally fall into 2^N populations or clusters, where N is the number of targets, assuming that each population is distinguishable.” EX1004, ¶41; EX2001, ¶76, 81. Using the tables below, Saxonov shows a single target A ($N=1$) yields two clusters ($2^1=2$); two targets A and B ($N=2$) yield four clusters ($2^2=4$), and three targets A, B, and C ($N=3$) yields eight clusters ($2^3=8$). EX1004, ¶41, EX2001, ¶81.

	Target A	Intensity
Population 2	+	Highest
Population 1	–	Lowest

	Target A	Target B	Intensity
Population 4	+	+	Highest
Population 3	+	–	Intermediate
Population 2	–	+	Intermediate
Population 1	–	–	Lowest

	Target A	Target B	Target C	Intensity
Population 8	+	+	+	Highest
Population 7	+	+	–	Intermediate
Population 6	+	–	+	Intermediate
Population 5	–	+	+	Intermediate
Population 4	+	–	–	Intermediate
Population 3	–	+	–	Intermediate
Population 2	–	–	+	Intermediate
Population 1	–	–	–	Lowest

EX1004, ¶41; EX2001, ¶81.

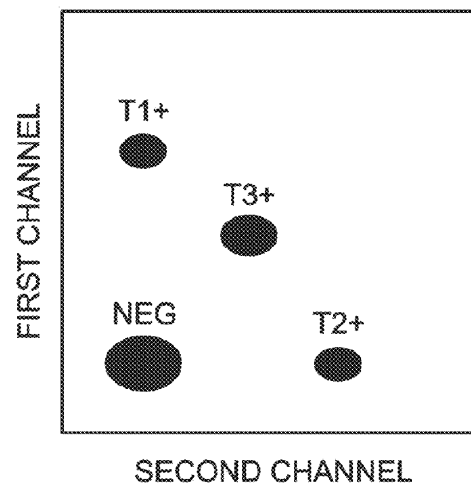
As explained below in §V.A.5., Saxonov's FIGS. 9 and 10 and ¶¶17, 18, 37, and 76-79 were only added on Saxonov's non-provisional filing date and thus are not prior art to the '921 Patent. EX2001, ¶82. Nonetheless, Petitioner relies on the

subject matter of Saxonov's FIG. 10 and ¶¶78-79, which is therefore briefly discussed below.

According to Saxonov, FIG. 10:

is a schematic representation of an exemplary graph showing droplet (or peak) intensities for a T1/T2/T3 droplet assay that may be performed with the droplets of FIG. 9, where data from the T1, T2, and T3 probes are collected in a first optical channel and a second optical channel and plotted as a function of intensity in the first channel (vertical axis) versus intensity in the second channel (horizontal axis), with intensities produced by exemplary populations or clusters of negative (NEG), T1-positive (T1+), T2-positive (T2+), and T3-positive (T3+) droplets represented by filled ellipses[.] EX1004, ¶18, FIG. 10; EX2001, ¶85.

Fig. 10



Saxonov states that in FIG. 10, “[t]o simplify the presentation, double-positive populations (T1+/T2+, T1+/T3+, and T2+/T3+) and the triple-positive population are *not shown*,” but alleges “the populations containing more than one target may be resolved and distinguishable from one another and from the single-target populations and the negative population.” EX1004, ¶¶78-79; EX2001, ¶86.

Examiner Negin examined both the '921 Patent and Saxonov. *See generally* EX2003; EX1004.

E. Related Proceedings

The '921 Patent is the subject of ongoing litigation between PO and Petitioner. On October 5, 2023, ChromaCode, Inc.—the exclusive licensee of the '921 Patent—filed an infringement lawsuit against Petitioner in the Central District of California. EX2010, 6. On October 13, 2023, ChromaCode filed an Amended Complaint, which PO joined as a plaintiff. EX1028. The case was transferred to the Northern District of California and consolidated with another action by ChromaCode seeking declaratory judgment of non-infringement of certain of Petitioner's patents. *See In re: ChromaCode Litig.*, No. 5:23-cv-04823 (N.D. Cal.), Dkts. 71, 73; *ChromaCode, Inc. v. Bio-Rad Labs., Inc.*, No. 5:23-cv-06360 (N.D. Cal.) (“the parallel litigation”), Dkts. 77, 78. The consolidated litigation is pending before Judge Eumi K. Lee.

On March 8, 2024, a Scheduling Order issued in the parallel litigation outlining deadlines for contentions, claim construction briefing, and discovery.

EX2005. Pursuant to the order, ChromaCode and PO served infringement contentions asserting infringement of the '921 Patent on March 21, 2024, and filed a Second Amended Complaint on March 27, 2024. EX2010, 10. The case schedule was amended to accommodate the Second Amended Complaint.

EX1027. Petitioner and PO served damages contentions and responses between March 29, 2024 and August 1, 2024. *See* EX2005, 2-3. Petitioner served invalidity contentions on May 13, 2024, which Petitioner amended on June 17, 2024. EX2006. Petitioner's contentions include invalidity grounds based on Larson and/or Saxonov for claims 1-10, 13-19, and include additional references such as Silverbrook for claims 11-12. EX2006, 20-26. These references are asserted here in Grounds 1-4.

On June 24, 2024, the court entered an ESI order. EX2010, 11. The parties completed *Markman* briefing on August 9, 2024. EX1027; *see also* EX2010, 11. A claim construction tutorial was held on December 3, 2024 and a *Markman* hearing was held on December 12, 2024. EX2013. Fact discovery is well under way, and is set to close on March 12, 2025. EX2015.

III. PERSON OF ORDINARY SKILL IN THE ART

For purposes of this IPR proceeding, PO does not contest Petitioner's description of qualifications for a person of ordinary skill in the art (POSA) set forth at Petition, 9-10.

IV. CLAIM CONSTRUCTION

Petitioner "requests that the Board understand the claims consistent with the apparent interpretations that [PO] is pursuing in parallel district court litigation[.]" Petition, 21-22. Accordingly, the Board should adopt PO's proposed constructions from the parallel litigation as follows:

Claim Terms	PO's Proposed Construction	Support
"non-degenerately," "degenerate" or "degeneracy" '921 Patent Claims 4, 13, 14.	For "degenerate" and "degeneracy": "degenerate" and "degeneracy" generally describe a situation where a legitimate result is not definitive, because it can indicate more than one possibility in terms of the presence or absence of an analyte.	EX1003, 9-11 EX2011, 27-28 EX2012, 18-19

In Grounds 1 and 2, Petitioner points to various allegations in PO's Preliminary Infringement Contentions for the '921 Patent as supposedly affecting how the Board should read the claims for purposes of the Petition. *See* Petition, 24-51. Petitioner's arguments lack merit. PO's preliminary infringement contentions are just that—preliminary. Discovery in the district court litigation is still ongoing, and PO expects to amend and/or supplement its infringement contentions to the extent it determines through fact and/or expert discovery that any such amendment or supplementation is warranted. For example, to the extent an accused product uses a *degenerate*—as opposed to *non-degenerate* encoding scheme—such product would not meet the *non-degeneracy* limitations of the asserted claims. Furthermore, PO's preliminary infringement contentions from a parallel proceeding are, at most, non-binding extrinsic evidence with respect to how claims should be construed in this proceeding. *Great West Casualty Company et. al. v. Intellectual Ventures II LLC*, IPR2015-01706, Paper 69 at 13 (Feb. 14, 2020); see also *Intex Recreation Corp. v. Bestway (USA), Inc.*, 2020 WL 3421699 at *11 (PTAB June 22, 2020) (“We do not regard the infringement contentions in the District Court as a claim construction proposed by Patent Owner in the proceeding before us.”). Such extrinsic evidence “of what a party [allegedly] subjectively thought was a proper construction is of limited value.” *Great West Casualty*, Paper 69 at 13. Accordingly, the Board should decline Petitioner's

invitation to circumvent *Philips* and should, instead, construe the present claims in view of the construction provided above and the intrinsic record. *Id.* (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005)).

V. THE BOARD SHOULD DENY INSTITUTION

A. Saxonov Is Not Prior Art

In Grounds 3 and 4, Petitioner alleges that certain subject matter within Saxonov renders the challenged claims unpatentable. Petition, 21; 51 *et seq.* However, while the two provisional applications to which Saxonov nominally claims priority were filed before the '921 Patent's earliest priority application, the provisional application upon which the Petitioner relies (the Saxonov Provisional) does not actually disclose all of the relied-upon subject matter. Instead, certain relied-upon subject matter was newly added when Saxonov was converted to a non-provisional, and is found ***only*** in the Saxonov non-provisional. Thus, for purposes of Grounds 3 and 4 advanced in the Petition, Saxonov is entitled only to its ***non-provisional*** filing date of July 12, 2012—***after*** the '921 Patent's earliest priority date of February 3, 2012. Because Petitioner's Grounds 3 and 4 rely heavily on the later-added subject matter (which is not prior art), the Board should deny institution for these Grounds.

1. Petitioner's Position on the '921 Patent and Saxonov

Petitioner expressly assumes the '921 Patent's priority claim to February 3, 2012: "For purposes of only this proceeding, it is assumed herein that the '921 patent is entitled to a February 3, 2012, priority date." Petition, 6. This priority date is *before* Saxonov's non-provisional filing date of July 12, 2012, so Petitioner relies on the earlier filing date of the Saxonov Provisional, arguing "Saxonov is §102(e) prior art as of at least the filing of the [Saxonov] provisional, July 20, 2011, because the [Saxonov] provisional supports Saxonov's method of performing a digital assay recited in its claim 1." *Id.*, 13.

2. By Assuming the '921 Patent Is Entitled to Its Earliest-Claimed Priority Date, Petitioner Has Failed to Shift the Burden to Patent Owner to Prove this Entitlement

"The Board cannot adopt arguments on behalf of Petitioner; 'the Board must base its decision on arguments that were advanced by a party.'" *Apple Inc. v. Telefonaktiebolaget LM Ericsson*, IPR2022-00348, Paper 9 at 4 n.2 (PTAB Sept. 21, 2022) (quoting *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016)). Here, Petitioner has not asserted (or even hinted) that the '921 Patent is not entitled to its February 3, 2012 priority date. To the contrary, Petitioner *explicitly assumes* the '921 Patent is entitled to this priority date. Petition at 6. Thus, Petitioner has not challenged the priority date at all, let alone shifted the

burden of production to PO to prove the '921 Patent is entitled to its February 3, 2012 priority date.

The Board's decision in *Ariosa Diagnostics, Inc. v. Illumina, Inc.* is instructive regarding Petitioner's failure to shift its burden on this issue. *See* IPR2014-01093, Paper 69 (PTAB Jan. 7, 2016). There, the challenged '794 patent claimed priority to an application filed before the filing date of petitioner's "prior art" reference—Fan. *Id.*, 3, 5. Fan, though, claimed priority to provisional applications filed before the '794 patent's priority claim. *Id.*, 5-6. The patent owner argued Fan was not prior art because it was not entitled to priority back to its listed provisional applications, it was petitioner's burden to establish Fan was prior art, and petitioner did not meet that burden. *Id.*, 7. Additionally, the patent owner argued petitioner acknowledged the '794 patent's priority claim and did not attempt to demonstrate that the '794 patent was not entitled to that priority date. *Id.*

The *Ariosa* petitioner argued it satisfied its burden to show Fan was prior art by stating Fan was prior art and noting the '794 patent's filing date (which was before Fan's filing date). *Ariosa*, IPR2014-01093, Paper 69 at 12. The petitioner asserted this shifted the burden to the patent owner to demonstrate the '794 patent was entitled to an earlier priority date (its provisional), which the patent owner purportedly failed to do. *Id.*

In holding that petitioner *failed* to show Fan was prior art, the Board noted “there was *no argument* in the Petition that the ’794 patent was not entitled to its earliest possible effective filing date....” *Ariososa*, IPR2014-01093, Paper 69 at 13.³ Thus, the Board found “a fair reading of the Petition would have put Patent Owner on notice, *at best*, that Petitioner was relying on the Fan application with an effective filling date of the [Fan] provisional; but *not* as putting Patent Owner on notice that Petitioner was contending that the ’794 patent was not entitled to priority back to” its provisional filings. *Id.*, 13-14. “Specifically, as Petitioner...*never argued* that the ’794 patent was not entitled to its earliest effective filing date, it did *not* shift the burden of production to [PO] to demonstrate that the ’794 patent was entitled to its earliest effective filling date.” *Id.*, 14.

Ariososa is squarely on point. Here, Petitioner similarly has not argued the ’921 Patent is not entitled to its provisional priority date of February 3, 2012, but instead *assumes* the ’921 Patent *is* entitled to that priority date. Thus—just as in *Ariososa*—Petitioner has not shifted the burden to PO to demonstrate the ’921 Patent is entitled to the February 3, 2012 priority date, which pre-dates Saxonov’s July

³ Emphasis added throughout except where noted.

12, 2012 filing date. In any event, the '921 Patent is indeed entitled to the February 3, 2012 priority date.

3. It Was Petitioner's Burden to Show the Relied-Upon Subject Matter from Saxonov Was Carried Over from the Saxonov Provisional

“In an [IPR], ‘the petitioner is master of its complaint,’ and ‘the petition [is] the center-piece of the proceeding.’” *Telefonaktiebolaget*, IPR2022-00348, Paper 9 at 4 (quoting *SAS Inst., Inc., v. Iancu*, 138 S. Ct. 1348, 1355, 1359 (2020)). “[A] petitioner carries a burden of production to show in its petition that the asserted references qualify as prior art.” *Id.* (citing *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1380 (Fed. Cir. 2015) (explaining that petitioners bear the initial burden to establish that the asserted references qualify as prior art)).

A petition must also identify, “in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim[.]” 35 U.S.C. §312(a)(3); 37 C.F.R. §42.104(b); *see Schlumberger Tech. Corp. v. Dynaenergetics Europe GmbH*, PGR2021-00089, Paper 13 at 40 (PTAB Dec. 14, 2021). Indeed, “[i]t is of the utmost importance that petitioners in IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim.’” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016)

(quoting 35 U.S.C. §312(a)(3)); *Schlumberger*, PGR2021-00089, Paper 13 at 40.

The rules also require that each petition include “[a] full statement of the reasons for the relief requested, including a detailed description of the significance of the evidence including material facts, and the governing law, rules, and precedent.” 37 C.F.R. §42.22(a)(2).

“A reference patent or published patent application can be entitled to the benefit of its provisional application’s filing date for [§]102(e) purposes on two conditions. **First**, the provisional application must provide sufficient support for at least one claim in the reference patent or published patent application.... **Second**, the provisional application must provide sufficient support for the **subject matter relied upon** for prior art purposes in the reference patent or published patent application.” *Google LLC v. Ikorongo Tech. LLC*, IPR2021-00058, Paper 14 at 10-11 (PTAB May 10, 2021) (citing, *inter alia*, MPEP §§2136(I) (9th ed. rev. 10.2019 June 2020), 2136.03(III), 2136); *see also Forescout Techs., Inc., v. Fortinet, Inc.*, IPR2021-01328, Paper 12 at 16-17 (PTAB Jan. 27, 2021).

Regarding the **second** requirement, Petitioner’s burden is to prove the relied-upon subject matter was **also** fully disclosed in a ground reference’s priority application. *See In re Giacomini*, 612 F.3d 1380, 1383 (Fed. Cir. 2010) (“[A]n applicant is not entitled to a patent if another’s patent discloses the same invention, which was carried from an earlier U.S. provisional application or U.S. non-

provisional application.”); *Forescout*, IPR2021-01328, Paper 12 at 8-10 (“[T]he subject matter disclosed in Thomas is **only** available as prior art to the ’421 patent to the extent it **also** is described in the earlier-filed Thomas Provisional. Thus, **[Petitioner] has an initial burden**, not just to compare the challenged claims with the disclosure in Thomas, but **to show that the subject matter that [Petitioner] relies on in Thomas is also found in the Thomas Provisional.**”) (denying institution because Petitioner had not met its initial burden in the Petition); *see also Ex Parte Mann*, 2016 WL 7487271, at *5 (PTAB Dec. 21, 2016) (applying pre-AIA “subject matter test” to hold that “the provisional application must **also** provide support for the subject matter relied upon in the rejection”) (emphasis in original).

Here, Petitioner fails to provide the necessary “full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence,” particularly a detailed explanation of whether the Saxonov Provisional fully discloses **the subject matter relied upon in the Petition**—which is Petitioner’s burden to show that Saxonov qualifies as prior art. *See Schlumberger*, PGR2021-00089, Paper 13 at 41-49 (“Given the multiple instances in which Petitioner relies on subject matter in Sokolove ’009 without a detailed explanation of how either of the two earlier provisional applications support its position, we determine that Petitioner has not adequately identified the grounds and evidence

that support the grounds with the required particularity.”); *Forescout*, IPR2021-01328, Paper 12 at 8-10.

Petitioner attempts to show the Saxonov Provisional supports Saxonov's claim 1 (*i.e.*, the first requirement described in, among other decisions, *Google* and *Forescout*). Petition, 15-17. However, Petitioner does **not** explain how either of the applications to which Saxonov nominally claims priority support the **disclosure** from Saxonov upon which Petitioner's invalidity grounds rely (*i.e.*, Petitioner does **not** satisfy the second requirement of, among other decisions, *Google*, *Forescout*, and *Giacomini*). See Petition, 51-67. In *Telefonaktiebolaget*, the Board explained: “Fatal to the Petition...[,] Petitioner did not establish that the subject matter relied upon for prior art was effectively filed in the provisional applications.... Petitioner does not assert, much less show, that the provisional applications satisfy the subject-matter requirement. Accordingly, Petitioner has not shown that [the asserted references] are entitled to priority dates of their provisional applications, and Petitioner has not shown a likelihood that it would prevail in its challenge to any claims of the [challenged] patent.” *Telefonaktiebolaget*, IPR2022-00348, Paper 9 at 6.

As explained below, this is exactly the case here.

4. Petitioner Failed to Meet Its Burden of Showing the Relied-Upon Material Was Carried Over

When arguing Saxonov renders obvious certain of the '921 Patent's claim limitations, the Petition cites Saxonov Provisional *only once, in a footnote*:

⁴ This approach wherein targets are detected and distinguished from one another based on combinations of colors is similarly taught in the provisional to which Saxonov claims priority, which teaches that signals "can be collected in one or more different channels" from "the same" target. See EX1007 at 9:8-10.

Petition, 59.

To the extent Petitioner argues this single parallel citation to the Saxonov Provisional in a footnote is sufficient to support the second prong of the "carried over" requirement, this argument should be rejected because it contradicts applicable Board decisions. For example, the Board has held that "[a]lthough parallel citations may be sufficient in cases where a provisional application is shown to have identical or nearly identical disclosure to the portions of an application or patent relied upon, in this case, Petitioner has not shown any such identity between [non-provisional] and the...Provisional." *Lyft, Inc. v. Ikorongo Tech. LLC*, IPR2021-00423, Paper 10, at 15–17 (PTAB July 26, 2021) (citing *Unified Patents, Inc. v. Longhorn HD LLC*, IPR2020-00879, Paper 10 at 15–16 (PTAB Nov. 12, 2020)). The same is true here. *Infra* §V.A.5.

The present case readily distinguishes the Board's decisions in, for example, *Illumina, Inc. v. Ravgen*, IPR2021-01271, and *Mastercard, Inc. v. OV Loop, Inc.*, IPR2023-01289, finding petitioners' reliance on citations to provisional applications was sufficient. In *Illumina*, the petitioner showed the non-provisional and provisional disclosures "appear[ed] to be nearly identical" (IPR2021-01271, Paper 12 at 45), whereas here the Saxonov Provisional omits several *key* paragraphs and figures upon which Petitioner relies (*Lyft*, IPR2021-00423, Paper 10 at 15–17 (PTAB July 26, 2021) (petitioner did not meet its burden when it did "not explain sufficiently (let alone explain with particularity) how [] nine disparate pages in the [provisional] sufficiently support the relied-upon subject matter in the five cited paragraphs in [the non-provisional]")). *Infra* §V.A.5.

In *Mastercard*, the petitioner's parallel citations to the provisional were sufficient because the patent owner failed to "identify what subject matter it contends is relied upon by Petitioner that lacks written description support from the...Provisional." IPR2023-01289, Paper 15 at 19 (PTAB March 20, 2024). That is not the case here. Petitioner explains in detail below how the Saxonov Provisional omits the key cited subject matter from Saxonov altogether. *Infra* §V.A.5.

This case is far more akin to *Lyft* because here, just like the petitioner in *Lyft*, Petitioner has utterly failed to meet its burden of explaining with particularity—in

the Petition—how Saxonov Provisional's disclosure supports Petitioner's relied-upon subject matter in Saxonov. *Lyft*, IPR2021-00423, Paper 10 at 15–17.

Petitioner's sole citation to the Saxonov Provisional is insufficient, at least because the Petition “does not explain sufficiently the significance of the citation[] to the...provisional”—if any—and because “determining the significance of the...citations would require [the Board] to play archeologist with the record,” which the Board should decline to do, as it has previously. *Google*, IPR2021-00058, Paper 14, 13–15.

5. The Relied-Upon Subject Matter of Saxonov Was Not Carried Over from the Saxonov Provisional

Petitioner's failure to detail the significance (if any) of the Saxonov Provisional to the claims challenged based on Saxonov is a symptom of a larger problem with the Petition: certain subject matter upon which Petitioner's Grounds 3 and 4 rely was ***not*** carried over from, or fully supported by, the Saxonov Provisional. Thus, for purposes of the grounds, Saxonov is not prior art any earlier than its ***non-provisional*** filing date of July 12, 2012, which was ***after*** the '921 Patent's earliest priority date (February 3, 2012).

For example, FIGS. 9 and 10 of Saxonov are absent from the Saxonov Provisional. EX2001, ¶88. Nor does any disclosure in the Saxonov Provisional, as understood by a POSA, support or disclose the subject matter relied on by

Petitioner from these figures. *Id.* As another example, Saxonov's ¶¶17, 18, 37, 44, 69-71, and 76-80 contain significant new subject matter which is not found in, or supported by, the Saxonov Provisional. *Id.*, ¶89. Grounds 3 and 4 rely upon certain of this ***newly added*** subject matter for the challenged claims, for example as shown below in the table below for Ground 3, claim 1. *See* Petition, 58-61.

Alleged disclosure of Saxonov	Petitioner's citation to subject matter in Saxonov (EX1004) not carried from Saxonov Provisional (EX1007)	Location in Petition of this citation to Saxonov
"Importantly, Saxonov's Figure 10 teaches an approach to detecting three targets based on just two colors, wherein a first target (T1) is identified by a first color signal a second target (T2) is identified by a second color signal, and a third target (T3) is identified by the presence of both color signals."	FIG. 10, ¶¶18, 78-79	58-59

Alleged disclosure of Saxonov	Petitioner's citation to subject matter in Saxonov (EX1004) not carried from Saxonov Provisional (EX1007)	Location in Petition of this citation to Saxonov
"Though the figure [FIG. 10] does not show the signals for the droplets that have multiple targets, Saxonov contemplates that one will be able to distinguish droplets any combinations of targets."	¶78	59
"A POSA would understand that the signals from droplets with different combinations of targets could be easily distinguished based on intensity, just as in Figure 10 of Saxonov."	FIG. 10, ¶78	61

Saxonov's FIG. 10 and ¶¶ 18 and 78-79, upon which Grounds 3 and 4 heavily rely, are **not** carried over from, and not fully supported by, the Saxonov Provisional. EX2001, ¶¶ 87-92. Therefore, Petitioner cannot establish that Saxonov is §102(e) prior art for purposes of Grounds 3 and 4. *Giacomini*, 612 F.3d at 1383; *Forescout*, IPR2021-01328, Paper 12 at 8–10; *Mann*, 2016 WL 7487271, at *5. The Petition's reliance on this very subject matter is not incidental, but **central** to its arguments; *see, e.g.*, Petition, 58 (“[i]mportantly, Saxonov's Figure 10 teaches an approach...”); Petition, 59 (reproducing FIG. 10); Petition, 60 (presenting doctored version of FIG. 10); EX2001, ¶¶ 90-91, 123-131.

Saxonov also claims priority to U.S. App. No. 61/507,082, filed July 12, 2011. EX1004, §(60). However, Petitioner does not indicate (let alone sufficiently explain) any reliance upon the subject matter or priority date of that application. EX2001, ¶92. Instead, Petitioner cites only to the Saxonov Provisional.

Thus, Petitioner fails to establish that Saxonov qualifies as prior art. Because Petitioner relies on Saxonov for Grounds 3 and 4 (and not just incidentally), Petitioner has not demonstrated it is reasonably likely to prevail with respect to Grounds 3 and 4.

B. The Challenged Claims Are Novel and Patentable over the Ground References

The '921 Patent claims are novel and patentable over Larson, whether alone or combined with Saxonov (which does not even qualify as prior art) and/or Silverbrook.

1. Ground 1, Claims 1-10, 13-19: Anticipation by Larson

Petitioner alleges Larson anticipates claims 1-10 and 13-19. Petitioner's arguments lack merit for at least the following reasons.

a. Challenged claim 1 and Larson differ in kind, not just degree

While the '921 Patent and Larson both aim to extend the number of analytes that can be examined simultaneously, they solve these problems in significantly different ways. EX2001, ¶¶98-110.

For example, Larson states it is “based on the singular nature of amplifications at terminal or limiting dilution that arises because most often only a single target allele is ever present in any one droplet even when multiple primers/probes targeting different alleles are present.” EX1017, ¶45; see also *id.*, ¶¶98, 99; EX2001, ¶99. That is, in Larson, the samples are sufficiently diluted that a single analyte is located within a droplet. EX2001, ¶99.

To detect different analytes, Larson extensively dilutes and partitions the sample into numerous droplets such that “some droplets contain zero target nucleic

acid molecules, some droplets contain one target nucleic acid molecule, and some droplets may or may not contain multiple nucleic acid molecules (corresponding to limiting or terminal dilution, respectively, as defined above).” EX1017, ¶52; EX2001, ¶100; *supra* §II.D.1. Droplets with zero analyte provide no information, but inevitably arise by the procedure. EX1017, ¶52; EX2001, ¶100; *supra* §II.D.1. This reduces the number of analytes in a droplet, making it easier to identify the analytes, with the easiest case being that of a single analyte per droplet. EX1017, ¶141; EX2001, ¶100; *supra* §II.D.1.

To the extent that some droplets may have “multiple occupancy” or contain a “heterogeneous population of molecules,” Larson expressly teaches excluding such droplets from analysis, and explains how to do so and the reasons why to do so. EX1017, ¶172; EX2001, ¶101; *supra* §II.D.1.

Larson not only is replete with examples of how to identify a single analyte within a droplet, but repeats this as a key inventive concept; in view of these teachings, a POSA reasonably would have considered this to be Larson’s principle of operation. EX2001, ¶¶102, 68, *quoting* EX1017, abstract, ¶¶7, 8, 11, 13, 18, 19, 20, 45, 46, 49, 68, 99, 100, 101, 107, 141, and claims 1, 3, 10, 11, and 15; *supra* §II.D.1.

Larson’s approach has a number of disadvantages. EX2001, ¶103. For example, as compared with the ’921 Patent’s approach, Larson’s principle of

operation requires partitioning a highly dilute sample into droplets, the majority of which provide no information (because the droplets are empty). *Id.* The significant number of empty droplets reduces the number of samples that can be analyzed in a given period of time, and the amount of information that can be gathered during that time. *Id.* Larson's approach also uses different optimal dilutions for different analytes, under each of which the vast majority of droplets are uninformative, *e.g.*, contain either no molecules or too many molecules. *Id.* Moreover, even different samples containing the same analyte as each other may have different concentrations of that analyte than each other, and none of these dilutions may be knowable in advance. *Id.* And, if any sample contains multiple analytes, the problem becomes even more complicated. *Id.* Additionally, Larson's teaching of excluding droplets containing multiple analytes adds further complexity and time to the assay, requires additional hardware components to perform the sorting, and is wasteful because droplets containing otherwise useful information about multiple analytes in the sample are simply discarded. *Id.*, ¶104.

In stark contrast, the '921 Patent solves the problem of detecting different analytes in a sample by measuring cumulative optical signals using a coding scheme. EX2001, ¶105. By doing so, the '921 Patent's approach—unlike Larson—does not depend on starting concentrations of the analytes. *Id.*

An important feature taught by the '921 Patent is how to choose probe colors and intensities that uniquely determine a given analyte, even if that analyte is mixed with other analytes at the same time. EX2001, ¶106. This avoids a degeneracy problem, where the same intensity values could be consistent for two different analytes. *Id.* For example, if intensity values 1, 2, 4, 8, 16, 32 are chosen for probes read in the same optical channel, every combination of present/absent analytes is unique. *Id.* This method of decoding cumulative signals is different in kind (not just degree) from Saxonov, and makes it much easier to analyze multiplexed samples. *Id.*

Challenged claim 1 recites an assay that is “capable of ***unambiguously*** detecting the presence or absence of each of said at least M analytes, ***in any combination of presence or absence, in a single sample volume***, based on detection of said F wavelength components, when M is greater than F.” EX1001, 67:16-20. Claim 14 of the '921 Patent recites a kit that likewise is “capable of ***unambiguously*** detecting the presence or absence of each of analyte of M analytes in a single sample volume, ***in any combination of presence or absence.***” EX1001, 68:31-34. The claimed assays and kits provide flexibility to detect ***any possible combination*** of the analytes within the single sample solution volume, in such a manner that each analyte may be uniquely distinguished from each other analyte. EX2001, ¶107; *supra* §II.B. At the time of the '921 Patent and its priority

applications, this was a new, non-obvious, and useful solution to the problem of how to increase the number of analytes that could be non-degenerately detected.

EX2001, ¶107; *supra* §II.B.

b. **Larson does not teach how to unambiguously identify three or more analytes within a single sample volume**

Larson teaches various complexities that could arise if two or more analytes are in a droplet, and expressly teaches how to avoid that situation: *diluting* and partitioning the sample into numerous droplets to reduce the likelihood of any droplets having “multiple occupancy,” or containing a “heterogeneous population of molecules,” and *excluding* such droplets. EX2001, ¶108; *supra* §II.D.1.

Moreover, Larson is *silent* as to how to analyze droplets having three or more analytes. EX2001, ¶109. This is because Larson had no need to solve that problem: the single-analyte droplets yielded the information that Larson sought—an identification of whether an analyte was present in the sample—and without having to resolve any of the complications caused by “multiple occupancy.” *Id.* Larson did not contemplate the solution provided by the '921 Patent, because there was no need in Larson to solve the problem of how to *unambiguously detect* three or more analytes. *Id.* Larson's limiting dilution and sorting/exclusion entirely avoided this issue. *Id.*

Indeed, the Petition itself states that “under *these* conditions”—that is, under the conditions of “terminal dilution, where the probability of a single target molecule in droplets is much greater than, and overwhelms that of multiple targets”—the detectable signal generated for each potential analyte in Larson is “distinct and readily distinguishable, providing ‘unambiguous’ detection of the analytes.” Petition, 29; EX2001, ¶109.

Petitioner appears to argue the ‘921 Patent claims are invalid because they are being asserted against assays and kits that purportedly resemble those described in ¶140 of Larson. *See, e.g.*, Petition at 27-32; EX2001, ¶110. This argument lacks merit for the reasons discussed at *supra* §V.B.1.a. Furthermore, as discussed above, claims 1 and 14 of the ‘921 Patent, and claims respectively depending therefrom, differ from Larson in several material aspects which go to the very core of Larson’s express teachings, inventive concepts, and principle of operation. EX2001, ¶¶98-110.

Accordingly, Petitioner fails to establish a reasonable likelihood they will prevail on Ground 1.

2. Ground 2 (Claims 2, 4, 6-7, and 14-19)

The Petition identifies dependent claims 2, 4, 6-7, and 14-19 as allegedly being obvious over Larson. Petition, 44-51. However, the many material differences between Larson and claim 1 described *supra* §V.B.1.a-b apply equally

to claims 2, 4, 6-7 depending from claim 1, independent claim 14 which recites similar limitations as discussed *supra* for claim 1, and claims 15-19 depending from claim 14. EX2001, ¶111.

In any event, Petitioner's remarks regarding claim 14 seem to amount to an argument that the word "kit" is not limiting, and that "it would have been obvious to combine the components disclosed in Larson together in a 'kit.'" Petition, 50-51; EX2001, ¶112. Such limited argumentation does not adequately explain why a POSA would have found it obvious to attempt to obtain the kit which is recited in claim 14, and in claims depending therefrom, based on the teachings of Larson considered as a whole (that is, including Larson's express teachings regarding diluting and partitioning the sample and excluding droplets containing more than one analyte), for at least the reasons set forth herein. EX2001, ¶112.

3. Ground 3 (Claims 1-10 and 12-19): Obviousness in view of Larson and Saxonov.

Petitioner's arguments in Ground 3 differ from those in Grounds 1 and 2, in that Ground 3 is based on the allegation that "Larson, alone or in combination with Saxonov, at a minimum renders obvious the 'unambiguous' detection of the 'presence or absence' of multiple analytes in such individual subvolumes." Petition, 51; EX2001, ¶113. However, Petitioner's theory in Ground 3 is even more misguided than in Grounds 1 and 2, because both Larson and Saxonov teach

something very different from what the '921 Patent claims recite. EX2001, ¶¶113-138.

a. Larson Eliminates the Very “Multiple Occupancy” Situations to Which Petitioner Points

Petitioner's Ground 3 alleges Larson teaches “that there may be multiple targets in a single individual droplet and that its methods accommodate such ‘multiple occupancy’ situations” and states “Larson's assays use conditions and parameters that do precisely this.” Petition, 52, *citing* EX1017, ¶¶129, 141 and EX1002 ¶321. However, Larson's *actual* accommodation of “‘multiple occupancy’ situations” is *incompatible* with an assay that is capable of unambiguously detecting the presence or absence of each of said at least M analytes, *in any combination of presence or absence, in a single sample volume*. EX2001, ¶114; *see* EX1001, 67:16-20, 68:31-34.

Indeed, a POSA considering Larson's ¶141 (cited in the Petition) and Larson as a whole, readily would have understood that Larson's statement “methods of the invention can accommodate these complications arising from multiple occupancy” refers to the strategies Larson *actually discloses*. EX2001, ¶¶45-68, 115. *First*, the POSA would have understood Larson's statement refers to increasing sample dilution as the number of analytes increases, to reduce the probability that one probe overlaps any of the other probes – that is, to reduce the probability that any

droplet contains even two analytes, let alone more than two. EX2001, ¶¶45-55, 115-116; *supra* §II.D.1.; Petition, 52 (*citing* EX1017, ¶129). ***Second***, the POSA would have understood Larson's statement refers to detecting, sorting away, and excluding droplets containing a heterogeneous population of molecules based on how many signals (one or two) each droplet produces, EX2001, ¶¶56-68, 115; *supra* §II.D.1. For at least these reasons, if a POSA wished to "accommodate" multiple occupancy situations, the full teachings of Larson would, at most, have motivated that POSA to try to ***eliminate*** such multiple occupancy situations by ***diluting*** the sample to reduce the probability that any droplet contains two or more analytes, and to ***exclude*** droplets containing two or more analytes. EX2001, ¶¶115-116. Such teachings of Larson do not render it at all obvious to instead ***try to obtain, and analyze, droplets that may obtain all possible different combinations of analytes.*** *Id.*

b. Larson does not teach or suggest analyzing multiple targets in a single droplet

Other portions of Ground 3 similarly try to contort Larson's express disclosure into something Larson clearly teaches away from. EX2001, ¶118. For example, Petitioner points to Larson's FIG. 9 as allegedly showing an "assay involving three targets and two colors, wherein one color is used to identify two of the targets and a second color identifies the third target," and alleges this "coding

scheme allows for determination of precisely which targets are present in a droplet *even when multiple targets are present in a droplet.*” Petition, 55-56; EX2001, ¶118. But again, as amply established herein, Larson expressly teaches *excluding* multiple-analyte droplets from analysis in order to *avoid* “complications” that arise in such droplets—not merely in a few selected examples, but as a core inventive concept and principle of operation. EX2001, ¶¶45-68, 118; *supra* §II.D.1.

Petitioner further alleges that from Larson’s FIG. 9C, a POSA:

would have understood that the various combinations of analytes would result in distinguishable signals for the three analytes because the signals from P_1 , P_2 , P_3 , P_1+P_2 , P_1+P_3 , P_2+P_3 , $P_1+P_2+P_3$, and so on have different intensities as the combinations are additive and would each sum to unique values in each of the two colors used.

Petition, 57, citing EX1002, ¶336; EX1017 FIG. 9C; EX2001, ¶¶45-68, 119.

Here, Petitioner and Dr. Batt hypothesize what scenarios “would result in distinguishable signals” from droplets containing different combinations of three analytes, and allege that the “foregoing coding scheme” is “[c]ritically, consistent with Larson’s teaching that its assays can accommodate ‘multiple occupancy.’” Petition, ¶56, citing EX1002, ¶¶335-337; EX2001, ¶119. But contrary to what is alleged, the scheme is not at all “consistent” with Larson’s teachings regarding

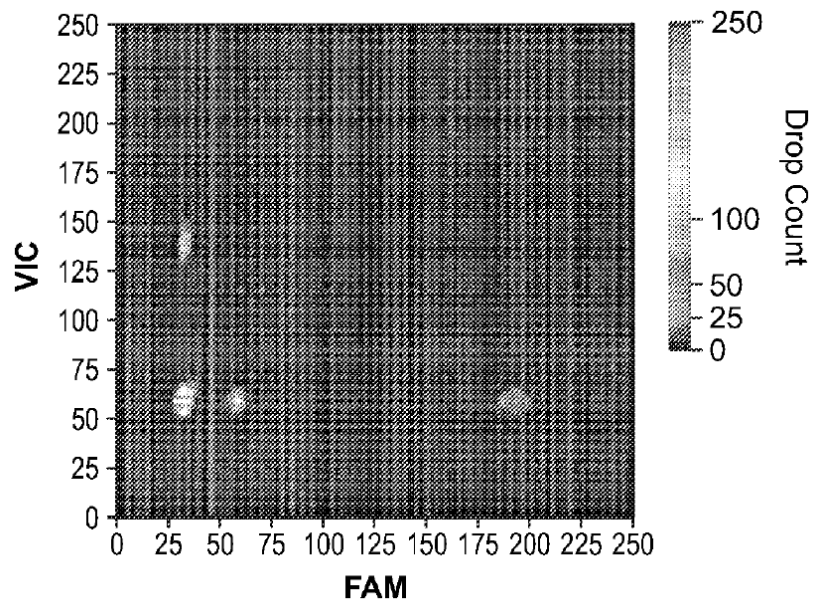
“multiple occupancy,” and indeed the Petitioner and Dr. Batt conveniently ignore the fact that Larson expressly *excludes* analyzing signals from droplets containing multiple analytes precisely *because* those droplets produce two signals (among other complications that Larson teaches arise within multiple-analyte droplets).

EX2001, ¶¶45-68, 119.

Even while Petitioner and Dr. Batt point to Larson's FIG. 9C, they conveniently ignore Larson's FIG. 9D:

FIG. 9D

Histogram showing four populations of droplets; with target1, with target2, with target3 and without any of the three targets.



EX1017, FIG. 9D; EX2001, ¶120.

According to Larson, FIG. 9D illustrates a “[h]istogram showing four populations of droplets; with target1, with target2, with target3 and without any of the three targets.” EX1017, ¶121; EX2001, ¶120. FIG. 9D does not disclose, and

indeed clearly *omits*, any clusters containing both target1 and target2, any clusters containing both target1 and target3, any clusters containing both target2 and target3, and any clusters containing all three targets. EX2001, ¶120. Accordingly, what appears to be actual data from Larson is entirely consistent with the interpretation of the reference as set forth *supra* §II.D.1., and not at all consistent with Petitioner's conjectures about what "would result" if Larson's teachings *were not actually followed*. EX2001, ¶¶45-68, 120. And, fatal to Petitioner's theory, nothing in Larson would have led a POSA to ignore Larson's express teachings—and indeed, to modify Larson's principle of operation—to try to obtain the scheme Petitioner proposes. EX2001, ¶¶120, 68 (*quoting* EX1017, abstract, ¶¶7, 8, 11, 13, 18, 19, 20, 45, 46, 49, 68, 99, 100, 101, 107, 141, and claims 1, 3, 10, 11, and 15; *supra* §II.D.1); *see Plas-Pak Industries, Inc. v. Sulzer Mixpac AG*, 600 Fed.Appx. 755, 758 (Fed. Cir. 2015) (finding that "combinations that change the 'basic principles under which the [prior art] was designed to operate,' . . . or that render the prior art 'inoperable for its intended purpose,' . . . may fail to support a conclusion of obviousness") (citing *In re Ratti*, 46 CCPA 976, 270 F.2d 810, 813 (1959); *In re Gordon*, 733 F.2d 900, 902 (Fed.Cir.1984)).

- (1) **Saxonov does not teach or suggest unambiguously analyzing three or more targets in a single droplet**

Similar to Larson, Saxonov also tried to extend the number of analytes that can be simultaneously identified in an assay. EX2001, ¶121. For example, Saxonov tried to use the “same optical channel” to detect different analytes, ostensibly to reduce the cost of additional optical channels and optical dyes. EX2001, ¶121, *supra* §II.D.2. And, like Larson, to detect different analytes, Saxonov extensively diluted and partitioned the sample into numerous droplets such that most droplets are empty (contain zero analyte molecules), and the next largest population of droplets contains a single analyte. EX2001, ¶121, *supra* §II.D.2. Saxonov is also replete with examples of how to identify a single analyte molecule within a droplet. EX2001, ¶121; *supra* §II.D.2. Indeed, for detecting multiple analytes in the same optical channel, droplets containing only a single analyte molecule are key to Saxonov's method. EX2001, ¶121, *supra* §II.D.

Because of the Poisson distribution, it is inevitable that some droplets will contain two analyte molecules, or even more than two (with frequency dropping quickly as dilution increases). EX2001, ¶122; *supra* §II.D.2. But such droplets are unnecessary in Saxonov's method for obtaining the desired results, because single-molecule droplets unambiguously provide the data Larson desires. EX2001, ¶122; *supra* §II.D.2.

Although Saxonov's FIG. 10 and ¶¶ 18 and 78-79, upon which Grounds 3 and 4 heavily rely, are **not** carried over from, and not fully supported by, the

Saxonov Provisional (*see* §V.A.5.), these very portions of Saxonov highlight Saxonov's deficient teachings in how to obtain meaningful information, from double-positive and triple-positive droplets. EX2001, ¶123.

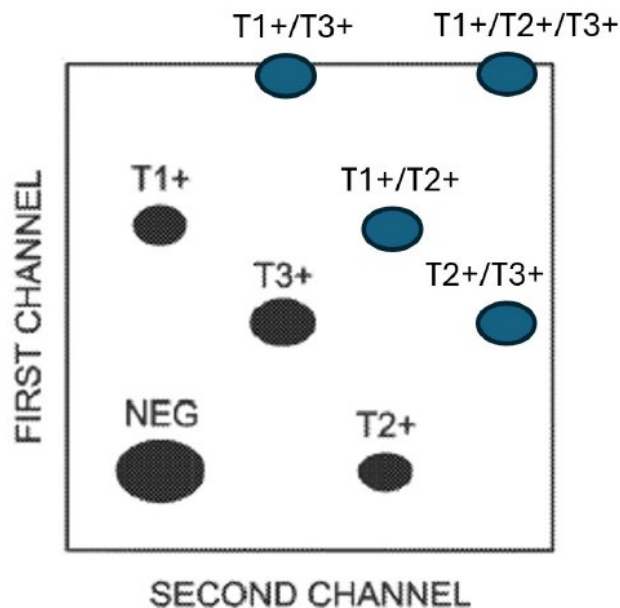
For example, Saxonov states that double-positive populations (T1+/T2+, T1+/T3+, and T2+/T3+) and the triple-positive population (T1+/T2+/T3+) in FIG. 10 are not shown “[t]o simplify the presentation” but “may be resolved and distinguishable from one another and from the single-target populations and the negative population.” EX2001, ¶124; EX1004, ¶¶78-79. Yet, Saxonov does not actually explain *how* populations of droplets that contain three or more analytes might actually be “resolved and distinguishable from one another”—let alone in the specific manner recited in the '921 Patent claims. EX2001, ¶124; EX1004, ¶¶78-79.

Saxonov's ¶20 further confirms that Saxonov did not really know, or teach, how to distinguish clusters of multi-analyte droplets—whether in one channel or multiple channels: “[t]hree targets, two in a first channel and one in a second channel, would again generate eight clusters or populations of data, but they would be separated in a two-dimensional intensity space *and so in principle more easily resolvable*.” EX2001, ¶125; EX1004, ¶20. This falls far short of teaching a POSA that the clusters are *actually* resolvable, let alone how to design the probes such

that the clusters not only are resolvable but are *unambiguously* detected. EX2001, ¶125.

Moreover, Petitioner proffers the following fabricated version of Saxonov's FIG. 10, which includes the double-positive and triple-positive clusters that Saxonov did not actually illustrate (*i.e.*, Petitioner's figure did *not* actually appear in Saxonov). EX2001, ¶126.

Fig. 10

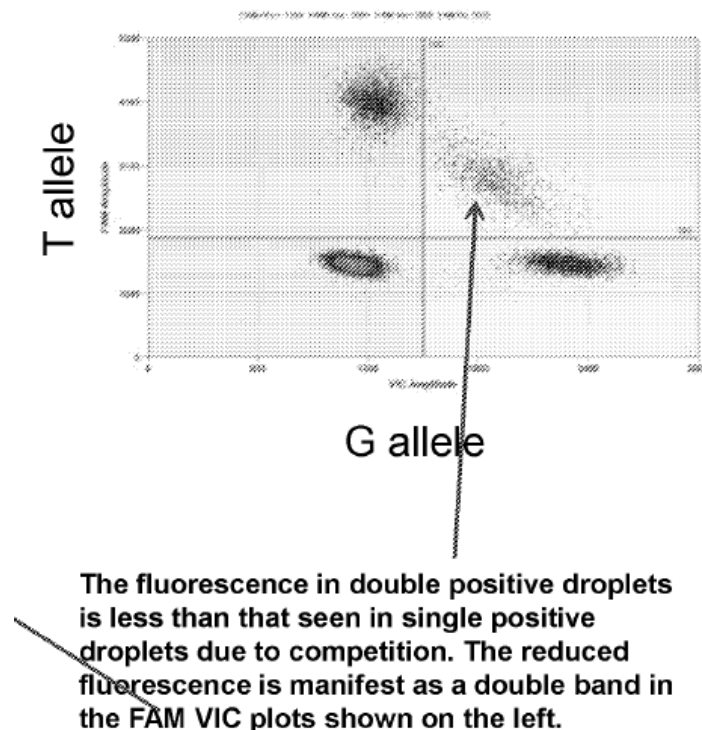


Petition, 60; EX2001, ¶126.

Here, Petitioner adds double-positive clusters T1+/T3+, T1+/T2+, T2+/T3+, and triple-positive cluster T1+/T2+/T3+, and states that “[a]s this modified figure shows, any combination of three targets may be uniquely identified.” Petition, 60; EX2001, ¶127. However, Petitioner does not explain its basis (if it had any) for

alleging the particular cluster locations added to FIG. 10. EX2001, ¶127. Instead, Petitioner's expert merely concludes that "this representation shows how easily each of three targets, however they may be distributed in droplets, are to identify." EX1002, ¶343; EX2001, ¶127.

The Board should not accept Petitioner's fabricated representation, for example because the Saxonov Provisional actually shows a double-positive result in a different location than Petitioner asserts. More specifically, the Saxonov Provisional shows a plot of two analytes (here, the T and G alleles) in two channels, plus an arrow and annotation:



EX1007, 58; EX2001, ¶128.

A POSA would have understood the lower right cluster to be “single positive” for the G allele and the upper left cluster to be “single positive” for the T allele. EX2001, ¶129. The Saxonov Provisional refers to the middle cluster (where the arrow points), as “[t]he fluorescence in *double positive* droplets.” EX1007, 58; EX2001, ¶130. A POSA would readily have understood that this double-positive cluster does *not* occur at a location corresponding to the neat and simple sum of the single positive clusters (as Petitioner's modified FIG. 10 represents), but instead is shifted to another location because of reduced fluorescence “*due to competition*.” EX1007, 58; EX2001, ¶130. Accordingly, a POSA would have expected double-positive and the triple-positive clusters (if any) to occur in *different locations* than Petitioner's modified FIG. 10 asserts. EX2001, ¶130. Accordingly, this modified figure (and Petitioner's discussion thereof, and reliance thereon) should be disregarded as fiction.

(2) Combining Larson with Saxonov falls short of the claimed subject matter

For the reasons set forth above, Saxonov and Larson are both materially deficient in teaching everything recited in the '921 Patent's claims 1 and 14. *Supra* §§II.B., II.D., V.B.1-3.b.(1); EX2001, ¶132. Nonetheless, Petitioner and its proffered expert try to rationalize why it would have been obvious to combine the references to obtain the '921 Patent claims. Petition, 58-61; *citing* EX1002, ¶¶339-

348. But even if Larson were combined with Saxonov for any reason (whether for Petitioner's proffered reason or otherwise), the resulting combination falls far short of what the '921 Patent claims. EX2001, ¶¶132-137.

For example, Petitioner uses Larson's "multiple occupancy" problem to try to justify combining Larson with Saxonov:

Incorporating Saxonov's teachings that droplets with different combinations of targets can be "separated by intensity" would have been a no-brainer and something a POSA would have been highly motivated to extract the most information possible from the experiment and address "multiple occupancy" situations.

Petition, 61, citing EX1002, ¶¶344-346; EX2001, ¶133.

The cited section of Dr. Batt's Declaration elaborates somewhat on Petitioner's position:

A POSA would have been highly motivated to do this as well, as discussed, to acquire the maximum amount of information from this kind of costly equipment...but also to adequately deal with the "multiple occupancy" situations that Larson discusses arise when loading targets into droplets with a Poisson distribution. See, e.g., EX1017¶¶ 129, 140-141. EX1002, ¶346; EX2001, ¶133.

However, to emphasize yet again, Larson teaches addressing the “multiple occupancy” problem as follows: *diluting* and partitioning the sample into numerous droplets to reduce the likelihood of any droplets ever containing two or more analytes, and using sorting to *exclude* any droplets with “multiple occupancy” or containing a “heterogeneous population of molecules.” EX2001, ¶134; *supra* §II.D.1.

Accordingly, if a POSA wished to address the “multiple occupancy” problem, the teachings of *both* Larson *and* Saxonov would have led them to attempt to *dilute* the sample further to reduce the occurrence of “multiple occupancy.” EX2001, ¶135; *supra* §II.D. And, to the extent that there were still droplets with “multiple occupancy,” the teachings of Larson would have led the POSA to use sorting to *exclude* any such droplets. EX2001, ¶135; *supra* §V.B.3.a. As such, nothing in Larson or Saxonov would have rationally motivated a POSA to try to modify Larson to *increase* the number of “multiple occupancy” droplets, e.g., by *increasing* concentration and/or by *not* excluding “multiple occupancy” droplets, which seem to be the only way any “multiple occupancy” droplets could be obtained by modifying Larson’s methods. EX2001, ¶135. And, fatal to this ground, Petitioner fails to explain why a POSA would have changed Larson’s entire principle of operation in such a manner. *Plas-Pak*, 600 Fed.Appx. at 758; EX2001, ¶135.

Moreover, a POSA would not even have been motivated to combine Larson and Saxonov, because Saxonov does not add any meaningful teachings to Larson. EX2001, ¶136. Petitioner admits Saxonov, like Larson, teaches loading droplets with targets according to the Poisson distribution. Petition, 58; EX2001, ¶136. Petitioner argues a POSA would have been motivated to combine the references' teachings because "Larson already teaches the same approach utilized in Figure 10 of Saxonov[.]" Petition 58-61; EX2001, ¶136. But Saxonov provides no additional teachings that cure Larson's deficiencies, and Petitioner does not identify any such fadditional teachings of Saxonov. Petition 58-61; EX2001, ¶¶132-136. Furthermore, a POSA would not have been motivated to combine the teachings of Larson and Saxonov because Saxonov would not have added anything meaningful and thus the combination would have been pointless. EX2001, ¶136.

Thus, Petitioner has failed to establish a reasonable likelihood that they will prevail on Ground 3.

4. Ground 4 (Claim 11): Obviousness In View of Larson, Saxonov, and Silverbrook

Petitioner alleges claim 1 is obvious over Larson combined with Saxonov and Silverbrook. Petition, 66-67. Sections V.B.1-5, *supra*, establish that claim 1 is not obvious over Larson in view of Saxonov. Even assuming Silverbrook teaches what Petitioner alleges (it does not), Petitioner has not explained how it cures

Larson's and Saxonov's many deficiencies detailed above. *See supra* §§V.B.1-5.

Thus, Petitioner has failed to show it has a reasonable likelihood of prevailing on Ground 4. EX2001, ¶138.

C. The Board Should Deny Under §314(a) and *Fintiv*

Overall, the *Fintiv* factors weigh in favor of discretionary denial.

1. Factor 1: Likelihood of a Stay

This factor is neutral. While Petitioner asserts “[t]his factor weighs in favor of institution because Petitioner will seek a stay if IPR is instituted and stays are favored in the Northern District of California” where the parallel action is pending (Petition at 70), the Board should “decline to speculate on how the district court might rule on a motion that has not been filed...[and] assess this factor as neutral” (*Carrier Fire & Security Ams. Corp. v. Sentrilock, LLC*, IPR2021-00665, Paper 12 at 8 (PTAB Sept. 16, 2021)). *See also Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15 at 12 (PTAB May 13, 2020) (“A judge determines whether to grant a stay based on the facts of each specific case as presented in the briefs by the parties. We decline to infer, based on actions taken in different cases with different facts, how the District Court would rule should a stay be requested by the parties in the parallel case here. This factor does not weigh for or against discretionary denial in this case.”); *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 14 (PTAB Dec. 1, 2020) (“Because the District Court has not ruled on the pending

motion to stay, we determine that this factor does not weigh for or against denying institution in this case.”); *Zomm, LLC v. Apple Inc.*, 391 F. Supp. 3d 946, 956 (N.D. Cal. 2019) (“Courts...must evaluate stay requests on a case-by-case basis.”); *see also Precision Planting LLC v. Maschio Gaspardo S.p.A.*, IPR2024-00008, Paper 12 at 16 (PTAB Mar. 26, 2024).

2. Factor 2: Proximity of Trial Date to a Final Written Decision

This factor weighs in favor of denial. Under PO's proposed schedule in the parallel litigation, trial will commence in the first half of January 2026, even assuming the district court does not issue a *Markman* order until two months after the hearing, which took place on December 12, 2024. *See* EX2014 at 18-20; EX2013. Thus, under PO's schedule, the Board's deadline to issue a final decision—March 30, 2026—is after the parallel litigation's trial will commence. This favors discretionary denial. *Fintiv*, IPR2020-00019, Paper 15 at 13 (factor 2 weighed in favor of denial where trial was scheduled to begin before FWD deadline). Moreover, to the extent Petitioner may argue that this factor does not favor denial because the district court has not set a trial date, this factor is not dispositive, and because all the factors must be weighed to determine the overall balance of the factors, the Board should still deny institution. *Fintiv*, IPR2020-00019, Paper 11 at 5, 9 (PTAB Mar. 20, 2020).

3. Factor 3: Investment in the Parallel Litigation

This factor also weighs in favor of denial. In *Fintiv*, the Board found this factor weighed somewhat in favor of denial in circumstances similar to those here. *See Fintiv*, IPR2020-00019, Paper 15 at 13–14. Particularly, contentions were served, the court had held a *Markman* hearing, fact discovery was in early stages, document production was ongoing, depositions were in early stages, expert reports were not due yet, and substantive motion practice was yet to come. *Id.* Thus, “the parties and the Court [had] invested effort in the District Court case..., [and while] further effort remain[ed] to be expended in this case before trial[,] [b]ased on the level of investment and effort already expended on claim construction and invalidity contentions in the District Court, this factor weighs somewhat in favor of discretionary denial in this case.” *Id.*; *see also Sand Revolution II, LLC v. Cont’l Intermodal Group – Trucking LLC*, IPR2019-01393, Paper 24 at 10–11 (PTAB June 16, 2020) (similar).

Here—as of the time of this filing—similar to *Fintiv* and *Sand Revolution*, ChromaCode and Caltech have served infringement contentions, Petitioner and Caltech have exchanged damages contentions, Petitioner has served invalidity contentions, the court has entered an ESI order, the court held a *Markman* hearing, and fact discovery is ongoing. Thus, while additional work remains, the parties

and the court have invested in the case, including but not limited to invalidity and claim construction.

This case will progress even further between now and when the Board decides institution, which is the proper time to assess this factor. *See T-Mobile USA, Inc. v. Wireless Alliance, LLC*, No. IPR2024-00607, Paper 16 at 11 (PTAB Sept. 10, 2024) (“We consider now the amount and type of work that will have already been completed in the parallel litigation by the court and the parties at the time of our institution decision.”). Particularly, the parties are well into fact discovery, which will continue to progress and which PO expects will close on within a few months of the court’s *Markman* order issuing. *Supra* §II.E. PO expects exchange of opening and rebuttal expert reports will be completed shortly thereafter. *See id.* The institution decision here is expected in the end of March 2025. “Because the Markman hearing [was] completed prior to the time of the institution decision and discovery will have proceeded to an advanced stage...by the time of this Decision, [the Board should] find that factor 3 weighs in favor of exercising discretion to deny institution.” *T-Mobile USA, Inc. v. Cobblestone Wireless, LLC*, IPR2024-00136, Paper 18 at 16–17 (PTAB June 5, 2024).

4. Factor 4: Overlap of Issues

In the parallel litigation—just as in the Petition—Petitioner contends the ’921 Patent claims are invalid as anticipated and obvious based on Larson alone,

and as obvious based on combinations of Larson, Saxonov, and/or Silverbrook⁴, as asserted here. *Compare, e.g.*, EX2008, EX2009, and EX2006 at 20-26 with Petition at 21. “[B]ecause the identical claims are challenged based on the same prior art in both the Petition and in the District Court, this factor weighs in favor of discretionary denial in this case.” *Fintiv*, IPR2020-00019, Paper 15 at 15.

While Petitioner asserts this factor is neutral given the “extensive additional art and issues” being litigated in the district court, Petitioner does not cite any authority to support this position. Petition, 73. Regardless of whether the ground references here are a subset of those Petitioner asserts in parallel litigation, the reality is that there is overlap. Moreover, Petitioner has not filed a *Sotera* stipulation. Thus, “as no *Sotera* stipulation has been filed and the same art and overlapping claims are at issue in the related cases, this factor weighs in favor of denial.” *Commscope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01293, Paper 18 at 15 (PTAB March 9, 2023).

⁴ In its invalidity contentions, Petitioner asserts Saxonov is prior art under §102(g) (*see, e.g.*, EX2006, 4), but in the claim charts appended to the contentions, Petitioner relies on the published Saxonov application relied on in the grounds here (*compare, e.g.*, EX2008 with Petition, 11).

5. Factor 5: Whether Petitioner Is the Defendant in the Parallel Litigation

Bio-Rad is both Petitioner here and defendant in the parallel litigation.

“Because the petitioner and the defendant in the parallel proceeding are the same party, this factor weighs in favor of discretionary denial.” *Fintiv*, IPR2020-00019, Paper 15 at 15; *see also Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 19 (PTAB Dec. 1, 2020) (“Petitioner and Patent Owner acknowledge the parties are the same in the *inter partes* proceeding and in the parallel proceeding. Thus, this factor supports denying institution.”); *Commscope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01293, Paper 18 at 15–16 (PTAB March 9, 2023) (“Petitioner is the defendant in several of the parallel proceedings. Petitioner does not dispute this. This factor weighs in favor of exercising our discretion to deny the Petition.”) (citations omitted); *T-Mobile*, IPR2024-00607, Paper 16 at 15 (“[W]e determine, applying Board precedent, that this factor weighs in favor of a discretionary denial” “where the parties in the parallel litigation are the same as in the *inter partes* proceeding.”) (internal quotation marks and citations omitted). Bio-Rad asserts that because this is common, this factor is neutral, but cites no supporting authority. Petition at 73.

6. Factor 6: Other Circumstances, Including the Merits

This factor favors denial at least because Petitioner has not demonstrated it is “highly likely” to prevail with respect to at least one challenged claim. “[A] full analysis of the merits is not necessary to evaluate this factor. It is sufficient that Patent Owner has pointed out that Petitioner’s case...is a close call.... [If so,] [t]he merits, taken as a whole, do not tip the balance in favor of Petitioner and instead also weigh in favor discretionary denial in a balanced assessment of all the circumstances.” *Fintiv*, IPR2020-00019, Paper 15 at 17.

“As [Director Vidal’s] Guidance Memo and [the Board’s] precedential decision in *OpenSky* make clear, the compelling merits standard is a **higher standard** than the standard for institution set by statute.” *Commscope*, IPR2022-01242, Paper 23 at 3; *OpenSky Indus., LLC v. VLSI Tech. LLC*, IPR2021-01064, Paper 102 at 49 (PTAB Oct. 4, 2022) (precedential). “A challenge can only ‘plainly lead to a conclusion that one or more claims are unpatentable’ if it is **highly likely** that the petitioner would prevail with respect to at least one challenged claim.” *Commscope*, IPR2022-01242, Paper 23 at 3–4 (quoting *OpenSky*, IPR2021-01064, Paper 102 at 49). “The patent system and the public benefit from instituting challenges where there is a showing of unpatentability by compelling merits, but it is **only** a finding under this **higher standard** that would

compel the Board to review claims for the public benefit when other considerations favor discretionary denial.” *Commscope*, IPR2022-01242, Paper 23 at 4.

Accordingly, each *Fintiv* factor either weighs in favor of denial or is neutral. Thus, even if the Board finds Petitioner has demonstrated a reasonable likelihood of successfully invalidating any of the '921 Patent's claims (which Petitioner has failed to do, see §§V.A–B), the Board should nevertheless exercise its discretion in view of *Fintiv* and deny institution.

VI. CONCLUSION

For at least these reasons, the Board should deny institution.

Respectfully submitted,

SHEPPARD, MULLIN,
RICHTER & HAMPTON LLP

/Jesse A. Salen/

Jesse A. Salen (Reg. No. 72,209)
Counsel for Patent Owner
California Institute of Technology

Date: December 30, 2024

12275 El Camino Real, Suite 100
San Diego, CA 92130
Tel: (858) 720-8900
Fax: (858) 509-3691

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on December 30, 2024, a copy of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE was filed through the Patent Trial and Appeal Case Tracking System (P-TACTS) and was served via Federal Express and E-Mail on the Petitioner at the following correspondence address provided by counsel of record for the Petitioner pursuant to 37 C.F.R. § 42.8(b)(4):

Derek C. Walter
Adrian C. Percer
WEIL, GOTSHAL AND MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
derek.walter@weil.com
adrian.percer@weil.com

Respectfully submitted,

SHEPPARD, MULLIN,
RICHTER & HAMPTON LLP

/Jesse A. Salen/

Jesse A. Salen (Reg. No. 72,209)
Counsel for Patent Owner
California Institute of Technology

Date: December 30, 2024

12275 El Camino Real, Suite 100
San Diego, CA 92130
Tel: (858) 720-8900
Fax: (858) 509-3691

**CERTIFICATE OF COMPLIANCE WITH
TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS,
AND TYPE STYLE REQUIREMENTS**

1. This Petition complies with the type-volume limitation of 14,000 words, comprising 13,523 words, as counted using the Microsoft Word software that was used to prepare this paper, excluding the parts exempted by 37 C.F.R. § 42.24(a).

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

Respectfully submitted,

SHEPPARD, MULLIN,
RICHTER & HAMPTON LLP

/Jesse A. Salen/

Jesse A. Salen (Reg. No. 72,209)

Counsel for Patent Owner

California Institute of Technology

Date: December 30, 2024

12275 El Camino Real, Suite 100
San Diego, CA 92130
Tel: (858) 720-8900
Fax: (858) 509-3691