

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 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>
I. INTRODUCTION	1
II. BACKGROUND	2
A. Technology	2
B. The '921 Patent and the Challenged Claims	7
C. The '921 Patent's Prosecution History	13
D. The Ground References.....	15
1. Larson.....	16
E. Related Proceedings	23
III. PERSON OF ORDINARY SKILL IN THE ART	23
IV. CLAIM CONSTRUCTION	24
V. PETITIONER HAS FAILED TO DEMONSTRATE THE CHALLENGED CLAIMS ARE UNPATENTABLE	27
A. The Challenged Claims Are Novel and Patentable over the Ground References.	27
1. Ground 1, Claims 1-10, 13-19: Anticipation by Larson.....	27
a. The challenged claims and Larson differ in kind, not just degree.....	27
b. Petitioner failed to show that a POSA would interpret Larson as disclosing how to unambiguously identify any combination of M analyte molecules within the single sample volume in which amplification is performed.....	32
c. Petitioner failed to show Larson discloses detecting different combinations of presence or absence of analyte molecules within the single sample volume in which amplification is performed.....	34
d. Petitioner failed to meet its burden for claims 4 and 13.....	36
2. Ground 2 (Claims 2, 4, 6-7, and 14-19).....	38

3.	Ground 3 (Claims 1-10 and 12-19): Obviousness in view of Larson and Saxonov.	39
a.	Larson Teaches Eliminating the Very “Multiple Occupancy” Situations to Which Petitioner Points.	40
(1)	Larson’s ¶¶140-141 do not teach detecting multiple target molecules in a droplet.	41
(2)	Larson’s Figure 9 and ¶121 do not teach detecting multiple target molecules in a droplet.	46
b.	Petitioner’s disparate theories of how and why to modify Larson fail.	54
(1)	The maintaining Larson at limiting or terminal dilution theory.	55
(2)	The reducing dilution in Larson theory.	59
c.	Petitioner further failed to meet its burden for claims 4 and 13.	62
4.	Ground 4 (Claim 11): Obviousness In View of Larson, Saxonov, and Silverbrook.	63
B.	Secondary Considerations of Non-Obviousness Support Patentability.	63
1.	There was a Long-felt Need for the Claimed Invention.	64
2.	Bio-Rad’s Infringing Products Covered by the Challenged Claims Were Commercially Successful as a Result of Using the Claimed Invention.	65
3.	The Caltech-ChromaCode License Entered into Outside of Litigation Supports Non-Obviousness.	66
4.	Praise for the ’921 Patent’s Claimed Invention Supports Patentability	66
VI.	CONCLUSION.	67

TABLE OF AUTHORITIES

	Page(s)
<u>Cases</u>	
<i>Apple Inc. v. Samsung Elecs. Co., Ltd.</i> 839 F.3d 1034 (Fed. Cir. 2016)	63
<i>Cal. Inst. of Tech. v. Bio-Rad Labs., Inc.</i> 5:25-cv-01701-EKL (N.D. Cal.)	23
<i>In re: ChromaCode Litig.</i> No. 5:23-cv-04823 (N.D. Cal.)	23
<i>ChromaCode, Inc. v. Bio-Rad Labs., Inc.</i> No. 5:23-cv-06360 (N.D. Cal.)	23
<i>Depuy Spin, Inc. v. Medtronic Sofamor Danek, Inc.</i> 567 F.3d 1314 (Fed. Cir. 2009)	45
<i>Great West Casualty Company et. al. v. Intellectual Ventures II LLC</i> IPR2015-01706, Paper 69 (PTAB Feb. 14, 2020)	25
<i>Harmonic Inc. v. Avid Tech., Inc.</i> 815 F.3d 1356 (Fed. Cir. 2016)	39
<i>Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino</i> 783 F.3d 1337 (Fed. Cir. 2013)	66, 67
<i>Intex Recreation Corp. v. Bestway (USA), Inc.</i> No. IPR2019-00454 (PTAB June 22, 2020)	25
<i>In re Magnum Oil Tools Int'l, Ltd.</i> 829 F.3d 1364 (Fed. Cir. 2016)	39, 59
<i>Plas-Pak Industries, Inc. v. Sulzer Mixpac AG</i> 600 Fed.Appx. 755 (Fed. Cir. 2015)	62
<i>WBIP, LLC v. Kohler Co.</i> 829 F.3d 1317 (Fed. Cir. 2016)	63, 64, 65

Statutes

35 U.S.C.
 § 102(e) 2, 15
 § 103.....39

UPDATED 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.
2016	<i>Dropworks, Inc. v. Lawrence Livermore Nat'l Sec., LLC</i> , No. IPR2021-00302, Ex. 2023.
2017	June 4, 2025 Cross Examination of Dr. Carl A. Batt.
2018	Supplemental Declaration of Kevin Struhl, Ph.D. in Support of the Patent Owner Response.
2019	QX ONE Droplet Digital PCR (ddPCR) System, available at https://www.bio-rad.com/en-us/life-science/digital-pcr/qx-one-droplet-digital-pcrddpccr-system (accessed June 19, 2025).

Exhibit No.	Description
2020	QX600 Droplet Digital PCR System, available at https://www.bio-rad.com/en-us/product/qx600-droplet-digital-pcr-system?ID=b07d12ac-0585-fc4c-a586-3ddf20d5c4a0 (accessed June 19, 2025).
2021	Bio-Rad SEC filing, available at https://www.sec.gov/Archives/edgar/data/12208/000119312520315015/d28972dex991.htm (accessed June 19, 2025).
2022	Plaintiffs ChromaCode, Inc. and California Institute of Technology's Opposition to Defendant's Motion to Transfer, Dkt. 29, <i>ChromaCode, Inc. et al. v. Bio-Rad Labs., Inc.</i> , No. 4:23-cv-06360-EKL (N.D. Cal. Nov. 20, 2023).
2023	Bio-Rad SEC filing, available at https://www.sec.gov/Archives/edgar/data/12208/000119312522053527/d901425dex991.htm (accessed June 19, 2025).

I. INTRODUCTION

After years of significant investment in research and development, inventors from the 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. Caltech protected its invention through a series of patents that includes U.S. Patent No. 11,827,921 (EX1001, “the ’921 Patent”), entitled “Signal Encoding and Decoding in Multiplexed Biochemical Assays.” On March 27, 2025, the Board instituted *inter partes* review of the ’921 Patent’s claims 1-19 (“the challenged claims”) based solely on Petitioner Bio-Rad Laboratories Inc.’s asserted ground that independent claim 1 is allegedly obvious over U.S. Publication No. 2011/0250597 (EX1017, “Larson”). Paper 11 at 37. Petitioner also contends the ’921 Patent is anticipated in view of Larson and obvious in view of Larson in combination with U.S. Publication No. 2013/0040841 (EX1004, “Saxonov”) and/or U.S. Publication No. 2011/0312704 (EX1009, “Silverbrook”). However, for multiple reasons discussed herein, Petitioner failed to meet its burden to show that any of the ’921 Patent claims are unpatentable under *any* grounds set forth in the Petition.

First, the Petition fails to establish by a preponderance of the evidence 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. ***Second***, for the grounds relying upon Saxonov in combination with Larson to allegedly render the claims obvious, the Board agreed with PO that Petitioner failed to establish Saxonov qualifies as prior art under 35 U.S.C. §102(e), or any other code section. Paper 11, 28-29. Thus, each of Petitioner's grounds relying on Saxonov necessarily fails.

In view of the Petition's substantial deficiencies, Petitioner failed to meet its burden to show any claim of the '921 Patent is unpatentable. The Petition should therefore be denied in its entirety.

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. EX2018, ¶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. EX2018, ¶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). EX2018, ¶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. EX2018, ¶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, including Larson's, tried to avoid this problem by (i) highly diluting the sample, (ii) physically dividing the diluted sample into droplets, (iii) performing PCR in each droplet to amplify the respective contents of the droplets, (iv) observing the intensity of light from each droplet, and (v) drawing conclusions about the single-analyte droplets 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 before PCR, different droplets may contain different numbers of unique analyte molecules. EX2018, ¶33. The "Poisson distribution" describes the statistics of how many analyte molecules the droplets contain. *Id.* In the "limiting dilution" regime, before PCR 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 before PCR almost all droplets are either empty or contain only a single analyte molecule, with droplets rarely containing multiple analyte molecules. EX2018, ¶33; *see* EX2017, 61:10-63:11, 100:9-101:13. At terminal dilution, to best avoid droplets containing multiple analyte molecules before PCR, most droplets are empty both before and after PCR, which wastes material and time. EX2018, ¶33; *see* EX2017, 61:10-63:11, 100:9-101:13.

Accordingly, the Poisson distribution describes the statistics of loading individual analyte molecules into the droplets of a collection of droplets before PCR. EX2018, ¶34. Because the analyte molecules are physically independent of one another, the droplets of the collection can contain any combination of presence or absence of such molecules. *Id.* In comparison, if a given analyte molecule contains more than one target, the statistics for those targets relative to each other are not described by the Poisson distribution. *Id.* For example, if a given polynucleotide analyte molecule (sometimes called a template) contains first and second targets (that is, contains first and second sequences it is desired to detect), the first and second targets are physically linked to each other. *Id.* Accordingly, the first and second targets are not physically independent of one another, and indeed will always co-occur with one another in the same droplet so long as they are linked by the same polynucleotide analyte molecule. *Id.*

Using a well-known technique called fragmentation, which may naturally occur or be performed intentionally, the first and second targets may be physically unlinked from one another, e.g., by fragmenting the polynucleotide analyte molecule on which these targets formerly resided. *Id.*, ¶35. This process results in two physically independent molecules—one containing the first target, and one containing the second target. *Id.* In this case, the Poisson distribution would describe the loading of the resultant molecules into droplets of a collection of droplets. *Id.* That is, the unlinking process (fragmentation) would allow the two resultant molecules to be independently loaded into droplets before PCR, and the Poisson distribution would describe the statistics of the combinations of presence or absence of those two resultant molecules in the droplets. *Id.* Thus, at limiting dilution, the co-occurrence of the two resultant molecules (and thus the co-occurrence of the two targets which had previously been linked on the same analyte molecule) would be low, as described by the Poisson distribution. *Id.* And at terminal dilution, the co-occurrence of those two resultant molecules (and thus the co-occurrence of the two targets which had previously been linked on the same analyte molecule) would be rare, again as described by the Poisson distribution. *Id.*; see EX2017, 61:10-63:11, 100:9-101:13.

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; EX2018, ¶36.

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); EX2018, ¶37.

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; *see also id.*, 8:58-62. To overcome this limitation, the inventors developed a technique to non-degenerately identify analyte molecules in a sample, using *fewer* fluorophores than the number of analyte molecules (in contrast to prior multi-channel techniques). EX1001, 8:63-9:19; EX2018, ¶38. 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).” EX1001, 8:66-9:5, 9:41-47; EX2018, ¶38.

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

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; EX2018, ¶39.

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 2× signal intensity in the

blue channel, while the result 1000 has only a $1\times$ signal intensity in the blue channel.

EX1001, 14:14-21; EX2018, ¶40.

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

7	3	3	3	pABCDEF
8	4	4	4	pABCDEFG

EX1001, 15:60-61; EX2018, ¶41.

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; EX2018, ¶42. 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; EX2018, ¶42.

The '921 Patent describes different ways to eliminate degeneracy such that every possible combination of analyte molecules has a unique cumulative intensity. EX1001, 22:11-23:56; EX2018, ¶¶42-44. One example method of eliminating degeneracy according to the '921 Patent encodes the individual analyte molecule states using intensity levels that are separated by integer $\log_2$ differences, ensuring that every possible combination of analyte molecules has a unique cumulative intensity, allowing for precise detection and differentiation. EX1001, 18:10-25, 23:38-56; EX2018, ¶43. Another example method of eliminating degeneracy according to the '921 Patent is to enumerate every legitimate result that can be obtained from the coding scheme, identify at least one legitimate result that is degenerate, and eliminate at least one potential analyte code from the coding scheme to eliminate degeneracy. EX1001, 17:60-18:9, 18:26-20:27, Table 6. EX2018, ¶44. Eliminating a given analyte molecule code from the coding scheme does not mean that a particular analyte molecule in an assay would be undetectable or ignored; instead, a different code would be selected to encode that analyte molecule. EX2018, ¶44.

The '921 Patent describes detecting a variety of different analyte molecules. *See, e.g.*, EX1001, 9:10-12, 24:59-26:29; EX2018, ¶45. However, the primary examples of analyte molecules are polynucleotides. *See* EX1001, 11:12-17, 24:14-58; EX2018, ¶45.

The '921 Patent claims are directed to the Caltech inventors' innovations providing assays and kits that are capable of unambiguously detecting the presence or absence of each of at least M analyte molecules, 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; EX2018, ¶46.

As is clear from the language of the claims and the original specification, the '921 Patent can detect three or more analyte molecules ($M \geq 3$) using multiple colors ($F \geq 2$). EX2018, ¶47. For example, the '921 Patent states “by utilizing at least two components of a signal during encoding, the methods described herein may be used to detect more than one analyte per fluorophore,” and the lowest number of analytes the '921 Patent discloses detecting per fluorophore is 1.5. *See* EX1001, 12:46-62; EX2018, ¶74. For this lower bound of $M=1.5$ analytes per fluorophore, the smallest value of F yielding an integer number of analytes (and yields a physical result) is $F=2$, for which $M=3$. *See* EX1001, 12:46-62; EX2018, ¶47. Other sections of the '921 Patent confirm that in all cases, $F \geq 2$ and $M \geq 3$. *See, e.g.*, EX1001, 21:18-23, 13:27-32, 13:41-47, 14:10-14; EX2018, ¶48.

Likewise, Petitioner's interpretation of the '921 Patent claims focuses on $F \geq 2$ and $M \geq 3$. *See, e.g.*, Petition, 1 (“[A]s Patent Owner has confirmed in parallel district court proceedings, the '921 patent encompasses detecting three polynucleotide targets using just two distinct signals.”); *see also* Petition, 28-29

(alleging Larson is anticipatory for purported disclosure of “using two colors to identify three target analytes, relying on the combination of two colors as the multi-color label for one analyte, with each of the two colors individually as a label for the other two targets. Here, M is three and F is two” (*citations omitted*)); *see also id.*, 24-26, 29, 35, 38-39, 49, 53, 55-58, 60. The Board’s institution decision similarly focuses its claim interpretation on $F \geq 2$ and $M \geq 3$. See Paper 11, 33.

Using the ’921 Patent’s encoding techniques, a single sample volume (not limited to droplets) can be loaded with any combination of analyte molecules before PCR is performed in that volume, and the ’921 Patent’s assays and kits can successfully analyze the contents of that volume after performing PCR. EX2018, ¶49; Paper 11, 33 (“the parties agree that the ‘single sample volume’ is not ‘limited to an individual ‘droplet,’ but rather includes any type or nature of volume, such as a ‘tube or bottle’”).

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,
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 M₁ is greater than F₁

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.

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

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.

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; EX2018, ¶50.

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. Petition, 21 *et seq.* As described below in §V.B., the Petition fails to establish the claims are anticipated by, or unpatentable over, Larson, whether alone or in combination with Saxonov and/or Silverbrook. As the Board found, Petitioner also did not establish Saxonov is §102(e) prior art against the '921 Patent for Grounds 3 and 4 in the Petition. *See* Paper 11, 26-29. Accordingly, Petitioner's Grounds 3 and 4 necessarily fail for the

same reasons PO discussed in its POPR and that the Board adopted in its institution decision. *Id.*; *see also* Paper 8, 29-42.

1. Larson

U.S. Patent Application Publication No. US 2011/0250597 to Larson et al. (“Larson”) was filed on February 11, 2011, and published on October 13, 2011. EX1017, §§(22), (43); EX2018, ¶51.

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. 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. This alleviates the complications that otherwise plague simultaneous competing reactions, such as varying arrival time into the exponential stage and unintended interactions between primers.

EX1017, ¶45; *see also id.*, ¶¶98-99.

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; EX2018, ¶53.

Larson asserts various advantages of having one allele per droplet. *See, e.g.*, EX1017, ¶¶99-100; EX2018, ¶54.

Accordingly, Larson's attempt to obtain “greater plexity” in ¶45 clearly is meant to be performed at terminal or limiting dilution, in which the sample is sufficiently diluted before PCR that most often a single analyte molecule is located within a droplet, to “alleviate[.]” the complications that come with multiple occupancy droplets. EX2018, ¶55; EX2017, 100:9-21, 127:12-130:4, 136:4-10. Larson discloses using PCR to amplify the single analyte molecule within its individual droplet, “alleviat[ing]” complications such as “varying arrival time into the exponential stage and unintended interactions between primers.” Larson, ¶¶44-45; EX2018, ¶45; EX2017, 103:9-105:6. Larson discloses analyzing the droplets one droplet at a time. Larson, ¶172, FIG. 9B; EX2018, ¶45; EX2017, 94:16-95:20.

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; EX2018, ¶56.

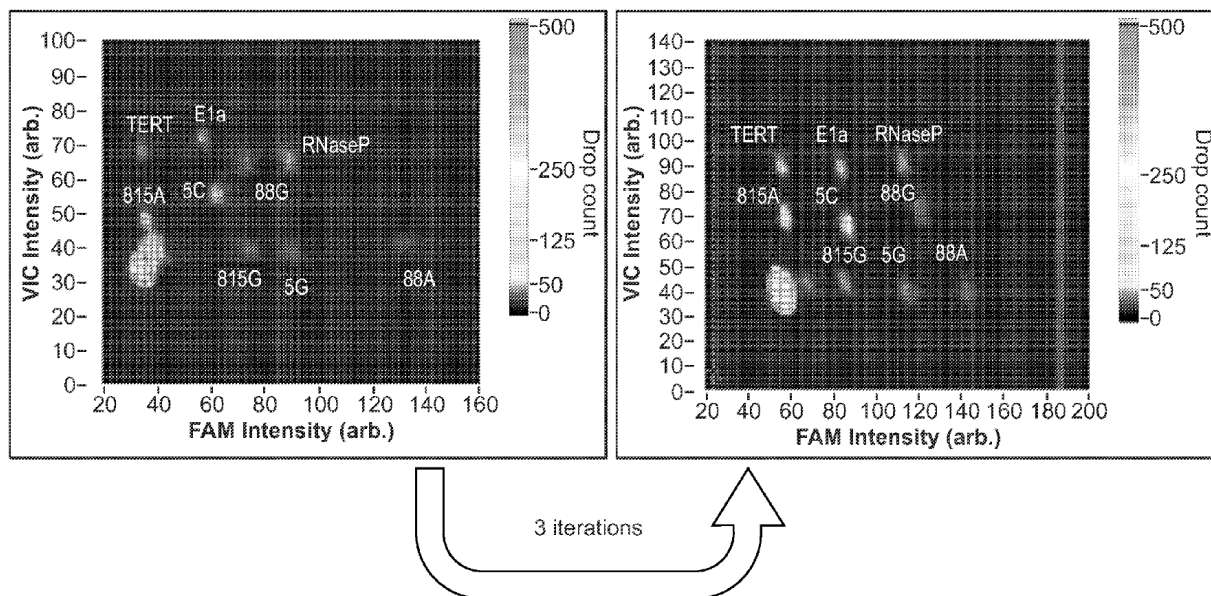


FIG. 15

Larson's FIG. 15 shows only single-analyte clusters (respectively TERT, 815A, E1a, 5C, 815G, RNaseP, 88G, 5G, 88A). EX1017, ¶35, FIG. 15; EX2018, ¶57. Other graphs in Larson similarly appear to show measurements from only single-analyte droplets/clusters, and conspicuously omit measurements from multi-analyte droplets/clusters. EX2018, ¶57, *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; EX2018, ¶58; EX2017, 167:8-169:23. Accordingly,

Larson expressly and fundamentally relies on *increasing* sample dilution before PCR as the number of analytes increases, to reduce the probability that one probe overlaps any of the other probes before and during PCR—that is, to reduce the probability that any droplet contains two or more analyte molecules before and during PCR. EX2018, ¶¶58-63; *see* EX2017, 167:8-169:23, 174:7-175:15.

To the extent any droplets nonetheless contain more than one analyte molecule before and during PCR, Larson expressly teaches *excluding* any such droplets from analysis after PCR, but before analyzing the droplets. EX2018, ¶64. 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.”³ EX1017, ¶172; EX2018, ¶55. 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; EX2018, ¶65. A POSA considering Larson as a whole would have readily understood that droplets containing a heterogeneous population of molecules after PCR produce two signals because they contain two different analytes, each analyte producing a different signal. EX2018, ¶¶65-67.

³ Emphasis added throughout except where noted.

In contrast to heterogeneous populations that produce two signals after PCR, 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; EX2018, ¶68. A POSA considering Larson as a whole would have readily understood that droplets containing a homogeneous population of molecules after PCR produce *one signal* because they contained only a single analyte molecule before PCR, producing a single signal after PCR. EX2018, ¶¶68-69.

Larson describes *how* to exclude “[d]roplets that produce two signals” after PCR from analysis in a dedicated section entitled “Droplet Sorting.” EX1017, ¶¶173, 178-181; EX2018, ¶¶70-72. 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; EX2018, ¶71. A POSA readily would have understood that Larson teaches *detecting* and *sorting* droplets after PCR based on the detected number of signals from those droplets: *two signals* from droplets containing a *heterogeneous* population of molecules after PCR, and *one signal* from droplets containing a *homogeneous* population of molecules after PCR; and *excluding* the droplets with *two signals* before the remaining droplets

are individually analyzed to determine which single analyte molecule (if any) is in each such remaining droplet. EX2018, ¶¶70-72.

Larson's reasons for excluding "multiple occupancy" droplets relate to complexities associated with "multiple occupancy:"

Generally, without wishing to be constrained by theory, the above three methods for higher-plex dPCR are simplest to implement under conditions of terminal dilution, that is when the probability of multiple different target molecules co-occupying the same droplet is very low compared to the probability of any single target occupying a droplet. 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; EX2018, ¶73; EX2017, 182:4-183:18.

A POSA readily would have understood, considering Larson's ¶141 in view of Larson as a whole, that "multiple occupancy" droplets contain a "heterogeneous population of molecules" After PCR. EX2018, ¶74. Moreover, they readily would

have understood Larson's statement "methods of the invention can accommodate these complications arising from multiple occupancy" refers to the strategies disclosed by Larson. **First**, increasing sample dilution before PCR 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 analyte molecules before and during PCR, let alone more than two. EX2018, ¶¶52-63, 75. **Second**, after PCR, using a dedicated detection module to detect, sort away, and exclude droplets containing heterogeneous populations of molecules based how many signals (one or two) the droplets produce. EX2018, ¶¶64-75. And **third**, after excluding such droplets, analyzing the contents of the remaining droplets. EX2018, ¶¶64-75.

Larson, including portions cited in the Petition, is replete with examples of how to identify a **single** analyte molecule within a droplet, repeats this as a key inventive concept, and indeed a POSA reasonably would have considered identifying a **single** analyte molecule within a droplet to be Larson's principle of operation. EX2018, ¶76, *citing* EX1017 abstract, ¶¶7, 8, 11, 13, 18-20, 45, 46, 49, 68, 99-101, 107, and claims 1, 3, 10, 11, and 15; EX2017, 105:7-108:3, 129:13-130:4.

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 February 18, 2025, PO also filed an action against Petitioner asserting U.S. Patent No. 12,168,797, which is related to the '921 Patent and has been consolidated with the parallel litigation. *See Cal. Inst. of Tech. v. Bio-Rad Labs., Inc.*, 5:25-cv-01701-EKL (N.D. Cal.).

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; and Grounds 3 and 4 point back to Grounds 1 and 2. *See* Petition, 24-51 (Grounds 1, 2), 51-67 (Grounds 3, 4). Petitioner’s arguments lack merit. PO’s preliminary infringement

contentions were just that—preliminary. Discovery in the district court litigation is still ongoing, and PO was and is entitled to amend and/or supplement its preliminary infringement contentions based upon fact and/or expert discovery or a claim construction order (which the court has not issued yet).

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 (PTAB Feb. 14, 2020); *see also Intex Recreation Corp. v. Bestway (USA), Inc.*, No. IPR2019-00454, 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.”). 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 *Phillips* 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)).

Moreover, on May 30, 2025 and June 17, 2025, PO served Petitioner with amended infringement contentions, including with respect to PO's assertions regarding the claimed “single sample volume” upon which Petitioner heavily

relies. This further reduces the weight (if any) that Petitioner or the Board should place on the extrinsic evidence from the preliminary infringement contentions. For example, the amendments clarify the claimed “single sample volume” does not include a volume that is subsequently partitioned into droplets, but, consistent with the express claim language, is where the reaction occurs (e.g., a droplet or well).

Still further, it is clear from PO's preliminary infringement contentions regarding “wherein the analytes are amplified in the single sample volume” that the single sample volume PO accuses is where amplification occurs: e.g., in a droplet, not in a pre-partitioned volume. EX1012 at 27-29 (*citing* BIO_CC00007427 at 7450 (“droplets are run through a thermal cycler, which performs PCR amplification of the nucleic acid target in each individual droplet”)).

Thus, Petitioner's arguments regarding PO's preliminary infringement contentions as set forth in the Petition are spurious and of at most marginal relevance, and should be rejected.

Finally, Petitioner's expert Dr. Batt conceded that when preparing his declaration he was not aware of the correct legal standard for interpreting the claims in view of PO's preliminary infringement contentions. EX2017, 47:8-49:15. So, the Board should reject all of Dr. Batt's testimony relying on PO's preliminary infringement contentions, on which Petitioner relied pervasively in Grounds 1, 2, 3, and 4. *See* Petition, 24-51 (Grounds 1, 2), 51-67 (Grounds 3, 4).

**V. PETITIONER HAS FAILED TO DEMONSTRATE THE
CHALLENGED CLAIMS ARE UNPATENTABLE**

**A. 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 Silverbrook. While Petitioner relies on Saxonov for Grounds 3 and 4, the Board found that the Petition fails to establish Saxonov qualifies as prior art. Paper 11, 28-29. Accordingly, and for the reasons PO discussed in its POPR (Paper 8, 29-42) the portions of Grounds 3 and 4 that rely upon Saxonov necessarily fail and PO does not further address them herein. *See also supra*, §II.D.

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

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

a. The challenged claims and Larson differ in kind, not just degree.

The '921 Patent and Larson take opposite approaches to extend the number of analytes that can be examined simultaneously. EX2018, ¶¶83-95.

While the '921 Patent is directed to detecting multiple analyte molecules in a single sample solution, Larson can only unambiguously distinguish analyte molecules from different sample volumes (i.e., droplets). This is because Larson is expressly "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; *id.*, ¶¶98-99; EX2018, ¶84; EX2017, 102:21-104:9. That is, in Larson, the samples are sufficiently diluted before PCR that for purposes of detecting analytes, most droplets before PCR either contain no analyte molecules or only a single analyte molecule. EX2018, ¶84.

To detect different analyte molecules, Larson extensively dilutes and partitions the sample into numerous droplets before PCR 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; EX2018, ¶85; *supra* §II.D.1. Droplets with zero analyte molecules provide no information, but inevitably arise by the procedure. EX1017, ¶52; EX2018, ¶85; *supra* §II.D.1. This reduces the mean number of analytes in a droplet before, during, and after PCR, making it easier to identify the analytes after PCR, with the easiest case being that of a single analyte per droplet before, during, and after PCR. EX1017, ¶141; EX2018, ¶85; *supra* §II.D.1; *see* EX2017, 182:4-183:18.

For the rare cases (if any) in Larson where droplets may have “multiple occupancy” before and during PCR, or contain a “heterogeneous population of

molecules” after PCR, Larson expressly teaches excluding any such droplets from analysis, and explains how to do so and the reasons why to do so. EX1017, ¶172; EX2018, ¶86; *supra* §II.D.1.

Larson is replete with examples of how to identify a single analyte molecule within a droplet, and repeats this as a key inventive concept; in view of these many teachings, a POSA reasonably would have considered this to be Larson’s principle of operation. EX2018, ¶¶87, 76, *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; EX2017, 103:21-108:3.

Larson’s approach has a number of disadvantages. EX2018, ¶88. For example, as compared with the ’921 Patent’s approach, Larson’s principle of operation requires partitioning a highly dilute sample into droplets before PCR, a large proportion of which provide no information after PCR (because the droplets are empty—that is, do not contain even a single analyte molecule). *Id.* The significant number of empty droplets before, during, and after PCR 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.* This wastes instrument time and PCR reagents. *Id.* Larson’s approach also uses different optimal dilutions before PCR for different analytes, under each of which the vast majority of droplets after PCR are uninformative, e.g., contain either no analyte molecules

or too many analyte molecules. *Id.* Moreover, even different samples containing the same analyte as each other before PCR 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 before PCR, the problem becomes even more complicated. *Id.* Additionally, Larson's teaching of excluding droplets containing multiple analytes after PCR 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.*, 89. But Larson did not recognize these aspects of its methods as drawbacks, indeed expressing that the benefits of these heavy dilutions are worth it to avoid the multiple occupancy problem: "The need for large dilutions ***strongly favors*** the large number of dPCR reactions." EX1017, ¶129.

In stark contrast, the '921 Patent solves the problem of detecting any and all combinations of different analytes, in the single sample volume in which amplification is performed, by measuring cumulative optical signals from that volume using a coding scheme. EX2018, ¶90. By doing so, the '921 Patent's approach—unlike Larson—does not depend on starting concentrations of the analytes before PCR, and does not require excluding any single sample volume(s) that contain multiple analyte molecules after PCR. *Id.*

Indeed, an important feature of the '921 Patent is how to choose probe colors and intensities that uniquely determine a given analyte molecule, even when that analyte molecule is mixed with other analyte molecules at the same time, in the same single sample volume, before, during, and after PCR, and at the time of detection. EX2018, ¶91. This avoids a degeneracy problem, where the same intensity values could be consistent for two different combinations of analyte molecules in the same single sample volume, when detection is performed after amplifying the analyte molecules in that same single sample volume. *Id.* For example, if intensity values 1, 2, 4, 8, 16, 32 are chosen for probes read in the same optical channel after amplification, every combination of present/absent analyte molecules in the single sample volume is unique. *Id.* This method of decoding cumulative signals is different in kind (not just degree) from Larson, and makes it much easier, quicker, and more efficient to analyze multiplexed samples than possible with Larson's limiting or terminal dilution. *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, . . . wherein the analytes are amplified in the single sample volume.” EX1001, 67:16-25. Claim 14 of the '921 Patent recites a kit with similar limitations. *See* EX1001,

68:31-38. The claimed assays and kits provide flexibility to detect *any possible combination* of the analyte molecules within the single sample solution volume where that combination of analyte molecules is amplified, in such a manner that each analyte molecule may be uniquely distinguished from each other analyte molecule. EX2018, ¶92; *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 in any combination in a single sample volume (such as a vial or droplet) within which amplification is performed. EX2018, ¶92; *supra* §II.B.

b. Petitioner failed to show that a POSA would interpret Larson as disclosing how to unambiguously identify any combination of M analyte molecules within the single sample volume in which amplification is performed.

Petitioner's arguments regarding Larson do not establish a proper legal basis upon which the Board could reasonably find Larson anticipates claim 1.

More specifically, the Board observes that Petitioner's Ground 1 is based on the assertion that "*if* the 'single sample volume' is taken to be a portion of the original sample mixture *prior to it being partitioned into droplets*," then Larson discloses 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.” Paper 11, 30; *citing* Petition, 54.

However, the '921 Patent claims *also* expressly recite that ***amplification is performed in the single sample volume***. See EX1001, 67:24-25, 68:37-38. For this limitation, Petitioner and Dr. Batt merely refer to PO's original infringement contentions in parallel litigation and state that “Larson again discloses the exact thing that Patent Owner now accuses of infringing in district court.” Petition, 31-32. PO has served Petitioner with amended infringement contentions further clarifying this, and in any case, the original infringement contentions merely constitute extrinsic evidence and do not change how a POSA would understand the claims. *Supra*, §IV.

Accordingly, Dr. Batt's interpretation of this limitation of the '921 Patent claims—which interpretation is based solely on PO's original infringement contentions, and a misleadingly deceptive read of those contentions no less—is fatally flawed. EX1002, §4B. *Supra*, §IV. As such, the Board should wholly disregard Dr. Batt's testimony and Petitioner's reliance thereon, and find that Petitioner did not establish a proper legal basis for finding that Larson anticipates claim 1, or any claim depending therefrom. Claim 14 recites similar limitations, and thus the Board should likewise find that Petitioner has not established a proper

legal basis for finding that Larson anticipates claim 14, or any claim depending therefrom.

- c. **Petitioner failed to show Larson discloses detecting different combinations of presence or absence of analyte molecules within the single sample volume in which amplification is performed.**

The Board correctly understands Petitioner's assertion to be "where the terminal dilution provides for a sample that is partitioned into droplets and each droplet contains only one analyte, Larson's assay detects unambiguously which analyte is in each droplet." Paper 11, 31. But the '921 Patent claims expressly recite more: the capability of "unambiguously detecting the presence or absence of each of said at least M analytes, *in any combination of presence or absence*," in the single sample volume in which the amplification is performed. EX1001, 67:16-21. Indeed, the Board states that "to meet the disputed claim limitation, Larson's assay must be capable of doing *more* than identifying only a single analyte in a single droplet, as some of the droplets (prepared from an original single sample volume) may contain more than one analyte." Paper 11, 34. Petitioner failed even to allege (let alone establish to a legally sufficient standard) that the POSA would consider Larson's ability to distinguish a first analyte in a first droplet from a second analyte in second droplet to be equivalent to being capable of "unambiguously detecting the presence or absence of each of said at

least M analytes, *in any combination of presence or absence*,” in the single sample volume in which the amplification is performed. Accordingly, the Board should find that Petitioner failed to meet its burden for showing Larson discloses this claim limitation as well.

Moreover, Larson teaches various complexities that arise if two or more analyte molecules are in a droplet during or after PCR (EX2017, 182:4-183:18), and expressly discloses how to avoid that situation: *diluting* and partitioning the sample *before* PCR into numerous droplets to reduce the likelihood of any droplets having “multiple occupancy,” or containing a “heterogeneous population of molecules” after PCR, and *excluding* any such droplets *after* PCR. EX2018, ¶93; *supra* §II.D.1.

Additionally, Larson is *silent* on how to analyze droplets having three or more analyte molecules. EX2018, ¶94. 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—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* multiple analytes in a single sample volume after performing PCR in that single sample volume. *Id.* Larson's limiting or terminal

dilution before PCR and sorting/exclusion after PCR entirely avoided this issue, and indeed Larson refers to the possibility of probes overlapping one another in multiple occupancy as an “error” which is alleviated by “large dilutions” which “strongly favors the large number of dPCR reactions. *Id.*, citing EX1017, ¶129; EX2017, 183:14-18.

For each of these reasons, Petitioner failed to meet its burden for Ground 1, particularly for claims 1 and 14 of the '921 Patent, and claims respectively depending therefrom.

d. Petitioner failed to meet its burden for claims 4 and 13.

Petitioner further failed to meet its burden regarding at least dependent claims 4 and 13.

First, Petitioner argued that claim 4 is anticipated by Larson's disclosure of:

adjusting the intensity values from color labels to avoid potentially ambiguous results, particularly to avoid overlap between signals for two different populations. EX1017 ¶¶35, 146 (describing optimizing intensities to adjust positions of signals in histograms), 150, Fig. 15; EX1002 ¶163...This adjustment of intensity eliminates a potential analyte code from the coding scheme because each analyte is also encoded by intensity of color signals. *See supra* §XI.A.2; EX1002 ¶165; EX1017 ¶¶35, 140, Fig. 15.

Petition, 34-35. In this, Petitioner points to Dr. Batt's testimony variously citing Larson's "Figure 15's depiction of optimizing droplet intensities," Larson's ¶146 "describing optimizing intensities to adjust positions of signals in histograms," and Larson's ¶150 "describing optimization of intensities depicted in Figure 15 to separate populations within the histogram." *See* EX1002, ¶163. Dr. Batt's position is that a "POSA would have understood that this adjustment is effectively no different than eliminating a potential analyte code from the coding scheme to eliminate degeneracy." EX1002, ¶¶165, 292; *see also* EX2017, 161:6-162:22. However, Dr. Batt also conceded that the optimization process shown in Larson's Figure 15 merely "shifted" the locations of different populations to make "discrimination between those nine targets much easier or much better resolution," and that he would be a "bit less confident" for the left side of Figure 15 than for the right. EX2017, 150:2-152:22; *id.*, 155:25-156:19; *id.*, 160:4-162:22. Dr. Batt does not explain why a POSA would reasonably consider that shifting populations' locations to improve resolution, providing a "bit" more confidence, is the same as "***eliminating*** a potential analyte code from the coding scheme to eliminate degeneracy," as Petitioner alleged.

Second, regarding claim 13, Petitioner alleged "Larson discloses, including in paragraph 140, assays that are innately non-degenerate or non-degenerate by construction," citing ¶¶206-213 of Dr. Batt's declaration for support. Petition, 39.

Dr. Batt elaborates that in Larson, “by using intensities, fine-tuning intensities, and using multiple fluorophores, each analyte is inherently non-degenerate.” EX1002, ¶208, *citing* EX1017, FIG. 15. *See also* EX2017, 162:23-165:3. But if Dr. Batt’s position is that fine-tuning intensities, as in Larson’s FIG. 15, means each analyte is “inherently non-degenerate” for purposes of invalidating **claim 13**, this same optimization of intensities (as in Larson’s FIG. 15) may not *simultaneously* be interpreted as meaning “eliminating a potential analyte code from the coding scheme to eliminate degeneracy” for purposes of invalidating **claim 4**.

Accordingly, Petitioner has further failed to show Larson anticipates claims 4 and 13.

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.A.1.a-c apply equally to claims 2, 4, and 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. EX2018, ¶96.

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; EX2018, ¶97. Such limited argumentation does not adequately explain why a POSA would have found it obvious to attempt to obtain the kit recited in claim 14, and claims depending therefrom, based on Larson's teachings considered as a whole (that is, including Larson's express disclosure regarding diluting and partitioning the sample before PCR and excluding multiple occupancy droplets after PCR), for at least the reasons set forth herein. EX2018, ¶97.

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

In instituting IPR of the challenged claims pursuant to 35 U.S.C. §103, the Board found Petitioner showed a reasonable likelihood of prevailing on its assertion that independent claim 1 is rendered obvious by Larson alone. Paper 11, 37. The relevant question under §103 is whether the claimed subject matter would have been obvious to a POSA at the time the invention was made. Petitioner has the burden of "show[ing] with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)). "[T]he burden of proof is on the petitioner to prove unpatentable those issued claims that were actually challenged in the petition for review and for which the Board instituted review." *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364 (Fed. Cir. 2016) (quoting *Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1334 (Fed. Cir. 2016)). Petitioner failed to meet this burden.

Portions of Petitioner's arguments in Ground 3 differ from those in Grounds 1 and 2, in that these portions of Ground 3 allege "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 sub-volumes."

Petition, 51.⁴ However, Petitioner's theory in Ground 3 is even more misguided than in Grounds 1 and 2, because Larson teaches something very different from what the '921 Patent claims recite. As explained below, Petitioner's varied and disparate proposals for modifying Larson are irreconcilable with Larson's express disclosure regarding "multiple occupancy," and indeed are irreconcilable with Petitioner's own purported rationales for making such modifications. EX2018, ¶¶113-138. Petitioner failed to establish that Saxonov is prior art, and as such PO does not substantively address Ground 3 to the extent it relies upon Saxonov.

Supra, §II.D.

a. **Larson Teaches Eliminating the Very "Multiple Occupancy" Situations to Which Petitioner Points.**

Petitioner's Ground 3 alleges Larson teaches "there may be multiple targets in a single individual droplet and that its methods accommodate such 'multiple occupancy' situations," stating "Larson's assays use conditions and parameters that

⁴ Other portions of Ground 3 simply refer to Petitioner's anticipation theory which is based on PO's preliminary infringement contentions. *See, e.g.*, Petition, 62-67.

do precisely this.” Petition, 52, *citing* EX1017, ¶¶129, 141; EX1002, ¶321.

However, Larson’s actual disclosure about accommodating “‘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 the single sample volume in which the analytes are amplified. EX2018, ¶99; *see* EX1001, 67:16-20, 68:31-34.

- (1) Larson’s ¶¶140-141 do not teach detecting multiple target molecules in a droplet.

Petitioner’s invalidity arguments hinge on Larson’s ¶¶140-141, citing ¶140 well in excess of fifty times and quoting it repeatedly. *See, e.g.*, Petition, 12-13, 23-24 (“Most important for the purposes of the present petition, in paragraph 140, Larson describes . . .”), 25, 28-35, 38-39, 41- 45, 47, 49, 52, 69. EX2017, 125:5-12. For example, Petitioner points to Larson’s ¶140 as disclosing “using two colors to identify three target analytes, relying on the combination of two colors as the multi-color label for one analyte, with each of the two colors individually as a label for the other two targets.” Petition, 28-29. The Board cited this very analysis in its institution decision. Paper 11, 30-31. To help the Board better appreciate the discrepancies between Larson’s express disclosure and Petitioner’s representations regarding such disclosure as pertain to the ’921 Patent claims, Larson’s ¶¶140-141 bear closer examination.

Both by its own terms, and properly read in view of Larson as a whole, Larson's ¶140 relates to analyzing droplets containing only a *single analyte both before and after PCR*:

Another method of the invention involves performing higher-plex assays using multiple different probe colors (i.e. fluorophores), however unlike the strategy above where each target is identified by single type of probe with a unique color and intensity, instead in this method a single target may be identified by multiple probes that constitute a unique signature of both colors and intensities. For example, a single droplet might contain four different probes for measuring three different targets (say, T1, T2, and T3). Two probes might be of color A (say, A1, and A2), and two probes might be of color B (say, B1 and B2). T1 is measured by probe A1, T2 is measured by probe B1, but T3 is measured by both probes A2 and B2. Thus, when a droplet contains T1 only increased fluorescence appears in color A. When a droplet contains T2 only increased fluorescence appears in color B. However when a droplet contains T3, increased fluorescence appears in both colors A and B.

EX1017, ¶140; EX2018, ¶100.

Larson's ¶140, reproduced above in its entirety, describes analyzing only three types of droplets after PCR: (1) droplets containing only the T1 molecule

(detected with fluorescence in color A); (2) droplets containing only the T2 molecule (detected with fluorescence in color B); and (3) droplets containing only the T3 molecule (detected with fluorescence in colors A and B). *See* EX1017, ¶140; EX2018, ¶¶101-102. Larson's ¶140 is silent on how to unambiguously distinguish **any** combination of presence or absence of the T1, T2, and/or T3 molecules in respective droplets after PCR. *See* EX1017, ¶140; EX2018, ¶¶101-102; EX2017, 126:14-127:11. Indeed, ¶140 of Larson is silent on a given droplet possibly even **containing** any combination of T1, T2, and/or T3 after PCR, let alone how to uniquely differentiate any combination of target molecules in a first droplet from any combination of target molecules in a second droplet, using the fluorescence in colors A and B from the droplets. *See* EX1017, ¶140; EX2018, ¶103; EX2017, 126:14-127:11.

Larson does not disclose how to analyze such multiple occupancy droplets because Larson seeks to avoid such droplets due to the many problems and complexities that “multiple occupancy” causes, e.g., as expressed in Larson's ¶141 which immediately follows ¶140:

Generally, without wishing to be constrained by theory, the above three methods for higher-plex dPCR are simplest to implement under conditions of terminal dilution, that is when the probability of multiple different target molecules co-occupying the same droplet is very

low compared to the probability of any single target occupying a droplet. 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; *see* EX2018, ¶¶73, 104. Petitioner and the Board focus on Larson's statement in ¶141 that "methods of the invention can accommodate these complications arising from multiple occupancy." *See, e.g.,* Paper 11, 31 (*citing* Petition, 55) (*internal citations omitted*). However, Larson's ¶141 does not actually explain how the methods of Larson's ostensible invention "accommodate these complications arising from multiple occupancy." *See* EX1017, ¶141; EX2018, ¶¶73, 105; EX2017, 170:4-21. And Larson both teaches away from having multiple target molecules in a droplet due to numerous associated downsides and complexities, and teaches it is advantageous to have a single target molecule per droplet. EX1017, ¶¶99-101, 107, 141; EX2017, 127:12-130:4. Dr. Batt admitted that his own opinions about why it would have been obvious to

modify Larson (discussed below at §V.A.3(b)) admittedly did not actually address the downsides of multiple occupancy that Larson expressly identifies. EX2017, 182:4-183:18, 184:18-185:15. Relatedly, “[a]n inference of nonobviousness is especially strong where the prior art’s teachings undermine the very reason being proffered” as to why a person of ordinary skill would have made the proffered modification. *Depuy Spin, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (applying the rule to a combination of known elements).

As such, a POSA considering Larson’s ¶141 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 using the strategies Larson **actually discloses**. EX2018, ¶¶52-76, 106. As such, the POSA would have understood Larson’s statement refers to increasing sample dilution before PCR as the number of analytes increases, to reduce the probability that one probe overlaps any of the other probes: reducing the probability that any droplet contains even two analytes before or during PCR, let alone more than two. EX2018, ¶¶52-63, 106-107; *supra* §II.D.1.; Petition, 52 (*citing* EX1017, ¶129); *see* EX2017, 168:14-169:23. The POSA also would have understood Larson’s statement refers to detecting, sorting away, and excluding droplets containing a heterogeneous population of molecules after PCR and before analysis, based on how many signals each droplet produces, EX2018, ¶¶64-76, 106; *supra* §II.D.1.

The POSA would have understood Larson's statement refers to—after excluding multiple occupancy droplets—analyzing the contents of the remaining empty or single-analyte droplets. EX2018, ¶¶56-67; *supra* §V.A.3.a.

For at least these reasons, if a POSA wished to “accommodate” multiple occupancy situations, Larson's full teachings would, at most, have motivated that POSA to try to **eliminate** multiple occupancy situations by **diluting** the sample to limiting or terminal dilution before PCR to reduce the probability that any droplet contains two or more analytes, and to **exclude** droplets containing two or more analytes after PCR and before analyzing the remaining droplets. EX2018, ¶¶106-107.

- (2) Larson's Figure 9 and ¶121 do not teach detecting multiple target molecules in a droplet.

Despite Larson's express disclosure on the subject of “accommodat[ing] these complications arising from multiple occupancy”—not **detecting** multiple target molecules in a droplet but rather **excluding** such droplets before analysis (*supra* §V.A.3.a)—Petitioner and Dr. Batt aver that Larson's Figure 9 teaches an assay that would accommodate such complications. EX1017 ¶ 121, Fig. 9A; EX1002 ¶ 333; Petition, 55. The Board appears to have relied on these assertions. *See* Paper 11, 31.

Indeed, Petitioner's invalidity arguments hinge on Larson's Figure 9 and ¶121, collectively cited over twenty times in the Petition. *See, e.g.*, Petition, 23, 24, 26, 28, 32, 33, 35, 39, 41, 42, 43, 44, 47, 48, 50, 53, 55, 56, 57. The Board cited multiple aspects of Dr. Batt's testimony regarding Larson's Figure 9 in its decision to institute IPR of the '921 patent. *See, e.g.*, Paper 11, 33-36. However, for the reasons discussed below, Larson's Figure 9, and its accompanying text at Larson's ¶¶29 and 121, do not actually teach or suggest how to "accommodate these complications arising from multiple occupancy" in the manner that Petitioner and Dr. Batt so specifically allege.

First, contrary to what Petitioner implies, Larson itself does not remotely represent that Figure 9 "accommodate[s] these complications arising from multiple occupancy" to which Larson's ¶141 refers (*see supra* §V.A.3.a); instead, the only two paragraphs in Larson that mention Figure 9 are the following:

FIG. 9 is a schematic depicting two-color detection of three genetic sequences with a microfluidic device.

EX1017, ¶29.

Methods of the invention involve performing accurate quantitation of multiple different DNA targets by dPCR using probes with the same fluorophore. FIG. 9 is a schematic depicting two-color detection of three genetic sequences with a microfluidic device. As shown in Panel

A of FIG. 9, a template DNA is amplified with three sets of primers: forward primers (F1, F2 and F3) and reverse primers (R1, R2 and R3). Probes (P1, P2 and P3) are labeled with fluorophores (color 1, color 2 and color 1) and bind to the target genetic sequences (target 1, target 2 and target 3) (Panels B and C). Microdroplets are made of diluted solution of template DNA under conditions of limiting or terminal dilution. Microdroplets containing target sequence 1 or 3 emit fluorescence of color 1 at two different intensities; and microdroplets containing target sequence 2 emit fluorescence of color 2. The number of microdroplets containing target 1, 2 or 3 is shown by histogram in Panel D.

EX1017, ¶121.

Given their criticality to Petitioner's position, and the Board's reliance on them, a closer analysis of Petitioner's and Dr. Batt's interpretation of Larson's Figure 9 and ¶121 is in order.

Turning now to Larson's FIG. 9A, reproduced below, Dr. Batt states "Figure 9 shows one such way to accommodate these complications. Larson depicts, in

FIG. 9A

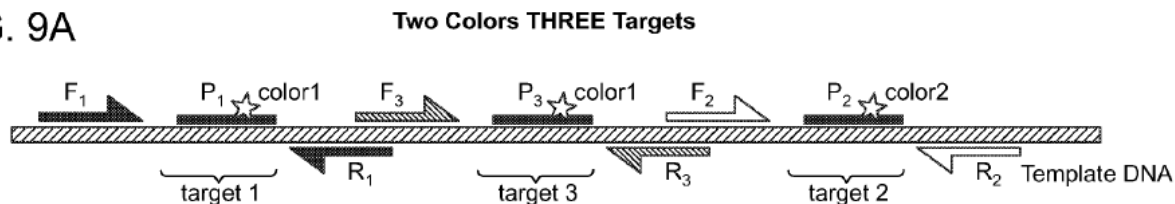


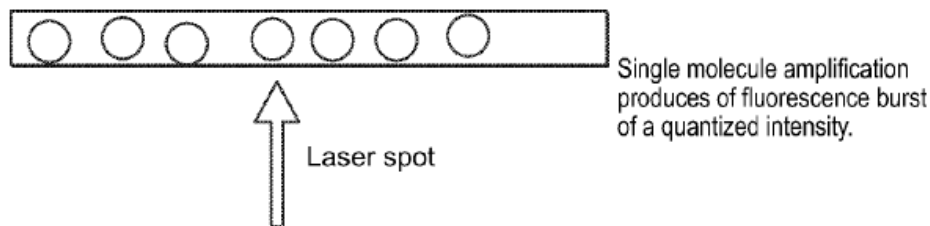
Figure 9A, a multiplex PCR which detects three targets using only two fluorophores.” EX1002, ¶333.

Petitioner and Dr. Batt argue that Larson's Figure 9 accommodates the “complications” which come with multiple occupancy. These arguments are simply wrong. Indeed, FIG. 9A does not even *show* multiple occupancy. EX2018, ¶111. Instead, FIG. 9A plainly illustrates a *single template DNA molecule* which includes three targets, consistent with Larson's description of this figure as illustrating “A template DNA is amplified with three sets of primers...Probes (P1, P2 and P3) are labeled with fluorophores (color 1, color 2 and color 1) and bind to the target genetic sequences (target 1, target 2 and target 3) (Panels B and C).” EX1017, ¶121; EX2018, ¶111. Because the three targets shown in Larson's FIG. 9A are linked on the same molecule, they are not physically independent of one another, and indeed will always co-occur with one another in the same droplet so long as they are linked by the same single template DNA molecule. EX2018, ¶112. Accordingly, a POSA would have readily understood that Larson's FIG. 9A, and the section of Larson's ¶121 describing FIG. 9A, do not teach or suggest “multiple occupancy,” let alone how to accommodate the “complications” which come with multiple occupancy as Petitioner and Dr. Batt allege. *Id.* Even Dr. Batt agrees that FIG. 9A “clearly” shows “multiple...targets on a *single molecule* [that]

would then segregate into a single droplet and therefore could be detected through Larson.” See EX2017, 210:12-25.

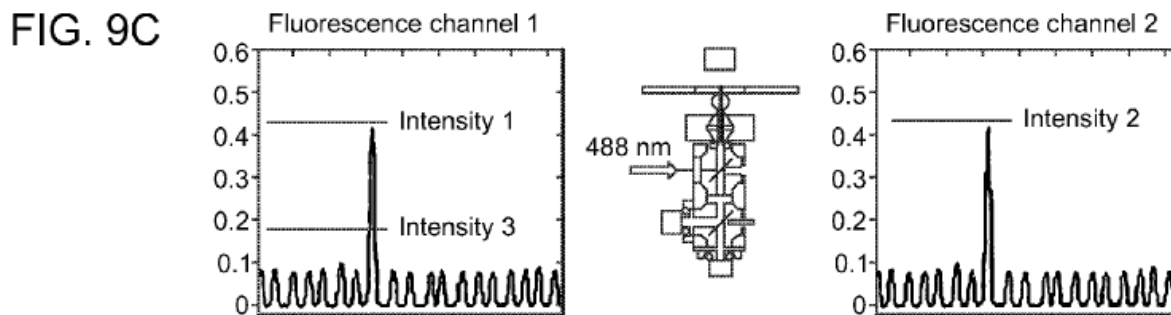
Given Petitioner and Dr. Batt's heavy reliance on Larson's Figure 9, it is noteworthy that they do not include or discuss Larson's FIG. 9B, reproduced below. See, e.g., Petition, 54-57; see, also, EX1002, ¶¶108-147, 169, 175, 188, 218-222, 295, 299, 313, 325-334, 371.

FIG. 9B



Larson's FIG. 9B is expressly directed to “*single molecule* amplification,” which directly contradicts Petitioner and Dr. Batt's “multiple occupancy” theory. EX1017, FIG. 9B; EX2018, ¶114; see, e.g., Petition, 60-61; EX1002, ¶312 et seq. So while this figure's omission from the Petition and Dr. Batt's declaration is noteworthy, it is also not surprising.

FIG. 9C of Larson, reproduced below, features prominently in Petitioner's arguments and Dr. Batt's analysis, and in the Board's institution decision:



Among other things, Petitioner alleged 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; EX2018, ¶¶52-76, 116.

Here, Petitioner and Dr. Batt hypothesize what scenarios “would result in distinguishable signals” from droplets allegedly 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 (quoting EX1002, ¶¶335-337); EX2018, ¶116. But

Petitioner's and Dr. Batt's hypothesis finds no support in Larson, which instead teaches "multiple occupancy." Indeed, Larson's express disclosure at ¶121 confirms that *all* of FIGS. 9A, 9B, and 9C are directed to the "single molecule" situation shown in FIG. 9A: "As shown in *Panel A* of FIG. 9, a template DNA is amplified with three sets of primers . . . Probes (P1, P2 and P3) are labeled with fluorophores (color 1, color 2 and color 1) and bind to the target genetic sequences (target 1, target 2 and target 3) (*Panels B and C*)."

EX1017, ¶121; EX2018, ¶117. As such, contrary to what Petitioner alleged, the scheme shown in FIG. 9C is only "consistent with Larson's teaching that its assays can accommodate 'multiple occupancy'" to the extent that this figure teaches detecting a *single molecule* in a droplet, that is, Larson's solution to the "multiple occupancy" problem. EX2018, ¶117; see Petition, ¶56 (citing EX1002, ¶¶335-337).

In its institution decision, the Board expressly "credit[s] Dr. Batt's testimony that Larson's results in Figure 9C exemplify 'an approach that differentiates three analytes by encoding them in one of two wavelengths of an intensity of fluorescent light (a part of the detecting signal) and allows for unambiguous detection of the three targets.'" Paper 11, 36. But, as Larson's express disclosure makes clear and as even Dr. Batt *agrees*, FIG. 9C relates to detection of a *single analyte molecule* that contains three target genetic sequences that are all linked on that molecule.

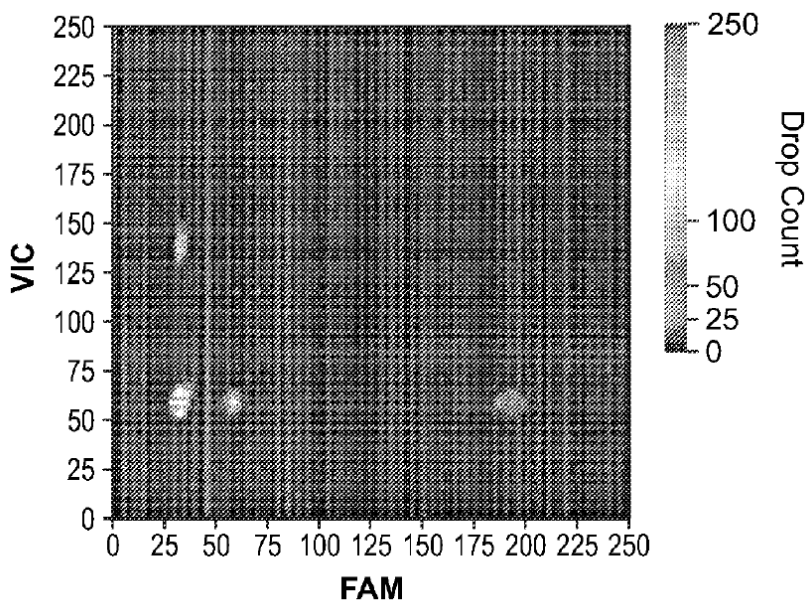
EX2018, ¶117; EX2017, 210:12-25 (FIG. 9A "clearly" shows "multiple . . . targets

on a *single molecule* [that] would then segregate into a single droplet and therefore could be detected through Larson.”). As such, contrary to Dr. Batt’s written testimony and Petitioner’s own position, Figure 9C merely exemplifies the situation in which three targets are all part of, and linked to one another by, a single analyte molecule. EX2018, ¶117; EX2017, 210:12-25.

Petitioner and Dr. Batt also, unsurprisingly, 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; EX2018, ¶119.

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; EX2018, ¶119. Moreover, Larson’s legend to FIG. 9D exclusively uses the disjunctive “or” to refer to the targets. EX1017,

¶121; EX2017, 114:13-22. Further, 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. EX2018, ¶119; EX2017, 113:6-19 (“you don’t know”). And even if FIG. 9D did include such clusters, Larson’s other disclosure regarding Figure 9 clearly indicates that such clusters come from the same *single molecule* embodiment described with reference to FIGS. 9A-9C. EX2018, ¶119.

Accordingly, Larson’s Figure 9 simply does not support the “multiple occupancy” story that Petitioner and Dr. Batt propound.

b. Petitioner’s disparate theories of how and why to modify Larson fail.

It is Petitioner’s burden to demonstrate why a POSA would have had sufficient motivation to modify Larson to obtain the ’921 Patent claims. Additionally, the purported motivation can only be properly analyzed in the context of the modification that Petitioner actually proposes to make to Larson. For the reasons that follow, Petitioner wholly fails to meet its burden of showing why it would have been obvious to modify Larson to arrive at the challenged claims.

To start, Dr. Batt contends that a POSA would have been motivated to use Larson’s assay to unambiguously detect up to three analytes in a single droplet, as

an alternative to “limiting an experiment to only single-target droplets.” See EX1002, ¶338. Petitioner’s arguments appear to depend on either (1) limiting Larson’s experiments to terminal dilution to detect the rare multiple occupancy droplets or (2) reducing dilution in Larson (thus increasing concentration) to obtain more multiple occupancy droplets for analysis. But Petitioner and Dr. Batt do not explain, to a legally sufficient standard, why a POSA would have been motivated to modify Larson in *either* of these two manners to arrive at the ’921 Patent’s claims.

- (1) The maintaining Larson at limiting or terminal dilution theory.

In some regards, Petitioner’s invalidity theory seems to rely on keeping Larson at limiting or terminal dilution while additionally analyzing the rare multiple occupancy droplets. Petition, 52; EX2018, ¶121. For example, Petitioner avers that:

Larson expressly teaches that there may be multiple targets in a single individual droplet and that its methods accommodate such ‘multiple occupancy’ situations. See EX1017 ¶¶ 129, 141; EX1002; ¶ 321. Larson’s assays use conditions and parameters that do precisely this.

EX1002 ¶321; Petition, 52. The sections of Larson Petitioner cites (¶¶129, 141) teach increasing dilution, so Petitioner’s reference to Larson’s “conditions and parameters” can only reasonably be interpreted as those which Larson actually

discloses, namely terminal or limiting dilution. EX2018, ¶121; *supra* V.A.3.a. Dr. Batt confirmed at times that Petitioner's theory included maintaining Larson's terminal or limiting dilution. EX2017, 175:16-177:14 ("Q. In [¶338,] are you referring to keeping the number of multiple analyte droplets the same, but just acquiring data from them? A. I believe so, yes.").

Fatal to Petitioner's arguments, the reasons Dr. Batt offers as allegedly motivating this modification are irrational and inconsistent with what a POSA reasonably would have believed in view of Larson's express teachings. EX2018, ¶122. For example, Dr. Batt opines "a POSA would have been motivated to use this strategy because limiting an experiment to only single-target droplets severely impacts the total data collected in that experiment." EX1002, ¶338. This purported motivation is irrational because multiple occupancy droplets are quite rare at limiting dilution, and extremely rare at terminal dilution. EX2018, ¶123; EX1002, ¶130. Dr. Batt fails to explain why the POSA would have thought that additionally analyzing the rare multiple occupancy droplets would have any meaningful "impact" on the "total data collected in that experiment." *See* EX1002, ¶338; EX2017, 175:16-177:14, 179:14-180:7.

Furthermore, a POSA readily would have recognized that when performing Larson's method at terminal or limiting dilution, the single-analyte droplets provide all the information required to identify the analytes present in the sample.

EX2018, ¶124. Dr. Batt fails to explain, given multiple occupancy droplets' rarity and that such droplets would not provide information beyond that from single analyte droplets, why the POSA nonetheless would have been rationally motivated to expend *any* additional effort to analyze the multiple occupancy droplets. *See* EX1002, ¶338; EX2018, ¶124; EX2017, 175:16-177:14.

As an additional purported motivation for modifying Larson, Dr. Batt states:

These assays, especially at the time of the '921 patent, were quite costly to set up and run, for example, as discussed in Larson, many reagents are required. *See, e.g.,* EX1017 ¶68. The ability to acquire data not just from a fraction of the droplets, but from all droplets in the experiment would thus be extremely cost effective.

EX1002, ¶138. But again, Petitioner's proposed modification to Larson requires using terminal or limiting dilution, such that it would be nonsensical for a POSA to expect this situation to somehow provide "the ability to acquire data not just from a fraction of the droplets, but from *all* droplets in the experiment," as Dr. Batt hypothesizes. EX2018, ¶125. Instead, Larson discloses that at both terminal or limiting dilution a large proportion of the droplets are *empty*. EX2018, ¶125; EX1017, ¶6. If Dr. Batt is proposing not to change Larson's dilution, then the number of empty droplets simply would not change. EX2018, ¶125. Dr. Batt does not explain why the POSA would rationally expect that adding analysis of multiple

occupancy droplets at limiting or terminal dilution would somehow provide the ability to acquire data “from all droplets” in the experiment or meaningfully impact the experiment’s cost—let alone be “*extremely* cost effective,” as Dr. Batt proposes. *Id.*; EX2017, 175:16-177:14.

As yet another purported motivation for modifying Larson, Dr. Batt states:

Additionally, by allowing more DNA into each droplet, the dilution factor for the sample decreases, meaning less sample exists and less run-time on the machine is necessary.

EX1002, ¶138. But, under Petitioner’s proposed modification to Larson of using terminal or limiting dilution (as it seems to), it would be nonsensical for a POSA to expect this situation to somehow “allow[] more DNA into each droplet” or decrease “the dilution factor for the sample” as Dr. Batt posits. EX2018, ¶126. Dr. Batt does not explain why the POSA would rationally expect either of these to result from adding analysis of multiple occupancy droplets. *Id.*

The Board relied upon these very nonsensical excerpts of Dr. Batt’s testimony when determining to institute IPR:

We also credit, on the current record, Dr. Batt’s testimony that a skilled artisan would have been motivated to use Larson’s assay to unambiguously detect up to three analytes in a single droplet, as an alternative to “limiting an experiment to only single-target droplets” because an

“ability to acquire data not just from a fraction of the droplets, but from all droplets in the experiment would...be extremely cost effective” and improves the “total data collected” in an experiment.

Paper 11, 37 (citing EX1002, ¶338).

But Dr. Batt's testimony is not based on evidence, is conclusory at best, inconsistent with this Petitioner's apparent theory of invalidity, and in any event does not come close to providing a legally sufficient basis for a POSA to modify Larson to arrive at the '921 Patent claims. EX2017, 175:16-177:14, 179:14-180:7, 181:6-182:3. Petitioners cannot satisfy their burden through “mere conclusory statements,” but “must instead articulate specific reasoning, based on evidence of record” that supports an obviousness determination. *In re Magnum Oil Tools*, 829 F.3d at 1380.

(2) The reducing dilution in Larson theory.

In direct tension with his terminal dilution theory, Dr. Batt inexplicably pivots to advance the exact opposite theory that Larson should be modified to ***undilute the sample***, thus increasing concentration and the number of multiple occupancy droplets for analysis. See EX1002, ¶338; EX2018, ¶127; EX2017, 177:15-179:13 (“Are you talking about increasing the concentration? I wouldn't be increasing, I would be reducing the dilution, right . . . It does say the dilution factor for the sample decreases, so that meaning the amount of dilution I carry out

is less”), 219:19-221:21 (“So if I was practicing Larson, I would do a less dilute sample so I could look at multiple occupancies, because I had the capabilities of doing it.”).

Dr. Batt opines “a POSA would have been motivated to use this strategy because limiting an experiment to only single-target droplets severely impacts the total data collected in that experiment.” EX1002, ¶338. As additional purported motivations for modifying Larson, Dr. Batt states:

These assays, especially at the time of the '921 patent, were quite costly to set up and run, for example, as discussed in Larson, many reagents are required. *See, e.g.*, EX1017 ¶68. The ability to acquire data not just from a fraction of the droplets, but from all droplets in the experiment would thus be extremely cost effective.

Additionally, by allowing more DNA into each droplet, the dilution factor for the sample decreases, meaning less sample exists and less run-time on the machine is necessary.

EX1002, ¶138.

These purported motivations demonstrate that Dr. Batt's theory is to modify Larson by increasing the number of multiple occupancy droplets, and decreasing the number of empty droplets, by reducing dilution (increasing concentration), ostensibly to “impact[] the total data collected in that experiment,” “acquire

data . . . from all droplets in the experiment,” “allow more DNA into each droplet,” and “the dilution factor for the sample decreases.” EX2018, ¶131; *see* EX1002, ¶338. Again, the Board appears to have given significant weight to these purported motivations for modifying Larson. *See* Paper 11, 37.

However, each of the purported motivations that Dr. Batt points to goes against Larson's express teachings. EX2018, ¶131. For example, despite the limits that heavy dilution imposes on the data collected, Larson asserts that the benefits of heavy dilutions are nonetheless worth it to avoid the “error” caused by the possibility of probes overlapping one another in multiple occupancy: “The need for large dilutions *strongly favors* the large number of dPCR reactions.” EX1017, ¶128; EX2018, ¶¶58-63, 89, 94, 132. Indeed, attempting to “acquire data . . . from all droplets in the experiment” and “allow more DNA into each droplet,” and decreasing the “dilution factor,” as Dr. Batt proposes, would all *aggravate* (if not make certain) the possibility of unintended “cross-reactivity” between analytes in a given droplet—which Larson teaches *must* be avoided: “[h]igher degrees of multiplexing would *require* greater dilution.” EX1017, ¶129; *see also id.*, ¶¶6, 96; EX2018 ¶¶33-34, 53, 58-63, 89, 94, 132.

Accordingly, fatal to Petitioner's theory, nothing in Larson would have motivated a POSA to ignore Larson's express teachings—and indeed, to modify Larson's principle of operation—to try to obtain the scheme Dr. Batt proposes by

reducing dilution (increasing concentration) in this apparent theory. EX2018, ¶¶119, 76 (*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”) (*quoting In re Ratti*, 46 CCPA 976, 270 F.2d 810, 813 (1959); *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984)). Moreover, Dr. Batt’s motivation an expectation of success arguments should be rejected because they are conclusory and he cites no evidence to support them. EX2017, 179:14-182:3.

c. Petitioner further failed to meet its burden for claims 4 and 13.

Petitioner further failed to meet its burden regarding at least dependent claims 4 and 13. As stated *supra* §V.A.3.c, Petitioner took the legally untenable position that the same disclosure in Larson (FIG. 15) anticipates claims 4 and 13. Petitioner takes the identical position regarding claims 4 and 13 in Ground 3, without further elaboration. *See* Petition, 62 (claim 4 “[d]isclosed and/or rendered obvious”); 64 (claim 13 “[d]isclosed”). Accordingly, Petitioner failed to establish obviousness of these claims for the same reasons as stated *supra* §V.A.3.c.

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

Petitioner alleged claim 11 is obvious over Larson combined with Saxonov and Silverbrook. Petition, 66-67. Claim 1 is not obvious over Larson. *Supra*, §V.A.3. Petitioner has not shown that Saxonov is prior art. *Supra*, §II.D. Even assuming Silverbrook teaches what Petitioner alleged (it does not), Petitioner has not explained how it cures Larson's many deficiencies detailed above. *See supra* §§V.B.1-5. Thus, Petitioner wholly failed to meet its burden of demonstrating that claim 11 is obvious in view of Larson, Saxonov, and Silverbrook. EX2018, ¶138.

B. Secondary Considerations of Non-Obviousness Support Patentability.

"Objective indicia of nonobviousness must be considered in every case where present." *Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016). "The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis. Indeed, [the Federal Circuit has] held that evidence of secondary considerations may often be the most probative and cogent evidence in the record." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (quotation marks omitted). Here, several secondary considerations further demonstrate the challenged claims' patentability.

1. There was a Long-felt Need for the Claimed Invention.

“Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.” *WBIP*, 829 F.3d at 1332.

Here, PO's innovations described and claimed in the '921 Patent addressed a long-standing problem in the field: as the number of analytes in a biological sample increases, it quickly becomes significantly more complicated and difficult to uniquely identify those analytes. EX1001, 1:35-47; EX2018, ¶29. Early assays used PCR to amplify (create copies of) each of the target polynucleotide analyte molecules, and often involved gel electrophoresis to separate the various PCR products that distinguished the analytes. EX2018, ¶29. 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. EX1001, 11:18-51, 8:33-62; EX2018, ¶30. Increasing the numbers of probe types (each with distinct fluorophore color) and channels (one per color) increases the number detectable analytes. EX1001, 12:39-45; EX2018, ¶31. But this has the limitation of the number of distinct colorimetric probes and optical channels that could be assayed simultaneously. EX1001, 12:39-45; EX2018, ¶31. The '921 Patent refers to analytes that are indistinguishable from one another in a given assay as being

“degenerate.” EX1001, 16:47-50; EX2018, ¶36. Existing technology sought to avoid degeneracy by operating at limiting or terminal dilution, where almost all droplets contain either zero or one analyte molecule. EX2018, ¶¶33-34, 83-92. Thus, such approaches wasted significant material and time and were more expensive and complex. *See* EX1001, 1:35-47, 8:45-62; EX2018, ¶¶36, 83-92. 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. EX1001, 1:35-47, 8:45-62; EX2018, ¶¶36, 83-92. The '921 Patent solved these long-felt problems by offering a solution that extended the number of uniquely identifiable analyte molecules without adding color channels. EX2018, ¶¶83-92. Thus, this secondary indicium further negates Petitioner's obviousness theories.

2. Bio-Rad's Infringing Products Covered by the Challenged Claims Were Commercially Successful as a Result of Using the Claimed Invention.

“Demonstrating that an invention has commercial value, that it is commercially successful, weighs in favor of its non-obviousness.” *WBIP*, 829 F.3d at 1337. Bio-Rad has heavily promoted the high throughput multiplexing aspects of its devices that run assays covered by the '921 Patent. EX2019 at 2

(describing QX ONE as “high throughput, multiplexed”); EX2020 at 2 (advertising QX600 as detecting up to 12 targets with six color channels). Bio-Rad's sales increased appreciably when it introduced the QX ONE product that runs assays covered by the '921 Patent. EX2021 at 3. Thus, this secondary indicium also weighs against Petitioner's obviousness theories.

3. The Caltech-ChromaCode License Entered into Outside of Litigation Supports Non-Obviousness.

Industry praise and licensing of the invention are also important secondary considerations that support patentability here. *See Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 783 F.3d 1337, 1344, 1346 (Fed. Cir. 2013). In this case, in 2015 ChromaCode, Inc. took an exclusive, royalty-bearing license to the '921 Patent family to develop and commercialize PCR products covered by the patents. *See* EX2022 at 2-3. ChromaCode did not license the patents under threat of litigation but rather to develop the valuable technology covered by PO's patents, including the '921 Patent. *Id.*

4. Praise for the '921 Patent's Claimed Invention Supports Patentability

Further demonstrating non-obviousness, in Petitioner's own SEC filings and marketing materials Petitioner itself has praised the multiplexing capability claimed in the '921 Patent as embodied in Petitioner's infringing products. EX2023, 21 (praising QX600 as having unequalled multiplexing and explaining it

was part of Bio-Rad's growth strategy); *see Institut Pasteur*, 783 F.3d at 1344, 1346. This secondary indicium, therefore, also demonstrates that the challenged claims are non-obvious.

VI. CONCLUSION

For at least these reasons, the Board should uphold patentability of all of the '921 Patent's claims.

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: June 20, 2025

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 June 20, 2025, a copy of the foregoing **PATENT OWNER'S RESPONSE WITH UPDATED EXHIBIT LIST AND EXHIBITS 2016-2023** were served via 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
dwalter@jonesday.com
Jones Day
555 California Street, 26th floor
San Francisco, CA 94104

Matthew W. Johnson
mwjohnson@jonesday.com
Jones Day
500 Grant Street, Suite 4500
Pittsburgh, PA 15219

/Jesse A. Salen/

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

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 13,751 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: June 20, 2025

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