

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

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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PETITIONER'S UPDATED EXHIBIT LIST

Exhibit #	Description
EX1001	U.S. Patent No. 11,827,921 “the ’921 patent”
EX1002	Declaration of Carl A. Batt, Ph.D.
EX1003	Joint Claim Construction Statement, filed on June 18, 2024, Dkt No. 65, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , Case No. 5:23-cv-06360, N.D. Cal.
EX1004	U.S. Patent Application Publication No. US 2013/0040841 A1 “Saxonov”
EX1005	Information Disclosure Statement noting Saxonov from Prosecution File History of U.S. Patent No. 10,068,051 filed on August 5, 2014
EX1006	Notice of Allowance from Prosecution File History of U.S. Patent No. 11,827,921 filed on August 10, 2023
EX1007	U.S. Patent Provisional Application No. 61/510,013 (filed July 20, 2011) (Serge Saxonov, Simant Dube, John F. Regan, applicants) (“the ’013 Provisional”)
EX1008	Intentionally Left Blank
EX1009	U.S. Patent Application Publication No. US 2011/0312704 A1 “Silverbrook”
EX1010	Intentionally Left Blank
EX1011	Intentionally Left Blank
EX1012	U.S. Patent No. 11,827,921 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, <i>ChromaCode, Inc. et al. v. Bio-Rad Laboratories, Inc.</i> , Case No. 5:23-cv-06360, N.D. Cal.
EX1013	Internet Archive WayBackMachine, Feb. 22, 2024, archived copy of Synbio Technologies, Precision and Accuracy with TaqMan Probes, https://synbio-tech.com/precision-and-accuracy-with-taqman-probes/ , https://web.archive.org/web/20240519044916/https://synbiotech.com/precision-and-accuracy-with-taqman-probes/ , accessed Sept. 12, 2024.
EX1014	Pamela M. Holland, et al., “Detection of specific polymerase chain reaction product by utilizing the 5' → 3' exonuclease activity of <i>Thermus aquaticus</i> DNA polymerase,” <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 88, pp. 7276-7280, August 1991 Biochemistry “TaqMan Paper”

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EX1015	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 10,770,170 filed on March 7, 2018
EX1016	Information Disclosure Statement from Prosecution File History of U.S. Patent No. 11,827,921 filed on May 1, 2020
EX1017	U.S. Patent Application Publication No. US 2011/0250597 A1 "Larson"
EX1018	Intentionally Left Blank
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EX1022	U.S. Patent No. 9,366,632 "Link"
EX1023	Federal Judicial Caseload Statistics (2023), at https://www.uscourts.gov/statistics-reports/analysis-reports/federal-judicial-caseload-statistics
EX1024	Civil Minutes - General, filed on December 7, 2023, Dkt No. 34, <i>ChromaCode, Inc. et al. v. Bio-Rad Laboratories</i> , Case No. 2:23-cv-08417, C.D. Cal.
EX1025	PO's Response to Non-Final Office Action from Prosecution File History of U.S. Patent No. 11,827,921 filed on March 28, 2023
EX1026	Final Rejection from Prosecution File History of U.S. Patent No. 11,827,921 filed on May 10, 2023
EX1027	Joint Stipulation and Order Regarding Filing of Second Amended Complaint and Amended Case Schedule, filed on March 27, 2024, Dkt No. 53, <i>ChromaCode, Inc. v. Bio-Rad Laboratories et al.</i> , Case No. 5:23-cv-06360, N.D. Cal.
EX1028	Amended Complaint for Patent Infringement of U.S. Patent Nos. 10,068,051 and 10,770,170, filed on October 13, 2023, Dkt No. 12, <i>ChromaCode, Inc. et al. v. Bio-Rad Laboratories</i> , Case No. 2:23-cv-08417, C.D. Cal.
EX1029	PO's Response to Final Office Action from Prosecution File History of U.S. Patent No. 11,827,921 filed on July 10, 2023
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EX1032	Intentionally Left Blank
EX1033	U.S. Patent No. 9,441,266 "Larson patent"
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EX1036	Nucleic Acids, https://www.genome.gov/genetics-glossary/NucleicAcids , updated July 7, 2024
EX1037	Introduction of Molecular Beacons, https://molecular-beacons.org/MB_introduction.html (downloaded July 10, 2024)
EX1038	Shivaprasad H. Sathyanarayana and Lauren M. Wainman, "Chapter 2, Laboratory approaches in molecular pathology: the polymerase chain reaction," <i>Diagnostic Molecular Pathology</i> , 2024
EX1039	U.S. Patent No. 10,068,051 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, <i>ChromaCode, Inc. et al. v. Bio-Rad Laboratories</i> , Case No. 5:23-cv-06360, N.D. Cal.
EX1040	U.S. Patent No. 10,770,170 Infringement Claim Charts from Infringement Contentions, served on March 21, 2024, <i>ChromaCode, Inc. et al. v. Bio-Rad Laboratories</i> , Case No. 5:23-cv-06360, N.D. Cal.
EX1041	Order of Consolidation filed August 16, 2024, Dkt. No. 77, <i>ChromaCode, Inc. v. Bio-Rad Laboratories, Inc.</i> , Case No. 5:23-cv-04823, N.D. Cal.
EX1042	Order Reassigning Case filed August 20, 2024, Dkt. No. 78, <i>In re: ChromaCode Litigation</i> , Case No. 5:23-cv-04823, Dkt. No. 78, N.D. Cal.
EX1043	Declaration of Carl A. Batt, Ph.D. in Support of Petitioner's Reply to Patent Owner's Response
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I. INTRODUCTION

In its Institution Decision, the Board correctly found that Ground 3 established a reasonable likelihood that the claims of the '921 patent are obvious in view of Larson and Saxonov. Patent Owner's (PO) response to this ground rests entirely on the unfounded assertion that Larson does not teach multiple targets per droplet. This argument is directly contradicted by the record: the Petition clearly and unequivocally demonstrates that Larson expressly describes methods adaptable for "multiple occupancy." During cross-examination, PO's own expert, Dr. Kevin Struhl, was confronted with Larson's disclosure—including Figure 11a, which provides both data and explicit instructions for detecting multiple targets—and was forced to concede that Larson addresses the detection of multiple targets within a single droplet. Saxonov, in turn, contains virtually identical teachings—including Figure 4—which is indisputably part of the prior-art '013 Provisional, and which Dr. Struhl also conceded discloses multiple occupancy.

Despite these clear admissions, PO's response relies entirely on Dr. Struhl's declaration to argue, without basis, that Larson is limited to one target per droplet. However, as detailed herein, Dr. Struhl's testimony is entitled to no weight: he was unfamiliar with the priority date, lacked knowledge of the historical development of the field, did not understand the claims, and failed to recognize the Petition itself. When presented with the clear and unambiguous examples in Larson and Saxonov,

Dr. Struhl resorted to the baseless and unsupported suggestion that the data might have been fabricated. Ultimately, as demonstrated below, the arguments in his declaration are not only unsupported, but are clear mischaracterizations of the record and should be disregarded entirely.

Moreover, Petitioner has advanced additional, independent grounds for unpatentability, including Ground 1—anticipation by Larson. PO's only response to this ground is a litigation-driven claim construction argument that is inconsistent with the position PO has maintained for years. PO offers no meaningful rebuttal under a proper claim construction and fails to address the substance of the anticipation ground. The record overwhelmingly supports unpatentability on multiple, independent bases.

II. DR. STRUHL'S TESTIMONY SHOULD BE ACCORDED NO WEIGHT

In all key aspects, PO's response to the Petition relies centrally on the testimony of Dr. Struhl, a chemistry professor at Harvard. Without Dr. Struhl's declaration, PO has no meaningful response to the Petition. Yet, despite his academic credentials, preparation, and substantial compensation (\$1200 per hour, with two full days of deposition preparation, EX1044 9:1–4, 11:19–20; EX2001 ¶ 2), Dr. Struhl confirmed unequivocally on cross-examination that the opinions in his declaration are worthless.

Perhaps most troubling, Dr. Struhl testified that he did not know either the priority date of the '921 patent or the importance of using the correct date, even though the field of multiplex PCR and analyte detection had evolved rapidly during the relevant timeframe. EX1044 32:19–33:4. When asked about the priority date, Dr. Struhl strangely responded, “I’ve not paid attention to priority dates. It’s not my job.” *Id.* 32:3–6; *see also id.* 32:7–10, 36:13–21, 37:24–38:4, 44:24–45:16, 46:6–47:3, 65:17–66:16, 71:2–10, 71:16–22. He stated, “I don’t know what date it is. I’m not a lawyer. I don’t—that’s a legal question.” *Id.* 32:19–35:12. When pressed, he admitted, “I don’t pay attention to priority dates. That wasn’t my job. I’m a scientific expert, not a priority date expert.” *Id.* 33:2–4.

Yet, “[u]nder U.S. patent law, the priority date is a crucial element in determining patent validity because it delineates the cutoff for prior art.” *Evonik Degussa GmbH v. Materia Inc.*, 53 F. Supp. 3d 778, 785 n.5 (D. Del. 2014) (citing *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1372 (Fed. Cir. 2011)). Indeed, every key issue relevant to obviousness—including motivation to combine and reasonable expectation of success—must be analyzed through the lens of a POSA **as of the priority date**. *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 714 F. Supp. 3d 652, 726 (N.D.W. Va. 2024) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966)) If, as Dr. Struhl confirmed, he did not know the priority date, he could not possibly have done a proper obviousness analysis.

Just as troubling as the foregoing, Dr. Struhl further admitted he did not know or consider the historical development of the art and that he had not investigated when key developments in multiplex PCR or related probe technologies became known or widely used. As Dr. Struhl stated, “I didn’t do a historical perspective at all.” EX1044 58:6–11. When asked about the timing of significant advances in the field, he responded, “why would I care exactly what year that was?” *Id.* 59:19–60:4; *see also id.* 52:9–53:7, 54:17–55:3, 55:8–25, 56:9–57:9, 57:13–20, 60:17–63:11 (“I don’t have the slightest idea.... I didn’t do a historical perspective. No normal person cares about that.”), 163:11–16, 179:21–180:19, 181:6–9. Dr. Struhl confirmed he did not anchor his analysis to the state of the art as of the priority date, admitting, “I have not done historical analysis of when things were first done.” *Id.* 62:15–23.

Dr. Struhl’s testimony that he did not “do a historical perspective at all” is disturbing because this is precisely what obviousness requires—a historical lookback through the eyes of a POSA to figure out how the POSA would have viewed the prior art and would have manipulated it. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000) (holding that the obviousness analysis requires “casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field”). Without “historical perspective,” there is no obviousness analysis.

Things don't get much better when one considers Dr. Struhl's understanding of the patent claims. To begin, he did not know the standard for claim construction, testifying that "I don't know the legal issues. I'm not a lawyer. I'm a scientist." EX1044 74:17–75:3; *see also id.* 72:4–15, 72:25–73:2, 77:3–78:8, 83:23–25, 84:1–12. Consistent with this, when asked about key claim language requiring each target to be encoded by "one component" of a signal, he bluntly admitted "I must say I don't really completely understand what this—this particular sentence means." *Id.* 97:16–98:11; *see also id.* 96:12–14. Likewise, his testimony about whether he even reviewed the dependent claims was incomprehensible. He stated, "I probably shouldn't even be opining on Claim 2 since I never looked at it before," but then stating, "If you mean did I see it, yes." *Id.* 100:14–23, 100:8–21 ("I'm not going to get into the difference between Claim 1 and 2. I haven't analyzed Claim 2."), 102:6–10, 102:20–103:8.

Dr. Struhl did not even have a reasonable grasp of the theories in the Petition. The Petition and supporting expert declaration extensively relied upon PO's district court infringement contentions, including its apparent claim interpretations and "coding tables." *See, e.g.,* Paper 1 at 10–12, 22 ("All other claim terms are interpreted consistent with Patent Owner's arguments and positions in the parallel district court proceeding." (citing EX1003)), 24, 27, 30, 32, 36, 42, 51; EX1002 ¶¶ 70–75, 113, 117–122, 137, 146, 178–181, 244, 282, 327. Although Dr. Struhl's

declarations state that he reviewed these contentions, he repeatedly disclaimed any understanding or opinion about these materials. EX1044 104:15–105:4, 106:2–24, 109:1–11, 111:3–15, 112:1–113:10, 114:23–115:6. When asked why he supposedly reviewed the infringement contentions, he said “I actually don’t know the answer. Maybe just to know that there was an infringement case. I don’t really know why.” *Id.* 111:16–25. When asked about Dr. Batt’s opinions that relied upon the contentions, Dr. Struhl admitted, “I had nothing to do with infringement.” *Id.* 112:1–113:10. He also could not recall or explain the content or significance of PO’s schemes discussed in the Petition and Dr. Batt’s declaration. *Id.* 109:19–110:6.

In fact, Dr. Struhl ultimately demonstrated a total lack of familiarity with the Petition itself. *Id.* 24:17–23, 22:20–23:12, 30:6–14. When asked if he had reviewed the Petition, he equivocated: “Well, it looks familiar, but I don’t see it on my list, so I don’t really know how to answer the question.” *Id.* 19:24–20:7; *see also id.* 21:5–22:7. Then, when shown the Petition, he stated “I can’t swear that this is exactly the same thing that I was citing, but ... it could be because it is a petition, and I cited a petition.” *Id.* 24:17–25:17. Based on such a poor familiarity with the record, Dr. Struhl’s opinions simply cannot be trusted.

III. PO’S NEW CLAIM CONSTRUCTIONS ARE ERRONEOUS

PO’s response relies upon two entirely new claim constructions that depart from the positions it has maintained throughout the past year and a half of district

court litigation. As documented below, the Board should reject these litigation-driven constructions, which appear to have been adopted solely for the purposes of this proceeding and lack any grounding in the claim language, specification, or prosecution history. Notably, PO fails to offer any response to the Petition under its original claim construction, confirming that PO's response fails.

A. PO's Construction of " $F \geq 2$ and $M \geq 3$ " Is Unsupported by the Intrinsic Record and Contradicted by Dr. Struhl's Testimony

PO asserts that "in all cases, $F \geq 2$ and $M \geq 3$." Paper 17 at 12. This new construction is a clear attempt by PO to avoid the explicit disclosures of Larson and Saxonov, rather than a position rooted in the intrinsic record. PO's attempt to impose additional limitations on the value of "F" and "M" is not only unsupported by the intrinsic record, but also directly contradicted by the very testimony on which it relies.

The language of claim 1 is clear, and expressly states:

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, based on detection of said F wavelength components, when M is greater than F.

EX1001 67:14–21. The claim language does not require "F" to be at least 2 or "M" to be at least 3 as PO contends—in fact, the claim is agnostic as to the specific value

of “F” and “M”; it simply requires that “M is greater than F,” meaning “F” can be any value less than “M,” including 1. *See, e.g.*, Paper 1 at 23, 28; EX1002 ¶¶ 111, 124. When Dr. Struhl was confronted with this unambiguous claim language, he unequivocally acknowledged that “F” can be 1: “According to—in this claim, F could be 1.” EX1044 85:9–22.

PO, however, disregards the clear claim language and instead relies on nothing but a few examples from the specification to artificially and improperly restrict the claims. *See* Paper 17 at 12 (citing EX2018 ¶ 47). PO attempts to bolster its reliance on examples from the specification with extrinsic evidence in the form of Dr. Struhl's testimony. But Dr. Struhl conceded that his opinions—like PO's arguments—were based on examples from the specification, not the claim language. EX1044 195:25–196:8, 196:24–197:14, 197:23–199:12. Dr. Struhl confessed that he did not understand the legal justification for his reliance on such examples, stating, “That's a legal thing.... I did not do legal stuff.” *Id.* 197:23–199:12. More significantly, Dr. Struhl admitted that the specification describes embodiments utilizing a single color, meaning “F” is 1, directly undercutting PO's position. *See id.* 68:15–23, 70:16–71:1. Specifically, Dr. Struhl conceded that the '921 patent's disclosure of a “single color coding scheme” at 22:18–62 is applicable to the claimed invention, and that this disclosure teaches the use of “two different intensities” of the same color—*i.e.*, “F” is 1 to distinguish “two analytes,” *i.e.*, “M” is 2. *Id.*; *see*

also EX1001 22:18–62, 23:38–47; *Epos Techs. Ltd. v. Pegasus Techs. Ltd.*, 766 F.3d 1338, 1347 (Fed. Cir. 2014) (“A claim construction that excludes a preferred embodiment...is rarely, if ever correct and would require highly persuasive evidentiary support.” (cleaned up)).

PO's motivation is clear: PO seeks to improperly rewrite the claim language by importing unclaimed features from non-limiting examples in the specification. The Federal Circuit, however, has repeatedly cautioned against such attempts to import features from exemplary embodiments “to bolster ... validity arguments,” *AC Techs. S.A. v. Amazon.com, Inc.*, 912 F.3d 1358, 1366 (Fed. Cir. 2019), and “it is well settled that ... courts do not redraft claims” to preserve their validity. *Quantum Corp. v. Rodime, PLC*, 65 F.3d 1577, 1584 (Fed. Cir. 1995).

B. PO's Shifting “Single Sample Volume” Construction Is Litigation-Driven and Contradicts the Intrinsic Record

PO also advances a new construction of “single sample volume” that is likewise fundamentally at odds with the record. In the parallel district court litigation, PO accused Petitioner's products of infringement under a construction that expressly encompassed scenarios where “the detection is performed in a single *sample volume* that is *subsequently* partitioned into multiple droplets.” Paper 1 at 30 (quoting EX1012 at 20). PO maintained this infringement theory for over a year and a half, fully aware of Petitioner's invalidity arguments. Only after the strength of Petitioner's validity challenges became clear did PO attempt to abandon

this construction, seeking to amend its contentions and now arguing here that “single sample volume” *excludes* volumes that are “subsequently partitioned into droplets” Paper 17 at 26.

The intrinsic record contradicts PO's new position. The claim language requires detecting “M analytes” in a “single sample volume,” with amplification occurring in that same volume. EX1001 67:9–26. The specification makes clear that a “single sample volume” is not limited to a droplet, but may be any volume, such as a “tube or a bottle.” *Id.* 38:63–65. Nothing in the claims or specification precludes the liquid in such volumes from subsequently being partitioned or separated—for example, using a common process known as “droplet-based microfluidics,” where a single sample volume is analyzed by creating uniform, picoliter-to-nanoliter-sized droplets that are suspended in an immiscible fluid. EX1043 ¶ 14. The specification describes both separated and non-separated scenarios, stating “the invention *could* be used with separation ...if desired.” EX1001 36:4–6 (emphasis added). The prosecution history is consistent: the claims were amended to remove a requirement that the assay be performed “in a single sample volume *without ... separation*,” replacing this limitation with broader language requiring only that amplification occur in the “single sample volume.” EX1029.002. Notably, when PO intended to exclude “separation” or limit claims to

“droplets” in other related patents, it did so. *See* Paper 9 at 2 (citing IPR2024-01177, EX1001; IPR2024-01178, EX1001). In the '921 patent, it did not.

PO offers no substantive reason to believe its original construction was incorrect, instead ignoring Petitioner's arguments and adopting a new, narrower interpretation solely to avoid invalidation.

IV. REPLY REGARDING GROUND 3:

Ground 3 asserts that the combined teachings of Larson and Saxonov render claims 1–10 and 12–19 obvious to a POSA, even under PO's newly proposed claim constructions. PO's arguments against obviousness are fundamentally undermined by the admissions of its own expert regarding the knowledge and capabilities of a POSA at the relevant time, particularly with respect to the very feature PO claims as novel—namely, “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).” Paper 17 at 8. As established in the Petition, *see* Paper 1 at 9–10, and confirmed during deposition, both PO and Dr. Struhl expressly agreed with the Petition's definition of a POSA, *see* EX1044 15:19–16:17, 38:5–15, 38:22–39:4, 194:13–24, including that “[a] POSA would have understood ... [t]echniques for labeling probes and detecting multiple targets using fewer differently colored fluorophores than polynucleotide targets.” Paper 1 at 9. Dr. Struhl further testified that a POSA would have been well-versed in multiplex

PCR, fluorescence-based detection, and the use of multiple probes and colors in PCR assays. *Id.* 38:22–39:17, 40:8–19, 42:5–9, 43:13–17, 44:8–13, 48:22–52:8. Critically, Dr. Struhl admitted that multiplex PCR was routine and obvious as early as 2002. *Id.* 36:1–12, 39:5–17, 41:2–11. He also conceded that the prior art, including Saxonov, disclosed essential technical concepts such as modulating the intensity of a TaqMan probe, EX1044 51:15–21, 52:9–18, and using different intensities and multiple colors in a two-dimensional analysis of different analytes. *Id.* 58:19–59:14. These admissions strike at the heart of PO's purported novelty, hollowing out any claim that the '921 patent's subject matter was not taught or suggested by the prior art.

To the extent PO offers any substantive response to Ground 3, it rests solely on the assertion that Larson fails to disclose detection of more than one analyte in a “single sample volume,” and therefore should be disregarded. However, the developed record clearly establishes that Larson does, in fact, teach detection of **multiple** targets within a single droplet. Likewise, Saxonov unequivocally discloses the detection and decoding of multiple targets in a single droplet, a critical teaching that PO neither disputes nor meaningfully addresses. Instead, PO relies exclusively on the Board's preliminary determination that certain portions of Saxonov are not prior art—a position that, as demonstrated herein, is incorrect. PO's Response fails

to rebut Petitioner's showing that the combined teachings of Larson and Saxonov render claims 1–10 and 12–19 obvious to a POSA.

A. Larson Discloses Detection of Multiple Analytes in a “Single Sample Volume”

PO contends that Larson is limited to detecting only a single target per droplet and that the claimed invention is distinct because it enables unambiguous detection of any analyte combination within a “single sample volume,” which, under PO's new construction, excludes later separation. Paper 17 at 27. Larson's disclosures, as confirmed by Dr. Struhl, directly contradict this position.

As the Petition detailed, *see, e.g.*, Paper 1 at 12–13, 22–34, 39–40, 51–57, however, Larson directly addresses the “complexit[ies]” of multiplex PCR, particularly when detecting more targets than available fluorophores (or colors), and explicitly states that its “methods of the invention can accommodate these complications arising from multiple occupancy.” EX1017 ¶ 141. Although most droplets contain a single analyte, Larson explains that the assay follows a Poisson distribution, resulting in some droplets containing multiple analytes. *Id.* ¶ 6. In the “limiting dilution” regime, reactions may have zero, one, or multiple DNA molecules, all consistent with the Poisson distribution. *Id.*; EX1043 ¶ 19. Importantly, Larson confirms that “the invention is compatible with all distributions of DNA loading that conform to limiting or terminal dilution,” making clear that the invention functions even when droplets contain multiple targets. *Id.* ¶ 52. Larson

repeatedly acknowledges the possibility of “multiple occupancy” and affirms that its methods are designed to accommodate these scenarios, despite any associated complications. *Id.* ¶ 141; EX1002 ¶ 332.

For example, Larson describes a method in which a single droplet contains four probes to detect three targets (T1, T2, T3). EX1017 ¶¶ 140–42; *see also* Paper 1 at 25–28. Two probes are labeled with color A (with intensities A1, A2) and two with color B (with intensities B1, B2). EX1017 ¶ 140. T1 is detected by A1 (color A), T2 by B1 (color B), and T3 by both A2 and B2 (colors A and B together). *Id.* The presence of each target is indicated by increased fluorescence in the corresponding color(s): T1 in A, T2 in B, and T3 in both. *Id.* This multiplexed scheme ensures each target is uniquely identified by its fluorescence pattern, with three targets encoded by individual or combined color components. *Id.* Larson also notes that “[i]n the simplest case targets are unlikely to reside on the same DNA fragments, such as when targets are from different cells,” and discloses primer/probe pairings for such cases. *Id.* ¶ 142. Larson further explains that the intensity of signals from color labels can be adjusted to prevent ambiguous results, specifically to avoid overlap between signals from droplets containing different target analytes. *Id.* ¶¶ 35, 146, 150; EX1002 ¶ 163. These methods directly address the challenge of multiple occupancy and enable clear, unambiguous detection of all analyte combinations within a single droplet. *See* Paper 1 at 48–49, 54–57.

This disclosure alone renders the claims of the '921 patent obvious, and the record developed during Dr. Struhl's deposition only reinforces this conclusion. Upon reviewing Figure 11a of Larson and its accompanying disclosure, Dr. Struhl conceded that Larson addresses the detection of multiple targets within a single droplet. EX1044 147:24–148:20, 149:18–150:10, 150:19–151:2, 155:17–156:18, 159:20–160:10, 160:14–161:14. Figure 11a of Larson provides clear, visual evidence of this capability: it depicts the detection of multiple targets in a single droplet and demonstrates the ability to distinguish droplets containing three different combinations of two targets—specifically, the genes BCKDHA and SMN2. *See* Paper 1 at 44, 50; EX1017 ¶¶ 281, 283, 313. The figure presents histograms of droplet fluorescence intensities for three distinct template DNA samples: a no template control (dotted line), BCKDHA only (solid line), and a 1:1 mixture of BCKDHA and SMN2 (dashed line). EX1017 ¶ 131. In the 1:1 BCKDHA to SMN2 case, Larson reports that “three populations were readily apparent,” with peaks at 0.08 V, 0.27 V, and 0.71 V. *Id.* Most notably, Larson further discloses that a “very small peak appeared at ~0.9 V, not visible on the scale of FIG. 11a, that corresponded to droplets occupied by **both genes**”—providing direct and compelling evidence of multiple occupancy. *Id.* ¶¶ 0130–0131 (emphasis added). Thus, Figure 11a also discloses the unambiguous detection of multiple analytes in a single sample volume.

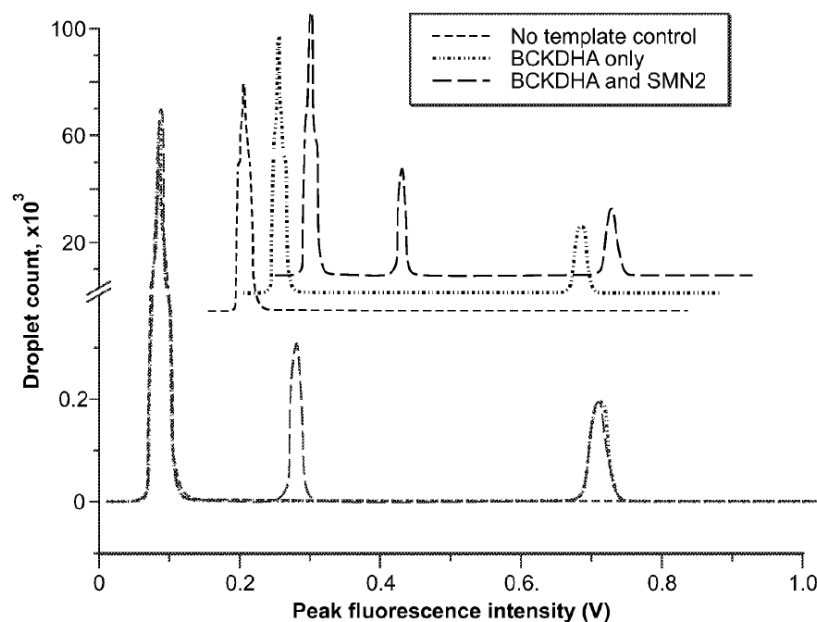


FIG. 11a

Dr. Struhl admitted that he “did not consider this in [his] declaration” and, in fact, did not recall this disclosure “at all.” EX1044 136:1–6. But after being presented with Figure 11a and its accompanying explanation, and when asked directly whether “there [is] any element of Claim 1 ... that is not part of Figure 11,” Dr. Struhl evaded the question and instead speculated, “How do we know they didn’t make it up?” *Id.* 154:6–155:1. This evasive response underscores the strength and relevance of the disclosure in Figure 11a, which Dr. Struhl failed to address substantively. In addition to the evidence provided by Figure 11a, Dr. Struhl further conceded that Larson elsewhere explicitly contemplates the presence of multiple targets within a single droplet. *Id.* 155:5–156:18; *see also* EX1017 ¶¶ 108–13.

Rather than directly addressing these disclosures or Dr. Struhl's admissions, PO focuses on unrelated portions of Larson, erroneously contending that Larson teaches "excluding" droplets that contain multiple analytes in all cases. *See generally* Paper 17 at 19–22, 28–39. PO, however, flatly mischaracterizes Larson.

The portions of Larson PO points to are directed to error correction—specifically, the exclusion of amplification products resulting from polymerase errors during PCR. Larson teaches that for applications demanding extremely high sensitivity—such as the detection of rare genetic mutations in a background of abundant wild-type DNA, as is often required in cancer diagnostics—false positive results can present a significant challenge. EX1017 ¶ 15–18, 168–73. One major source of such false positives is the inherent error rate of DNA polymerases used during PCR amplification. EX1033 ¶ 25. These enzymes can occasionally incorporate incorrect nucleotides, resulting in artificial mutations that are not present in the original sample. *Id.* When searching for naturally occurring mutations, such as those associated with cancer, these polymerase-induced errors can be mistakenly interpreted as true mutations, thereby compromising the accuracy of the assay. *Id.* Recognizing this problem, Larson discloses specific methods for detecting and excluding amplification products that arise from polymerase errors. EX1017 ¶ 15–18, 168–73. By identifying and removing these erroneous products from the analysis, Larson's approach ensures that only genuine, naturally occurring mutations

are detected, thereby enhancing the reliability and specificity of mutation detection in highly sensitive applications. EX1033 ¶ 25.

PO improperly mischaracterizes this disclosure and disregards Larson's separate discussion of droplets containing more than one true analyte ("multiple occupancy"). Dr. Struhl confirmed this distinction, *see* EX1044 118:8–121:1–9, 126:8–18, 128:4–21, 134:25–135:4, in essence conceding that PO's reliance on Larson's disclosure of polymerase error is misplaced and irrelevant. In fact, Dr. Struhl did not appear to recognize that Larson was addressing polymerase errors at all, stating he was "not sure what [Larson was] getting at," and was "not sure why [polymerase errors were] relevant to anything," *id.* 120:17–25, which is "why [he] didn't opine on it." *Id.* 127:3–12. Dr. Struhl reiterated this point multiple times, saying: "And as I said, I don't think it's very important, which is why I didn't opine on it." *Id.* 127:20–128:3; *see also id.* 119:1–24, 121:1–9, 122:25–123:16, 124:19–126:7.

B. PO Fails to Address Key Saxonov Disclosures and Obviousness Arguments

While the argument set forth above with respect to Larson is sufficient to confirm obviousness based on Ground 3, PO also fails to address Saxonov's relevant disclosures. Instead, PO relies solely on the Board's preliminary view that Figure 10 and paragraphs 78 and 79 of Saxonov are not prior art. *See* Paper 17 at 40; Paper 11

at 29. The full record that has developed following institution, however, leaves no doubt that Saxonov includes invalidating disclosure that is bona fide prior art.

Crucially, the vast majority of Saxonov's disclosure—including key teachings relevant to obviousness—are identical to those in the '013 Provisional, as confirmed by PO's own evidence and expert. *See, e.g.*, EX2001 ¶¶ 88, 89; EX2007. Dr. Struhl testified that "FIGS. 1–8A and 8B of Saxonov generally correspond to, and are carried over from, FIGS. 1–8 of the Saxonov Provisional," and that "¶¶ 2–16, 19–36, 38–53, 45–68, and 72–75 of Saxonov generally correspond to page 1, line 10 through page 20, line 22 of the Saxonov Provisional." EX2001 ¶¶ 88, 89. PO does not address these admissions by its own expert, which are fatal to its position, as there is no dispute that these disclosures of Saxonov constitute prior art. *See* Paper 12 at 10 ("[PO] is cautioned that any arguments not raised in the response may be deemed waived."); *Microsoft Corp. v. IPA Techs., Inc.*, No. IPR2019-00813, 2020 WL 6084149, at *67 (P.T.A.B. Oct. 15, 2020) ("To the extent PO has not responded to Petitioner's arguments and evidence with respect to this claim limitation, we find that PO has waived any such argument.").

The "carried over" portions of the '013 Provisional—which PO ignores in its response—clearly teach detecting targets using color combinations and distinguishing between droplet types containing "two, three, four, or more targets," without requiring later separation. EX1007 9:15. Specifically, Saxonov describes

methods utilizing two colors to detect three distinct targets, resulting in eight separate data clusters within a two-dimensional color/intensity space for enhanced resolution. *See id.* 5:19–6:3. This approach is further reinforced at 10:8–11:13, where both textual and tabular disclosures clearly show that multiple targets per droplet yield eight unique populations based on color combinations.

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

Id. 11:3.

PO's own Preliminary Response (Paper 8) expressly acknowledged these disclosures. PO admits that Saxonov ¶ 41—which corresponds to the '013 Provisional at 10:8–11:3—explicitly teaches that the number of distinct droplet populations is determined by 2^N , where N is the number of targets, and even reproduces Saxonov's tabular representation. *See* Paper 8 at 22–23. Similarly, PO concedes that Saxonov ¶ 20—which corresponds to the '013 Provisional at 5:19–6:3—teaches that eight different populations of droplets “would be separated in a two-dimensional intensity space.” *Id.* 56–57; *see also* EX1044 167:1–170:9 (Dr. Struhl confirming that Saxonov discloses distinguishing eight populations of

droplets from three targets in ¶ 20). Thus, the '013 Provisional contains, *verbatim*, the substance of Saxonov ¶¶ 20 and 41, as corroborated by PO's own exhibits and expert testimony. See EX2001 ¶¶ 88–89; EX2007. Indeed, Dr. Struhl's testimony provides additional support for the conclusion that the claims of the '921 patent are obvious in light of Saxonov's teachings.

During his deposition, Dr. Struhl was questioned regarding his views on Saxonov's Figure 4, which is indisputably included in the '013 Provisional. See EX2001 ¶¶ 88, 89. Figure 4 depicts “an exemplary graph 102 of data corresponding to an exemplary digital PCR assay for Target 1 and Target 2 performed in droplets.” EX1007 15:12–17:3.

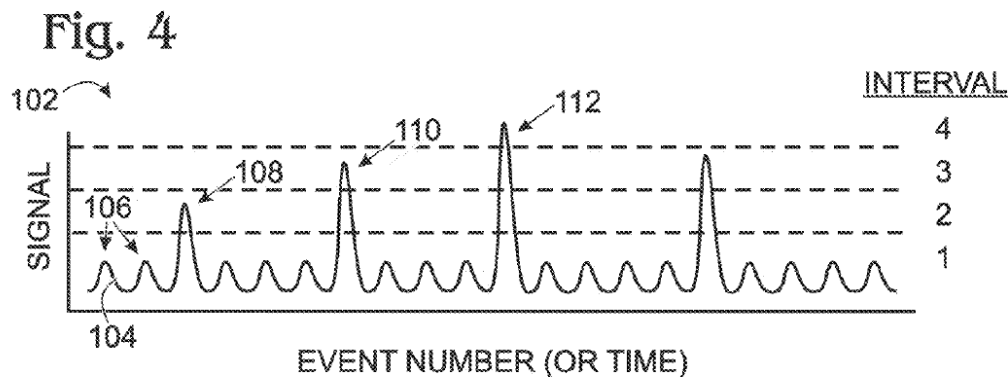


Figure 4 illustrates a signal 104 corresponding to light collected within a “single channel,” which can be analyzed to determine “whether neither Target, Target 1 alone, Target 2 alone, or ***both Targets 1 and 2*** are present in each droplet.” *Id.* 15:17–19 (emphasis added). In a dual-target system, Saxonov teaches that the

“strength or intensity of the signal” can be divided into four distinct ranges, each corresponding to: “no Target (Interval 1[, Peak 106]), Target 1 alone (Interval 2 [, Peak 108]), Target 2 alone (Interval 3[, Peak 110]), or *both Targets 1 and 2* (Interval 4[, Peak 112]).” *Id.* 15:19–16:20 (emphasis added). This is the exact situation depicted in Larson’s Figure 11a. EX1043 ¶¶ 30, 37.

When presented with this disclosure, Dr. Struhl attempted to dismiss its significance—just as he did when questioned about Larson’s Figure 11a—by asserting, “Figure 4 is not real data.” EX1044 174:3–24. Nevertheless, he was compelled to admit that Peak 112 indeed represents “droplets that have both targets.” *Id.* Importantly, the PCR assay depicted in Figure 4 is substantively identical to the one disclosed in Figure 11a of Larson, as discussed above in Section.IV.A. EX1043 ¶¶ 30, 37. This direct correspondence powerfully reinforces Dr. Batt’s position that a POSA would have been clearly motivated to combine these teachings. Larson already demonstrates the same methodology, EX1002 ¶¶ 344–48, and contrary to PO’s assertions, this motivation does not hinge on restricting Larson’s disclosure to terminal dilution or reducing dilution altogether. Paper 17 at 54–62; *contra* EX1043 ¶¶ 36–37. Instead, both references—Larson and Saxonov—expressly endorse this approach.

V. REPLY REGARDING GROUNDS 1, 2, AND 4

PO's response to Grounds 1, 2, and 4 reiterates the same arguments raised under Ground 3, relying on the same litigation-driven claim constructions and an overly-narrow reading of Larson that disregards the reference's explicit disclosures. PO further argues that Larson does not disclose amplification within a "single sample volume." Paper 17 at 34–36. This argument is directly contradicted by Larson's explicit teachings. After the sample volume is separated into droplets, Larson clearly states that "the droplets are collected off-chip...in a PCR thermal cycling tube"—which constitutes the same "single sample volume"—"and then thermally cycled in a conventional thermal cycler." EX1017 ¶ 79. Larson reiterates this point: "Approximately 25 uL of the PCR reaction mixture was collected as an emulsion from the droplet generation chip and thermally cycled in a DNA Engine (Bio-Rad, Hercules, Calif.)." *Id.* ¶ 193; *see also* Paper 1 at 31–32. These disclosures leave no doubt that Larson teaches amplification within a "single sample volume," directly refuting PO's contention.

For claims 2, 4, and 6–7, PO merely asserts that the same arguments "apply equally" to those claims, offering no additional analysis or substantive response. For claims 4, 13, and 14, PO's arguments are entirely conclusory and fare no better than its other contentions. Notably, PO contends that the same disclosure of Larson cannot invalidate both claims 4 and 13, *see* Paper 17 at 38, but provides no

supporting authority for this assertion. With respect to claim 14, PO simply asserts—without any meaningful analysis—that a POSA would not have found it obvious to assemble the assay of claim 1 into a “kit,” merely echoing Dr. Struhl’s conclusory statements. *Id.* at 38–39. But neither PO nor Dr. Struhl address the detailed explanation in the Petition and Dr. Batt’s declaration, which demonstrate that combining known assay components into a “kit” was routine and would have been obvious to a POSA—an understanding of skill that Dr. Struhl does not dispute. *See* Paper 1 at 40–43; EX1002 ¶¶ 214–254.

In all events, PO’s recycled arguments fail to address or refute Petitioner’s un rebutted evidence demonstrating that Larson expressly anticipates claims 1–10 and 13–19, renders claims 2, 4, 6, 7, and 14–19 obvious, and that the combination of Larson, Saxonov, and Silverbrook renders claim 11 obvious.

VI. REPLY REGARDING SECONDARY CONSIDERATIONS

The Federal Circuit has made clear that weak secondary considerations “do not overcome a strong prima facie case of obviousness.” *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010). PO’s alleged secondary considerations are conclusory and presume Bio-Rad’s products infringe. PO relies on Bio-Rad’s products as evidence of commercial success and industry praise but provides no credible basis for the Board to conclude these products embody the challenged claims. Paper 17 at 65–67. For long-felt need, PO merely

references Dr. Struhl's flawed analysis of Larson, which, for all the reasons shown above, is unpersuasive. *Id.* 65.

VII. CONCLUSION

For these reasons, the claims of the '921 patent should be cancelled.

Dated: September 12, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 5,559 words as calculated by the "Word Count" feature of Microsoft® Word for Microsoft 365, the word processing program used to create it.

Dated: September 12, 2025

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The undersigned hereby certifies that the foregoing **PETITIONER'S
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