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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIO-RAD LABORATORIES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

Case IPR2019-00567
Patent 9,689,024 B2

Before ERICA A. FRANKLIN, RICHARD J. SMITH, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Bio-Rad Laboratories, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 2, 5, 8, 10, 11, 13, 15–17, 19, 21, and 22 ("the challenged claims") of U.S. Patent No. 9,689,024 B2 (Ex. 1001, "the '024 patent"). Paper 2 ("Pet."). 10X Genomics, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. *See* 35 U.S.C. § 314; 37 C.F.R. § 42.4(a). The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, we deny the Petition and decline to institute an *inter partes* review for that reason. Additionally, based upon the circumstances involved, we exercise our discretion to deny the Petition under § 314(a).

A. Related Proceedings

The parties identify the following matters involving the '024 patent: *10X Genomics, Inc. v. Bio-Rad Laboratories, Inc.*, 3:18-cv-00209-JST (N.D. Cal.); *In re Certain Microfluidic Systems and Components Thereof and Products Containing Same*, Inv. No. 337-TA-1100 ("the ITC proceeding"). Pet. 53; Paper 3, 2.

B. The '024 Patent

The '024 patent relates to methods for preparing droplet-based samples for use in downstream applications, such as the detection and quantification of analytes for molecular biology and medical diagnostics. Ex. 1001, 1:21–23. The Specification explains that when the starting material for a sample is cells or tissue, the sample may need to be manipulated to permit the extraction of target molecules. *Id.* at 1:31–34. Sample preparation may also involve attaching "unique identifiers" to molecules. *Id.* at 1:34–37. For example, the Specification states that "[o]ligonucleotide barcodes, in some cases, may be particularly useful in nucleic acid sequencing. In general, an oligonucleotide barcode may comprise a unique sequence (e.g., a barcode sequence) that gives the oligonucleotide barcode its identifying functionality." *Id.* at 12:43–47. Attaching the barcode to a nucleic acid of interest associates the barcode sequence with the nucleic acid of interest, allowing the barcode to "then be used to identify the nucleic acid of interest during sequencing, even when other nucleic acids of interest (e.g., comprising different barcodes) are present." *Id.* at 12:48–53.

In one aspect, the Specification describes a "method for sample preparation comprising combining a microcapsule comprising an oligonucleotide barcode and a target analyte into a partition, wherein the microcapsule is degradable upon the application of a stimulus to the microcapsule . . . [causing] the microcapsule to release the oligonucleotide barcode to the target analyte." *Id.* at 2:59–65. The partition may be a droplet, and the microcapsule may comprise a polymer gel, a bead, or a gel bead. *Id.* at 2:65–3:3. According to the Specification, "[i]n cases where a

partition is a droplet, an analyte and reagents may be combined within the droplet with the aid of a microfluidic device. For example, a droplet may be generated that comprises a gel bead (e.g., comprising an oligonucleotide barcode) a nucleic acid analyte, and any other desired reagents." *Id.* at 19:23–28. At a first junction of two or more channels of the microfluidic device, the gel bead, nucleic acid analyte, and reagents, in an aqueous phase, may be combined. *Id.* at 19:28–30. At a second junction of two or more channels of the device, a droplet may be generated comprising the resulting mixture by contacting the aqueous mixture combined at the first junction with an oil continuous phase. *Id.* at 19:30–34.

C. Illustrative Claim

Claim 1 of the '024 patent, reproduced below, is the only independent claim, and is illustrative of the claimed subject matter.

> 1. A method for sample preparation, comprising:
> (a) providing a droplet comprising a porous gel bead and a target nucleic acid analyte, wherein said porous gel bead comprises at least 1,000,000 oligonucleotide molecules comprising barcode sequences, wherein said oligonucleotide molecules are releasably attached to said porous gel bead, wherein said barcode sequences are the same sequence for said oligonucleotide molecules;
> (b) applying a stimulus to said porous gel bead to release said oligonucleotide molecules from said porous gel bead into said droplet, wherein upon release from said porous gel bead, a given oligonucleotide molecule from said oligonucleotide molecules attaches to said target nuclei acid analyte; and
> (c) subjecting said given oligonucleotide molecule attached to said target nucleic acid analyte to nucleic acid amplification to yield a barcoded target nucleic acid analyte.

Ex. 1001, 33:56–34:7.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1, 2, 5, 8, 10, 11, 13, 15–17, 19, 21, and 22 of the '024 patent on the following grounds:

Claims	**Basis**	**References**
1, 2, 5, 8, 10, 11, 13, 15–17, 19, 21, and 22	§ 103	Saxonov[1] and Church[2]
1, 2, 5, 8, 10, 11, 13, 15–17, 19, 21, and 22	§ 103	Saxonov, Church, and Hinz[3]

Petitioner also relies upon the declaration of Michael Metzker, Ph.D. (Ex. 1003) to support its contentions. Patent Owner relies upon the declaration of Paul Dear, D.Phil. (Ex. 2001).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review based on a petition filed after November 13, 2018, such as the present Petition, the Board interprets a claim term by applying "the standard used in federal courts, in other words, the claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b), which is articulated in *Phillips*."[4] 83 Fed.

[1] Saxonov, US Patent 9,347,059 B2, issued May 24, 2016 ("Saxonov") (Ex. 1004).
[2] Church et al., US Patent 9,902,950 B2, issued Feb. 27, 2018 ("Church") (Ex. 1018).
[3] Hinz et al., US 2010/0304982 A1, published Dec. 2, 2010 ("Hinz") (Ex. 1007).
[4] *See* Changes to the Claim Construction Standard for Interpreting Claims in

Reg. 51,340, 51,343. Under that standard, the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (citations omitted). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner and Patent Owner propose constructions for various terms based upon the constructions adopted in the ITC proceeding or otherwise asserted to represent the plain meaning of the terms. Based upon our analysis, however, we determine that constructions of those claim terms are not necessary for the purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,344 (Oct. 11, 2018) (to be codified at 37 CFR pt. 42).

According to Petitioner, a person of ordinary skill in the art would have "either (1) a Ph.D. in molecular biology, molecular genetics, chemistry, engineering or equivalent disciplines with two years of experience or (2) a Bachelor of Science in such fields with five years of experience, with such experience including library preparation methods, microfluidics technology and bead attachment chemistries." Pet. 5 (citing Ex. 1003 ¶ 21). According to Patent Owner, the skilled artisan would have a "master's degree in bio-engineering, genetics, biochemistry or a related discipline, with two to three years of academic, research, or industry experience in the field of genomic sequencing solutions." Prelim. Resp. 6. Additionally, Patent Owner asserts that "[a] person with higher levels of education but less relevant practical experience, or with more practical experience but less education, may also meet this standard." *Id.*

At this stage in the proceeding, we find that the level of ordinary skill in the art includes both descriptions provided by the parties. For example, Petitioner's description includes those having a Ph.D. or a Bachelor's degree, with varying amounts of experience, but does not include those having a Master's degree with such experience. On the other hand, Patent Owner's description is directed to those having a Master's degree with particular amounts of experience. We find that a description of the level of skill in the art includes all three degrees, with the specified amount of experience. Similarly, we find that such degrees and experience may be satisfied in each of the disciplines and fields specified by the parties.

Accordingly, at this stage of the proceeding, we determine that the person having ordinary skill in the art is one who has either (1) a Ph.D. in molecular biology, genetics, biochemistry, chemical engineering, bio-

engineering, or a related or equivalent discipline, with at least two years of academic, research, or industry experience in such fields, including familiarity with sequencing methods, microfluidics technology, and bead attachment chemistries, (2) a M.S. or B.S. in one of those fields with at least five years of experience in such fields, including familiarity with sequencing methods, microfluidics technology, and bead attachment chemistries. We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

C. Obviousness over Saxonov and Church

Petitioner asserts that claims 1, 2, 5, 8, 10, 11, 13, 15–17, 19, 21, and 22 are obvious over the combination of Saxonov and Church. Pet. 15–43. Patent Owner disagrees. Prelim. Resp. 33–48.

1. Saxonov

Saxonov is directed to methods and compositions for nucleic acid analysis, including methods of generating droplets. Ex. 1004, Title; 13:3–7. The methods include barcoding or tagging analytes to "enable one to pool samples of nucleic acids in order to reduce the cost of sequencing per sample, yet retain the ability to determine from which sample a sequence read is derived." *Id.* at 3:53–56. In particular, Saxonov teaches that a sample of polynucleotides may be separated into a plurality of partitions, e.g., droplets, and each of the plurality of partitions can be provided with a unique set of adaptors comprising a barcode. *Id.* at 3:42–45. Saxonov explains that each sample may have a separately prepared library, and its own unique barcode. *Id.* at 3:56–58. "The separately prepared libraries . . . can then be pooled and sequenced," and "[e]ach sequence read of the

resulting dataset can be traced back to an original sample via the barcode in the sequence read." *Id.* at 3:58–62.

2. Church

Church is directed to "methods and compositions for obtaining and analyzing nucleic acid sequences derived from many single cells at once." Ex. 1018, 1:21–23. In one aspect, the methods involve barcoding many single cells in a complex mixture of cells, wherein each cell is provided with a unique individual barcode that associates each cell's nucleic acids with the original cell. *Id.* at 2:35–40. Church explains that its method "efficiently produces bar-coded beads coated with clonal copies of the bar-coded oligonucleotides having the correct sequence." *Id.* at 2:28–30.

3. Analysis

"[O]ne must have a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue." *Intelligent Bio-Sys, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Id.*

Independent claim 1 recites a method for sample preparation. We view the parties' primary dispute as centered upon whether the combination of Saxonov and Church teaches the first step of that method, i.e., "providing a droplet comprising a porous gel bead and a target nucleic acid analyte, wherein said porous gel bead comprises at least 1,000,000 oligonucleotide molecules comprising barcode sequences, wherein said oligonucleotide molecules are releasably attached to said porous gel bead."

Petitioner's Position

Petitioner asserts that Saxonov teaches each element of the first step of the claimed method. Petitioner asserts that Saxonov describes a method for library preparation for sequencing polynucleotides, wherein a sample of polynucleotides are separated into a plurality of partitions having a unique set of adaptors comprising a barcode, and wherein the "'[*l]ibrary preparation can be performed in each of the plurality of partitions (e.g., droplets).*'" Pet. 16 (quoting Ex. 1004, 3:40–50).

In particular, Petitioner asserts that "Saxonov contemplates the use of 'porous gel beads' for the delivery of the 'at least 1,000,000 oligonucleotide molecules.'" *Id.* To support that assertion, Petitioner directs us to the teaching in Saxonov that "adaptor barcodes may be delivered through a 'first partition,'" *id.* (citing Ex. 1004, 1:27–39), and that "[a] partition can be formed by any mode of separating that can be used for digital PCR," *id.* at 17 (quoting Ex. 1004, 12:64–65). Further, Petitioner relies upon the disclosure in Saxonov that the partition may be "an area on an array surface." *Id.* (quoting Ex. 1004, 13:1). According to Petitioner, it was well-known in the art that beads could be used as a method for separation in digital PCR, and that they were considered a type of array surface. *Id.* (citing Ex. 1003 ¶ 68).

Additionally, Petitioner asserts that Saxonov contemplates the use of beads by referring to Drmanac,[5] as a reference that describes "methods of barcode tagging." Pet. 17 (quoting Ex. 1004, 6:19–21). Petitioner notes that

[5] Drmanac et al., US 2011/0033854, published Feb. 10, 2011 (Ex. 1023) ("Drmanac").

Drmanac teaches that "'***[a] wide variety of supports may be used*** with the compositions and methods of the invention to form random arrays,' and that in one aspect, '**the support comprises beads**, wherein the surface of the beads comprise reactive functionalities or capture probes that ***can be used to immobilize polynucleotide molecules***.'" *Id.* quoting Ex. 1023 ¶ 424.

Petitioner also asserts that Saxonov contemplates the use of porous gel beads by teaching that its adaptors may be bound to a support such as controlled pore glass (CPG). Pet. 17–18 (citing Ex. 1004, 11:65–12:7). According to Petitioner, "[a] person of ordinary skill in the art "would have known that CPG includes porous glass beads used commercially for the synthesis of oligonucleotide molecules, such as barcode molecules." *Id.* at 18 (citing Ex. 1003 ¶ 70). Petitioner notes also that Saxonov refers to a 454 sequencing system that employs Sepharose beads, which Petitioner asserts a person of ordinary skill in the art would understand to be porous gel beads. *Id.* at 19–20 (citing Ex. 1003 ¶ 76–80).

Further, Petitioner asserts that when Saxonov discusses protein expression and nucleic acid information, Saxonov treats beads and burstable droplets interchangeably for delivering barcodes by teaching that "antibodies can be linked to beads coated with short DNA fragments with a unique barcode," and that "antibodies could also be linked to droplets containing DNA fragments – which can be burst as appropriate." *Id.* at 18–19 (quoting Ex. 1004, 36:59–60).

According to Petitioner, Saxonov also teaches barcodes that are "releasably attached" to the porous gel bead, as required by claim 1. Pet. 23. To support that assertion, Petitioner directs us to the teaching in Saxonov that its adaptor can comprise one or more 5'-end modifications, including a

5'-thiol, and that such modification may be attached to a nucleic acid strand through a linker, wherein the linker may be a "PC (photocleavable) spacer." *Id.* at 23–24 (quoting Ex. 1004, 12:10–36). Petitioner asserts that a person of ordinary skill in the art "would have understood that a thiol group can form disulfide bonds and that a photocleavable [] spacer describes a linker group that is cleaved in response to an environmental stimulus." *Id.* (citing Ex. 1003 ¶ 89). Petitioner also asserts that Saxonov describes that its adaptor may comprise endonuclease cleavage sites, and that a person of ordinary skill in the art would have understood that such a cleavage site was included to make the barcode releasable from the bead. *Id.* at 24 (citing Ex. 1003 ¶ 91).

As for Church, Petitioner asserts that reference teaches a droplet comprising a porous gel bead by disclosing the "'[c]apture of [a] cell and barcoded bead in an emulsion.'" Pet. 21 (quoting Ex. 1018, 3:50–51). Petitioner asserts also that Church discloses the use of barcodes on beads by providing methods for "creating clonal copies of barcode sequences [] and delivering the barcode sequences into a plurality of single cells." *Id.* at 19 (quoting Ex. 1018, 5:8–11). Additionally, Petitioner asserts that Church describes one aspect of its invention wherein "a plurality of unique nucleic acid sequences comprising a degenerate barcode are amplified on a support (e.g., a bead) such that each discrete area of the support (e.g., each bead) will be coated with clonal copy of a starting nucleic acid sequence." *Id.* (quoting Ex. 1018, 5:11–15) (emphasis omitted).

Petitioner asserts that Church discloses barcodes that are "releasably attached" to beads by referring to Sundberg[6] for its description of how to functionalize support beads, i.e., with a spacer molecule to allow for attachment of oligonucleotide molecules, wherein the spacer molecule may have a cleavage site. *Id.* at 25 (citing Ex. 1018, 12:50–53, Ex. 1021, 8:42–59). Additionally, Petitioner asserts that Sundberg teaches the use of polyacrylamide beads. *Id.* at 20 (citing Ex. 1018, 12:38–42; Ex. 1021, 5:33–38).

In terms of combining the teachings of Saxonov and Church, Petitioner asserts that the challenged claims "merely entail the simple substitution of one known element (the beads of Church) for another (the droplets or beads of Saxonov)." Pet. 40. Beyond that rationale, Petitioner asserts that a person of ordinary skill in the art "would have recognized that the beads of Church are more stable than the burstable droplets of Saxonov and would solve any issues regarding stability in transport for commercial applications." *Id.* at 42 (citing Ex. 1003 ¶ 125). Petitioner asserts also that a person of ordinary skill in the art "would have recognized that burstable droplets are not an ideal delivery mechanism for barcodes when being delivered to a larger droplet due to problems with releasing the barcodes." *Id.* (citing Ex. 1003 ¶ 126). According to Petitioner, "if the mechanism for releasing the barcodes from the smaller droplet is a temperature adjustment, the larger droplet would have to be engineered to have a different bursting temperature so that it stays intact when the temperature is adjusted to release

[6] Sundberg et al., US Patent 5,919,523, issued on Jul. 6, 1999 (Ex. 1021) ("Sundberg").

the barcodes from the smaller droplet," whereas Petitioner asserts "the beads of Church do not have this problem." *Id.* Further, Petitioner asserts that, unlike Saxonov, Church provides an "error-checking mechanism" to confirm that each bead has a unique barcode by sequencing beads post-emulsion PCR for one base of their barcode to show that each bead has a unique barcode. *Id.* at 42–43 (citing Ex. 1018, 19:64–66; Ex. 1003 ¶ 127).

Petitioner asserts that a person of ordinary skill in the art would have had a reasonable expectation of success in substituting the beads of Church for the beads or droplets of Saxonov because (1) "they are both used for the exact same application, namely, as a partition or support for barcode molecules," (2) "Church provided detailed examples of methods for preparing and using barcoded beads," and (3) "there was a high degree of predictability because Church teaches that both its beads and functionalization methods were known in the art at the time of the invention." *Id.* at 43 (citing Ex. 1003 ¶ 127).

Patent Owner's Position

Patent Owner asserts that Petitioner has not demonstrated how combining the elements taught by Saxonov and Church would have led a person of ordinary skill in the art to achieve the claimed invention. Prelim. Resp. 33. In particular, Patent owner asserts that "Petitioner never shows 1 million oligonucleotide molecules ***attached to a bead***," as required by independent claim 1. *Id.* Patent Owner asserts also that "Petitioner does not specifically identify any beads in droplets it alleges has a releasable attachment, and no disclosure in Saxonov, Church, or Sundberg." *Id.* at 42.

Discussion

Based on our review the arguments and the cited art, we agree with Patent Owner that Petitioner has not demonstrated a reasonable likelihood of successfully demonstrating that independent claim 1 would have been obvious over the combination of Saxonov and Church. In particular, Petitioner's characterizations regarding certain teachings or suggestions of Saxonov and Church are inadequately supported for institution. For example, Petitioner asserts that "Saxonov contemplates the use of 'porous gel beads' for the delivery of the 'at least 1,000,000 oligonucleotide molecules.'" Pet. 16. Petitioner bases that assertion on Saxonov's teaching that barcodes may delivered through a first partition. *Id.* According to Petitioner, a person of skill in the art would have understood from Saxonov's description that a partition may be (a) formed by any mode of separating that can be used for digital PCR, and (b) an area on an array surface. Based upon that assertion, Petitioner contends that the skilled artisan would understand that beads are partitions. *Id.* at 17.

As Patent Owner asserts, however, Petitioner has not demonstrated a reasonable likelihood of successfully establishing that it was well-known in the art that beads could be used as a method for separation in digital PCR. Prelim. Resp. 34 (citing Ex. 2001 ¶ 83). Petitioner's declarant, Dr. Metzker, cites to Qui[7] without explaining how the reference supports its position. Ex. 1003 ¶ 68. As explained by Patent Owner's declarant, Dr. Dear, a review of Qui reveals that it describes a single study using beads in droplets, wherein

[7] Qui et al., (Ex. 1032) ("Qui").

the emulsification (i.e., the droplet) serves as the mode of separation and not the beads. Ex. 2001 ¶ 83 (citing Ex. 1032, 3).

Similarly, Petitioner has not demonstrated a reasonable likelihood of successfully establishing that it was well-known in the art that beads are "an area on an array surface," so as to qualify as a partition in Saxonov by simply referencing a "BeadArray," without any further discussion. Pet. 17 (citing Ex. 1003 ¶ 68). That deficiency is underscored by Dr. Dear's showing that a person of ordinary skill in the art would have understood Saxonov's use of the phrase "an area on an array surface," refers to "an area on a substantially flat surface of an array." Ex. 2001 ¶ 84. In support of that assertion, Dr. Dear directs us to Petitioner's reference, Drmanac,[8] which describes supports as "rigid solids that have a surface, preferably a ***substantially planar*** **surface**." Ex. 1023 ¶ 424. Further, as Patent Owner asserts, Petitioner and Dr. Metzker do not explain how a BeadArray discloses a droplet comprising a porous gel beads, as required by the challenged claims. Prelim. Resp. 34; Ex. 2001 ¶ 89.

Insofar as Petitioner asserts that Saxonov also contemplates the use of porous gel beads by teaching that its adaptors may be bound to a support such as controlled pore glass (CPG), Pet. 17–18 (citing Ex. 1004, 11:65–12:7), we find that assertion inadequate for institution too. According to Petitioner, a person of ordinary skill in the art would have known that CPG includes porous glass beads. *Id.* at 18 (citing Ex. 1003 ¶ 70). Petitioner, however, does not explain why such *glass* beads would also have been

[8] Drmanac et al., US 2011/0033854, published Feb. 10, 2011 (Ex. 1023) ("Drmanac").

considered to be porous *gel* beads, or that they could be substituted with porous gel beds, as required by the challenged claims.

Another example of the Petition failing to support its characterization of Saxonov's teachings involves Petitioner's assertion that "Saxonov also explains that the barcodes are 'releasably attached' to the porous gel bead." Pet. 23. According to Petitioner, Saxonov teaches "that the 5'-end of the oligonucleotide barcode molecules attached to the support may be modified to allow for the release of the molecule from the bead." *Id*. For that teaching, Petitioner directs us to a disclosure in Saxonov describing certain 5' end modifications, including a 5'-thiol that may be attached to a nucleic acid strand through a linker, wherein the "'linker can be, e.g., ***PC (photocleavable) spacer***.'" *Id.* (quoting Ex. 1004, 12:10–36). According to Petitioner, "a thiol group can form disulfide bonds and [] a photocleavable [] spacer describes a linker group that is cleaved in response to an environmental stimulus, such as exposure to a reducing agent or a particular wavelength of light." *Id.* at 24. Petitioner asserts also that Saxonov describes "the addition of endonuclease cleavage sites that would allow for the release of the barcode molecule from the bead." *Id.* (citing Ex. 1004, 10:22–11:6). Petitioner also refers to Saxonov's teaching that droplets can be burst to release barcodes. *Id.* (citing Ex. 1004, 26:45–51).

None of those teachings in Saxonov, however, describe barcodes being releasably attached to a porous gel bead. Rather, at most, those references to disulfide bonds, photocleavable spacers, and endonuclease cleavage sites relate to features that *may* be utilized to achieve the releasable attachment of barcodes from such beads – if Saxonov taught or suggested providing its oligonucleotide molecules with a releasable attachment to

porous gel beads. Petitioner, however, as not identified such a teaching or suggestion in Saxonov. Indeed, as Patent Owner notes, Petitioner has not directed us to any disclosure in Saxonov wherein a bead or a bead in a droplet includes a 5'-thiol or photocleavable spacer. Prelim. Resp. 42. Nor has Petitioner identified any disclosure in Saxonov of a bead or a bead in a droplet with an attached adaptor having a restriction cleavage site. *Id.* Moreover, Petitioner does not articulate that its challenge of the claims involves modifying Saxonov to include such features to provide for oligonucleotide molecules that are releasably attached to porous gel beads.

Petitioner's reliance on Church provides yet another example of the Petition failing to support its characterization of reference teachings. In particular, Petitioner relies upon Church, and a reference therein to Sundberg, as "disclos[ing] barcodes that are 'releasably attached' to beads." Pet. 25. According to Petitioner, "Sundberg teaches that bead surfaces can be functionalized with a spacer molecule to allow for the attachment of oligonucleotide molecules," and "further teaches that the spacer molecules may have a cleavage site such that the oligonucleotide molecule may be released when exposed to a chemical stimulus, such as an acid or base." *Id.* at 25–26 (citing Ex. 1021, 8:42–45, 57–59). However, as Patent Owner has asserted, Prelim. Resp. 45–46, a review of those disclosures in Sundberg reveals that they do not describe a releasable attachment to a bead. Rather, the teachings in Sundberg relied upon by Petitioner relate to its "Pin-Based Methods," that are presented separately from its "Bead Based Methods." *Compare* Ex. 1021, 8:23–59 ("Pin-Based Methods") *with id.* at 8:60–9:47 ("Bead Based Methods"). Petitioner has not asserted that pins are beads, nor explained why the teachings relating to pin-based methods should be applied

to the bead based methods. Indeed, Petitioner has not acknowledged that the teachings it relies upon in Sundberg address pins and not beads. In other words, as Patent Owner contends, Petitioner provides no reason that those disclosures would apply to beads, or specifically, beads in droplets. Prelim Resp. 46. Moreover, as Patent Owner has correctly observed, "Church identifies Sundberg as relevant only for the ***addition*** of functional groups," and Petitioner has not demonstrated that a person of ordinary skill in the art would look to Sundberg for a ***releasable*** attachment to a bead. *Id.* at 45 (citing Ex. 2001 ¶ 100; Ex. 1021, 1; Ex. 1018, 12:50–53).

Based on the foregoing discussion and our review of the Petition, Petitioner has not explained how combining the elements taught by Saxonov and Church would have led a person of ordinary skill in the art to arrive at the claimed invention. In particular, for at least the reasons just discussed, Petitioner has not demonstrated a reasonable likelihood of successfully establishing that the combination of Saxonov and Church teaches or suggests oligonucleotide molecules, comprising barcode sequences, releasably attached to a porous gel bead, as required by the challenged claims. Rather, Petitioner merely identifies various teachings in Saxonov and Church, as well as in art cited by those references, that appear to address certain claim elements in a manner that is isolated and detached from the remaining associated claim elements, without explaining sufficiently for institution how or why those teachings would have been combined to yield the claimed invention.

Moreover, Petitioner's "exemplary rationales to support a finding of obviousness," each involve modifying Saxonov by substituting the droplets or beads of Saxonov for the beads of Church. Pet. 40–43. What is missing

from those rationales to combine, however, is an explanation sufficient for institution as to why a person of ordinary skill in the art would have considered the identified droplets or beads in Saxonov to be interchangeable with the beads disclosed in Church, beyond the fact that the beads in Church were known. *Id*.

Insofar as Petitioner asserts that a person of skill in the art would have had a reasonable expectation of success in combining Saxonov and Church because the beads of Church and the beads or droplets of Saxonov "are both used for the exact same application, namely, as a partition or support for barcode molecules," *id.* at 43, we do not find that Petitioner has supported that assertion adequately for institution, for the reasons set forth above. In particular, Petitioner has not acknowledged the differences in the structure, function, and application of beads or droplets disclosed in Saxonov and Church, or explained why it relies on disclosures relating to the pin-based method disclosed in Sundberg. Nor has Petitioner explained, in view of those differences, why a person of ordinary skill in the art would have reasonably expected that using Church's beads in Saxonov's method would successfully provide a barcode releasably attached to a porous gel bead and providing a droplet comprising that material in the manner claimed.

Thus, based on the information presented, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of independent claim 1 over the combination of Saxonov and Church. Having considered the challenged dependent claims, we also determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 2, 5, 8, 10, 11, 13,

15–17, 19, 21, and 22 over the combination of Saxonov and Church for the same reasons discussed regarding the independent claim.

D. Obviousness over Saxonov, Church, and Hinz

Petitioner asserts that claims 1, 2, 5, 8, 10, 11, 13, 15–17, 19, 21, and 22 would have been obvious over the combination of Saxonov, Church, and Hinz. Pet. 43–52. Patent Owner disagrees. Prelim. Resp. 48–58. Saxonov and Church are discussed above, in Section II. C.

1. Hinz

Hinz is directed to methods of making nucleic acid polymer particles that "allow polynucleotides to be attached throughout their volumes for higher loading capacities than those achievable solely with surface attachment." Ex. 1007, Abstract. Hinz states that "[n]ucleic acid polymer particles of the invention are particularly useful in multiplex genetic assays . . . where polynucleotide analytes, i.e., target polynucleotides, in a sample must be amplified in the course of analysis." *Id.* at ¶ 54. Hinz explains that such analytical techniques use a wide variety of amplification methodologies which can be used with nucleic acid polymer particles of the invention. *Id.* When describing one of those methodologies, i.e., bridge PCR amplification on surfaces, Hinz teaches that "[i]n some embodiments, one of primers A and B may have a scissile linkage for its removal to obtain a single population on [the substrate] surface." *Id.* at ¶ 55. Hinz explains that, with its method, "a bridge PCR may be performed on nucleic acid polymer particles described herein." *Id.* at ¶ 56. Additionally, Hinz teaches that "[t]he method may be employed to make amplicon libraries without the use of emulsion reactions." *Id.*

2. Analysis

Petitioner asserts that independent claim 1 is obvious over Saxonov and Church for the same reasons explained for the ground challenging the claims over the combination of those references. Pet. 44. As discussed in Section II. C, we have determined that Petitioner has not demonstrated that the combination of Saxonov and Church teaches certain claim limitations, including the requirement that the oligonucleotide molecules are releasably attached to a porous gel bead. According to Petitioner, that claim limitation is also obvious over Saxonov in light of Church in further view of Hinz. *Id.* Thus, we consider here whether Petitioner's combination including Hinz meets that limitation.

Petitioner's Position

Petitioner asserts that "Hinz describes the release of oligonucleotide primers having scissile linkages from its beads and the stimuli that would release them." Pet. 44. In support of that assertion, Petitioner relies upon Hinz's statement that "[i]n some embodiments, one of primers A and B may have a scissile linkage for its removal to obtain a single population on [the substrate] surface." *Id.* at 45 (quoting Ex. 1007 ¶ 55). Petitioner asserts that "Hinz teaches the use of particles (e.g., beads) made of polymer networks derivatized with thiol groups and the use of thiol derivatized oligo-nucleotides," by disclosing an embodiment wherein "nucleic acid polymer particles are made by first making polymer networks that incorporate either bromoacetyl groups or alternative thiol groups, then reacting either a thiol derivatized oligonucleotide or a bromoacetyl-derivatized oligonucleotide respectively." *Id.* (quoting Ex. 1007 ¶ 37). According to Petitioner, a person of ordinary skill in the art "would have understood that sites with

thiol modifications would be susceptible to cleavage using reducing agents and could remove the barcode adapter molecule at the point of contact with the bead." *Id.*

Additionally, Petitioner asserts that Hinz teaches that the polymer networks are stable within a defined pH range by disclosing, "[i]n one aspect, the invention includes compositions comprising populations of such solid phase amplicons. In one aspect, ***polymer networks are stable in a wide pH range, e.g. from 4 to 10, and especially from 6 to 9***, and they are chemically and physically stable in physiological salt solutions and/or electrolytes . . . ." *Id.* at 45 (quoting Ex. 1007 ¶ 26) (emphasis added by Petitioner). According to Petitioner, a person of ordinary skill in the art "would have understood that the pH-based or redox chemistry-based cleavable linker or linkage can be placed at any point including at the terminal end contacting the bead," and that "the use of acid or base that would change the pH outside the stable range would result in the porous gel bead becoming unstable." *Id.* at 45–46 (citing Ex. 1003 ¶ 134).

As for the combined teachings of Saxonov, Church and Hinz, Petitioner asserts that the challenged claims "merely entail the simple substitution of one known element (the beads of Hinz) for another (the droplets or beads of Saxonov and Church)." Pet. 49. Petitioner provides additional rationales for combining those elements (a) based upon asserted improved qualities of the beads of Hinz, such as increased stability and increased surface area from porous beads to facilitate the attachment of large numbers of oligonucleotide molecules, and (b) as a result of "naturally explor[ing] other means of attachment and release" of oligonucleotides from the beads, via, e.g., the use of thiol groups, pH adjustment, and scissile

linkages. *Id.* at 49–51. According to Petitioner, a skilled artisan would have had a reasonable expectation of successfully "substituting the beads of Hinz for the beads or droplets of Saxonov or Church because the beads of Hinz are used for the exact same application, namely, as a support for oligonucleotide molecules." *Id.* at 51–52. (citing Ex. 1003 ¶ 146).

Patent Owner's Position

Patent Owner asserts that "Hinz does not describe a releasable attachment on a bead in a droplet or any release from a bead into a droplet." Prelim. Resp. 50. Patent Owner explains that the description in Hinz relied upon by Petitioner as teaching the release of oligonucleotide primers having scissile linkages from its beads does not mention beads. *Id.* (citing Pet 44–45; Ex. 1007 ¶ 55). Further, Patent Owner notes that the portion of Hinz cited by Petitioner for its contention relates to bridge PCR that occurs on what Hinz depicts in Figure 3 as a flat surface. *Id.* (citing Ex. 2001 ¶ 108; Ex. 1007 ¶ 55; Ex. 1007, Fig. 3). In that embodiment, Patent Owner asserts that Hinz teaches that during bridge PCR, the scissile linkage is used to eliminate one of the two complementary strands attached to the surface, so that the strand that will not be sequenced, i.e., the unwanted product, will be removed. *Id.* at 51 (citing Ex. 2001 ¶ 108; Hinz ¶¶ 55, 56). According to Patent Owner and Dr. Dear, "the reason for the presence of scissile linkage is specific to particular concerns of creating the sequence substrate and excising the unwanted material," and not to sample preparation. *Id.* (citing Ex. 2001 ¶ 108).

Patent Owner notes that in another embodiment, not relied upon by Petitioner, Hinz describes bridge PCR on a bead, but does not teach the presence of a scissile linkage in the bead embodiment. *Id.* at 50 (citing Ex. 2001 ¶ 108; Ex. 1007 ¶ 56).

Next, Patent Owner asserts that Petitioner's contention that Hinz's disclosure of particles with a thiol demonstrates a releasable attachment is not supported by the reference. Prelim. Resp. 51–52. Patent Owner asserts that Petitioner's contention is based upon an unreliable assumption that the thiol group includes a disulfide bond, and that bond may be broken with a reducing agent. *Id.* According to Patent Owner and Dr. Dear, thiols show many reactions beyond disulfide formation, in other words, "[t]hiols do not necessarily disclose a disulfide." *Id.* (citing Ex. 2001 ¶ 109). Moreover, Patent Owner asserts that Hinz does not disclose using a reducing agent. *Id.* Further, Patent Owner asserts that a person of ordinary skill in the art would not have been motivated to use a reducing agent with a thiol or to break a disulfide bond, if one existed, because doing so would have resulted in "the loss of the nucleic acids from the sequencing substrate, making it inoperable because there would be nothing attached to the substrate for sequencing" in Hinz. *Id.* at 52.

Discussion

Based on our review of the arguments and the cited art, we agree with Patent Owner that Petitioner has not demonstrated sufficiently for institution how combining the elements taught by Saxonov, Church, and Hinz would have led a person of ordinary skill in the art to arrive at the claimed invention. Petitioner describes the combination as involving the substitution of Hinz's beads for the droplets or beads of Saxonov and Church. Pet. 51–

52. Petitioner, however, does not explain the combination further, in terms of what teachings of Church are involved in the combination, or how the beads of Hinz operate in the method of Saxonov.

Further, we do not find that Petitioner has accurately characterized the beads in Hinz or persuasively supported its assertions that "Hinz describes the release of oligonucleotide primers having scissile linkages from its beads and the stimuli that would release them." Pet. 47. In particular, Petitioner has not demonstrated sufficiently for institution that Hinz's teaching relating to scissile linkages applies to its embodiment using beads or explained why a person of ordinary skill in the art would have applied such linkages to the sample preparation in Saxonov. Nor has Petitioner demonstrated that a person of ordinary skill in the art would have understood Hinz as disclosing a releasable attachment by including thiol groups in its particles or beads, as Hinz does not mention breaking disulfide bonds or using reducing agents, as required by Petitioner's assumption. Thus, we do not find that Petitioner has explained adequately for institution how the asserted teachings in Hinz disclose oligonucleotide molecules releasably attached to a bead, in the context of the claimed invention directed to providing a droplet comprising that material.

Thus, based on the information presented, and for at least the foregoing reasons, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of the challenged claims over the combination of Saxonov, Church, and Hinz.

E. Denial Based Upon Advanced Stage of ITC Proceeding

In the Preliminary Response, Patent Owner asserts that the Board should deny institution under 35 U.S.C. § 314(a) because Petitioner's

challenge of the ’024 patent at the U.S. International Trade Commission (“ITC”) has already been fully argued and will be decided, using the same claim construction standard as the Board, at least a year before the Board is likely to render a final decision. Prelim. Resp. 58–59. Patent Owner notes that the ITC proceeding issued an initial determination on May 30, 2019, and set a target date of September 30, 2019. *Id.* at 59.

On July 12, 2019, the ITC Administrative Law Judge (“ALJ”) issued the final Initial Determination (“ID”) for the ITC proceeding. On July 18, 2019, pursuant to our instruction, the parties filed the Notice of the ID along with a redacted version of the ID. Exhibits 1055, 2067, and 2078. In the ID, the Administrative Law Judge (“ALJ”) determined that, among other things, “[n]o claims of the ’024 patent have been shown to be invalid.” *See, e.g.*, Ex. 2067, 2. The ALJ provides a detailed discussion in the ID regarding the teachings of Saxonov, Church, and Hinz, alone and in combination. *Id.* at 33–47. The ALJ also discusses her consideration of the testimony of Dr. Metzker (Petitioner’s Declarant) and Dr. Dear (Patent Owner’s Declarant). *Id.* Further, the ALJ provides an analysis of those teachings and testimony with respect to independent claim 1 of the ’024 patent. *Id.* In other words, the ALJ has considered the same references cited in the grounds presented in the Petition, with respect to a challenge of the same independent claim, as well as the testimony of the same declarants relied upon by the parties here.

In an authorized submission regarding the ID, Petitioner addresses, for the first time, the issue of discretionary denial under § 314(a). Paper 16, 1. According to Petitioner, such discretion should not be exercised because the Petition relies upon a number of references that were not relied upon by the ALJ. *Id.* Petitioner asserts also that the Petition includes evidence and

arguments concerning certain dependent claims that were not addressed in the ID. *Id.* However, as Patent Owner notes in its authorized submission, none of the additional references listed by Petitioner are a part of any ground in the Petition. Paper 20, 1. The references cited for the grounds in the Petition are the same as those considered by the ALJ. Further, as Patent Owner correctly asserts, the arguments and evidence set forth in the Petition to address the dependent claims are not relevant to an analysis of the sole independent claim of the '024 patent. *Id.*

Based on the facts and circumstances involved, we agree with Patent Owner that the status of the ITC proceeding provides a favorable basis for denying the Petition. *See* Office Trial Practice Guide August 2018 Update[9] referenced at 83 Fed. Reg. 39,989 (Aug. 13, 2018), at 10 (quoting 35 U.S.C. § 316(b)) ("There may be other reasons beside the 'follow-on' petition context where the 'effect . . . on the economy, the integrity of the patent system, the efficient administration of the Office, and the ability of the Office to timely complete proceedings,'" as set forth in 35 U.S.C. § 316(b), favors denying a petition, including "events in other proceeding related to the same patent, either at the Office, in district courts, or the ITC.").

Specifically, in view of the fact that the ITC proceeding involves (a) the same parties here, (b) a challenge to the validity of the same independent claim of the '024 patent challenged here, (c) application of the same claim construction standard that would be applied in an *inter partes* review, (d) consideration of the same prior art set forth in the grounds presented in the Petition, i.e., Saxonov, Church, and Hinz, (e) consideration

[9] Available at https://go.usa.gov/xU7GP.

of the testimony from the same declarants relied upon here, i.e., Drs. Metzker and Dear, and, particularly, (f) the ALJ's recent issuance of the ID analyzing and discussing the teachings of that prior art and testimony, in the context of addressing a validity challenge to the '024 patent claims, we determine that, even if the Petition would have met the threshold standards for institution, instituting a trial would be an inefficient use of Board resources. Accordingly, we exercise our discretion to independently and additionally deny institution under § 314(a).

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing the unpatentability of at least one of the challenged claims of the '024 patent based upon the grounds presented. Moreover, based upon the issuance of the final Initial Determination in the ITC proceeding addressing the same challenged patent over the same prior art presented in the Petition, and based upon the same claim construction standard that would be applied in an *inter partes* review, we additionally determine that a trial would be an inefficient use of Board resources.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's request for an *inter partes* review of claims 1, 2, 5, 8, 10, 11, 13, 15–17, 19, 21, and 22 of the '024 patent is *denied*.

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