

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NANOSTRING TECHNOLOGIES, INC.,
Petitioner

v.

PRESIDENT AND FELLOWS OF HARVARD COLLEGE,¹
Patent Owner

Case IPR2024-00526
U.S. Patent No. 11,542,554

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

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¹ While 10x Genomics, Inc. is the exclusive licensee and the real party-in-interest, President and Fellows of Harvard College is the Patent Owner.

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	OVERVIEW OF THE 554 PATENT.....	3
III.	OVERVIEW OF PETITIONER’S ASSERTED ART.....	6
	A. Zhuang did not disclose a system that uses MERFISH to determine three-dimensional positional information of RNA molecules in individual cells.....	7
	B. Petitioner’s relied-upon teachings in Cai did not disclose a system for determining three-dimensional positional information of nucleic acids in a sample	13
IV.	PERSON OF ORDINARY SKILL IN THE ART	16
V.	CLAIM CONSTRUCTION	16
VI.	PETITIONER FAILS TO ESTABLISH A REASONABLE LIKELIHOOD OF PREVAILING ON ANY OF ITS GROUNDS.....	16
	A. Petitioner fails to establish that the prior art teaches or suggests all the elements of the claimed system.....	17
	1. Petitioner fails to show that Zhuang teaches or suggests a system comprising a temperature control apparatus operatively coupled to the sample holder, as claimed	18
	a. The Bioptechs FCS2 flow chamber in Zhuang’s system does not necessarily include temperature control capability	18
	b. The Bioptechs objective heater in Zhuang’s system is not a temperature control system that is operatively coupled to a sample holder	22
	2. Petitioner fails to show that Zhuang teaches or suggests a system comprising a pump that provides fluid reagents from “one or more reservoirs” to a sample holder, as claimed	23
	3. Petitioner fails to show that its asserted art teaches or suggests determining three-dimensional positional information of one or more nucleic acid molecules, as claimed.....	24

a.	Zhuang does not teach or suggest determining three-dimensional positional information of one or more nucleic acid molecules	24
b.	Petitioner fails to show that Cai teaches or suggests determining three-dimensional positional information of nucleic acid molecules	34
4.	Petitioner repeatedly fails to meet the legal standards for inherency throughout the Petition	41
B.	Petitioner fails to establish a reason to modify Zhuang’s system to arrive at the claimed system with a reasonable expectation of success	46
1.	Zhuang teaches away from determining three-dimensional positional information of RNA molecules in its system	47
2.	Petitioner fails to explain why or how a POSA would have combined and modified Zhuang’s MERFISH-based system with Cai’s light sheet microscope system with a reasonable expectation of success.....	48
VII.	THE PETITION SHOULD BE DENIED FOR FAILING TO COMPLY WITH 35 U.S.C. § 312 AND 37 C.F.R. §§ 42.22(a)(2) AND 42.104	51
A.	The Petition improperly cross-references its other sections without providing explanations.....	52
B.	The Petition relies on improper incorporation by reference of its expert declaration to expand conclusory statements.....	55
VIII.	THE PETITION CANNOT MEET THE COMPELLING MERITS STANDARD OF A FINTECH ANALYSIS.....	59
IX.	CONCLUSION	60

EXHIBIT LIST

Exhibit No.	Description
2001	Stahl <i>et al.</i> , “Visualization and analysis of gene expression in tissue selections by spatial transcriptomics,” <i>Science</i> 353(6294):78-82 (July 1, 2016), with attached Supplementary Materials
2002	Declaration of Laura Waller, Ph.D.
2003	International Patent Application Publication No. WO 2012/140224 A1 to Frisen <i>et al.</i> , published October 18, 2012
2004	“No-Heat Flow Cell (FSC2),” Bioptechs Inc., accessible at https://bioptechs.com/product/no-heat-flow-cell-fcs2/ (last accessed May 24, 2024)
2005	“FCS2 Chamber,” Bioptechs Inc., accessible at https://bioptechs.com/product/fcs2-chamber/ (last accessed May 24, 2024)
2006	Prosecution File History of U.S. Patent No. 11,542,554
2007	Fang, <i>et al.</i> , “Three-dimensional single-cell transcriptome imaging of thick tissues,” <i>eLife</i> , August 16, 2023, accessible at https://elifesciences.org/reviewed-preprints/90029 (last accessed May 23, 2024) (“Zhuang 2023”)
2008	Lu, <i>et al.</i> , “Spatially resolved epigenomic profiling of single cells in complex tissues,” <i>Cell</i> 185:4448–4464 (2022)
2009	Su, <i>et al.</i> , “Genome-Scale Imaging of the 3D Organization and Transcriptional Activity of Chromatin,” <i>Cell</i> 182:1641–1659 (2020)
2010	Cox, Jr., <i>et al.</i> , “Organizing your space: The potential for integrating spatial transcriptomics and 3D imaging data in plants,” <i>Plant Physiology</i> 188:703-712 (2022) (“Czymmek 2022”)
2011	Ghani, <i>et al.</i> , “Optimisation of MERFISH Data Analysis and Visualisation,” May 21, 2019, accessible at https://www.ucl.ac.uk/~ucbpngh/MiniProject3.pdf (last accessed May 28, 2024)
2012	<i>Curriculum Vitae</i> of Laura Waller, Ph.D.

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<i>Apple Inc. v. ContentGuard Holdings, Inc.</i> , IPR2015-00355, Paper 9 (P.T.A.B. June 26, 2015)	3
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<i>Bayer Healthcare v. Watson</i> , 713 F.3d 1369 (Fed. Cir. 2013)	60
<i>Cisco Sys., Inc. v. C-Cation Techs., LLC</i> , IPR2014-00454, Paper 12 (P.T.A.B. Aug. 29, 2014).....	56, 58, 59
<i>Coherus Biosci., Inc. v. AbbVie Biotech. Ltd.</i> , IPR2017-01008, Paper 11 (P.T.A.B. Sept. 7, 2017)	34
<i>CommScope Techs. LLC v. Dali Wireless, Inc.</i> , IPR2022-01242, Paper 23 (P.T.A.B. Feb. 27, 2023).....	59, 60
<i>Corephotonics, Ltd. v. Apple Inc.</i> , 84 F.4th 990 (Fed. Cir. 2023)	19
<i>DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.</i> , 567 F.3d 1314 (Fed. Cir. 2009)	47
<i>EiKO Global, LLC v. Blackbird Tech LLC</i> , IPR2017-00980, Paper 16 (P.T.A.B. Sept. 1, 2017)	53, 55, 56, 58
<i>E-One, Inc. v. Oshkosh Corp.</i> , IPR2019-00162, Paper 16 (P.T.A.B. June 5, 2019)	51
<i>Floodbarrier, Inc. v. ILC Dover, LP</i> , IPR2019-01543, Paper 12 (P.T.A.B. Mar. 11, 2020).....	17, 24
<i>GlaxoSmithKline LLC v. Fibrogen, Inc.</i> , IPR2016-01318, Paper 13 (P.T.A.B. Jan. 11, 2017)	46

<i>Harmonic Inc. v. Avid Tech., Inc.</i> , 815 F.3d 1356 (Fed. Cir. 2016)	16, 51
<i>In re Antor Media Corp.</i> , 689 F.3d 1282 (Fed. Cir. 2012)	37
<i>In re Hogan</i> , 559 F.2d 595 (C.C.P.A. 1977).....	33
<i>OpenSky Indus., LLC v. VLSI Tech. LLC</i> , IPR2021-01064, Paper 102 (P.T.A.B. Oct. 4, 2022).....	60
<i>Par Pharm., Inc. v. TWI Pharms., Inc.</i> , 773 F.3d 1186 (Fed. Cir. 2014)	20, 41, 45
<i>Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.</i> , 315 F.3d 1335 (Fed. Cir. 2003)	33
<i>Polaris Industries, Inc. v. Arctic Cat, Inc.</i> , 882 F.3d 1056 (Fed. Cir. 2018)	47, 48
<i>POSCO v. ArcelorMittal</i> , IPR2019-01275, Paper 7 (P.T.A.B. Jan. 8, 2020)	34
<i>Raytheon Techs. Corp. v. General Electric Co.</i> , 993 F.3d 1374 (Fed. Cir. 2021)	37
<i>Samsung Elecs. Co., Ltd. v. Mojo Mobility, Inc.</i> , IPR2023-01091, Paper 11 (P.T.A.B. Jan. 8, 2024)	35
<i>Whole Space Industries Ltd. v. Zipshade Industrial (B.V.I.) Corp.</i> , IPR2015-00488, Paper 14 (P.T.A.B. July 24, 2015).....	55

Statutes

35 U.S.C. § 312	51, 55
35 U.S.C. § 312(a)(3).....	18, 51, 52, 59
35 U.S.C. § 314(a)	16

Regulations

37 C.F.R. § 42.104.....	23, 51, 52, 55
37 C.F.R. § 42.104(b)	18
37 C.F.R. § 42.104(b)(4).....	51, 59
37 C.F.R. § 42.104(b)(5).....	51, 59
37 C.F.R. § 42.22(a)(2)	51
37 C.F.R. § 42.6(a)(3).....	23, 51, 55, 58
37 C.F.R. § 42.65(a)	43

I. INTRODUCTION

The Board should deny institution of *inter partes* review of claims 36-70 of U.S. Patent No. 11,542,554 (“the 554 patent”) because the Petition fails to meet its burden of establishing a reasonable likelihood of prevailing with respect to any challenged claim.

First, the Petition fails to show that its combinations of art teach or suggest all elements of at least challenged independent claim 36. For example, there is no dispute that the Petition’s primary reference (Zhuang) fails to explicitly disclose claim 36’s “temperature control apparatus” element. In an attempt to backfill the missing claim element, the Petition relies on inherency, yet fails to establish that the missing claim element is *necessarily* present in Zhuang. The Petition also completely ignores claim 36’s element that a pump is configured to provide fluid reagents from “one or more reservoirs” to a sample holder, failing to address the required relationship between the pump and one or more reservoirs altogether. And the Petition’s arguments for claim 36’s “determining three-dimensional positional information” element are founded on a fundamental misreading of Zhuang and the secondary reference, Cai. These failures in challenging independent claim 36 infect the Petition in its entirety because the remaining challenged claims 37-70 all depend directly or indirectly from claim 36. This failure alone is more than sufficient for the Board to deny institution.

Second, the Petition exacerbates its defects in addressing the claim elements by repeatedly and incorrectly relying on numerous, undeveloped and unproven inherency arguments. The Petition relies on inherency to satisfy several elements of claim 36 in addition to the “temperature control apparatus” element, while failing to establish that the missing claim elements are indeed *necessarily* present in the asserted prior art. The Petition commits the same error to meet dependent claims as well, *e.g.*, claims 46, 61, and 63.

Third, the Petition fails to explain why or how a skilled artisan would have combined the asserted references with a reasonable expectation of success. For example, the Petition argues that the skilled artisan would have combined Zhuang’s disclosure of RNA imaging that uses MERFISH with a high-resolution, small working distance, 100x oil-immersion microscope objective and Cai’s disclosure of RNA imaging using a light sheet microscope system comprising a low-resolution, large working distance, 20x water-immersion objective. Yet the Petition fails to (i) address these and other significant differences in the two systems; and (ii) explain why or how the artisan would have modified these systems with a reasonable expectation of success in view of these fundamental differences.

Finally, the Board should exercise its discretion to deny institution because the Petition blatantly violates the Board’s rules and precedent against improper

incorporation by reference and cross-referencing. The Petition, which asserts 13 different Grounds of unpatentability spanning at least 16 different references in numerous combinations, repeatedly makes bare, conclusory arguments with only citations to its expert declaration for support. But the rules are clear and the Board has consistently held that relying on expert declarations to expand thin arguments in the Petition is an improper incorporation by reference. Such is the case here. The Petition further compounds this issue by repeatedly cross-referencing other sections of the Petition, which in turn cross-reference still other sections of the Petition. This argument format “leaves it to the Board [and 10x] to ascertain what gaps to fill, and then presents vague statements regarding what the prior art suggests,” forcing the Board and 10x to play detective throughout the Petition to try and decipher Petitioner’s arguments. *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00355, Paper 9, at 11 (P.T.A.B. June 26, 2015) (“*Apple*”).

While each of the foregoing failures alone provides the Board with a sufficient reason to deny institution, their cumulative weight against instituting trial cannot be ignored. The Board should accordingly exercise its discretion under 35 U.S.C. § 314(a) to deny institution.

II. OVERVIEW OF THE 554 PATENT

The 554 patent relates to methods and apparatus for volumetric imaging (*i.e.*, three-dimensional imaging) of molecules, such as nucleic acids, within a

fixed biological specimen. EX1001, 1:53-59, 2:27-36. For example, the patent provides in one embodiment a “three-dimensional imaging device (*i.e.*, volumetric imaging device) ... that can measure, resolve and optionally localiz[e] light signals in three-dimensional space to measure fluorescently- or optically-encoded nucleic acid sequencing” EX1001, 5:19-25.

Challenged claims 36-70 are directed to a system for determining three-dimensional positional information of one or more nucleic acid molecules in a sample, wherein the system comprises a stage, a fluidics system, an optical system, a z-axis motion control system, and a computing system. EX1001, 33:29-34:16.

Independent claim 36 recites:

36. A system comprising:

(a) a stage comprising:

- (i) a sample holder configured to receive a substrate comprising a sample having a volume;
- (ii) a temperature control apparatus operatively coupled to said sample holder; and
- (iii) an XY motion control system;

(b) a fluidics system comprising:

- (i) one or more reservoirs configured to contain one or more fluid reagents; and
- (ii) a fluid dispenser operationally coupled to a pump, which pump is configured to provide

said one or more fluid reagents from said one
or more reservoirs to said sample holder; and

(c) an optical system comprising:

(i) an objective;

(ii) two or more light sources, wherein each light
source of said two or more light sources is
configured to deliver light to said volume,
wherein said two or more light sources are
configured to emit two or more colors of
light; and

(iii) one or more detectors configured to receive
light signals from said volume;

(d) a Z-axis motion control system configured for Z-
motion of an objective focal plane through said
volume; and

(e) a computing system comprising at least one computer
readable storage medium having program
instructions stored thereon, which program
instructions are executable by at least one processor
of said computing system to cause said at least one
processor to perform a method comprising:

receiving a plurality of images of at least a portion of said
volume from a plurality of read-out cycles,

wherein said plurality of images comprises a plurality of
light signals received from said volume during said
plurality of readout cycles,

wherein said plurality of light signals is associated with
one or more nucleic acid molecules within said
volume,
wherein each light signal of said plurality of light signals
has a three-dimensional spatial position within said
volume;
determining a plurality of optically-encoded signals from
said plurality of light signals obtained from said
plurality of read-out cycles,
wherein each optically-encoded signal is associated with a
nucleic acid molecule of said one or more nucleic
acid molecules,
wherein said plurality of optically-encoded signals
comprises said two or more colors of light detected
by said one or more detectors in series;
identifying said one or more nucleic acid molecules based
on said plurality of optically-encoded signals; and
determining three-dimensional positional information of
said one or more nucleic acid molecules.

EX1001, 33:29-34:16.

Dependent claims 37-70 depend directly or indirectly from claim 36 and
recite additional features of the claimed system.

III. OVERVIEW OF PETITIONER'S ASSERTED ART

The Petition relies on the combination of Zhuang (EX1003), Cai (EX1004),
and Shen (EX1032) in Ground 1 challenging independent claim 36 and certain

dependent claims, and further includes the same three-reference combination along with additional references scattered throughout Grounds 2–13. Pet., 21–22. In total, the Petition asserts 13 different Grounds comprised of at least 16 different references in various combinations. *Id.*

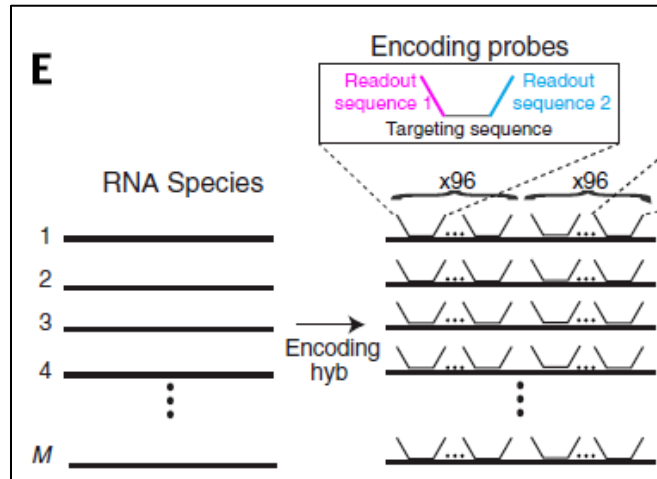
This Preliminary Response is supported by the Declaration of Dr. Laura Waller, who is an expert in biological imaging and systems. EX2002, ¶¶11-23.

A. Zhuang did not disclose a system that uses MERFISH to determine three-dimensional positional information of RNA molecules in individual cells

All 13 of the Petition’s Grounds rely on its primary reference, Zhuang (EX1003). Zhuang disclosed a system using “multiplexed error-robust FISH,” *i.e.*, MERFISH, for imaging RNA molecules and determining their two-dimensional, and not three-dimensional, positional information in individual cells. EX1003, 001, 011, 012; EX2002, ¶¶37-47.

MERFISH uses a series of hybridization and imaging of fluorescently labeled nucleic acid probes to detect target RNA molecules in the cells. EX1003, 001, 003, FIG. 1; EX2002, ¶¶38-41. As Zhuang explained, the target RNA molecules were first hybridized to “encoding probes,” which contain (i) a “central RNA-targeting region” that hybridizes to the target RNAs; and (ii) two readout sequences, each flanking the RNA-targeting region. EX1003, 003, FIG. 1;

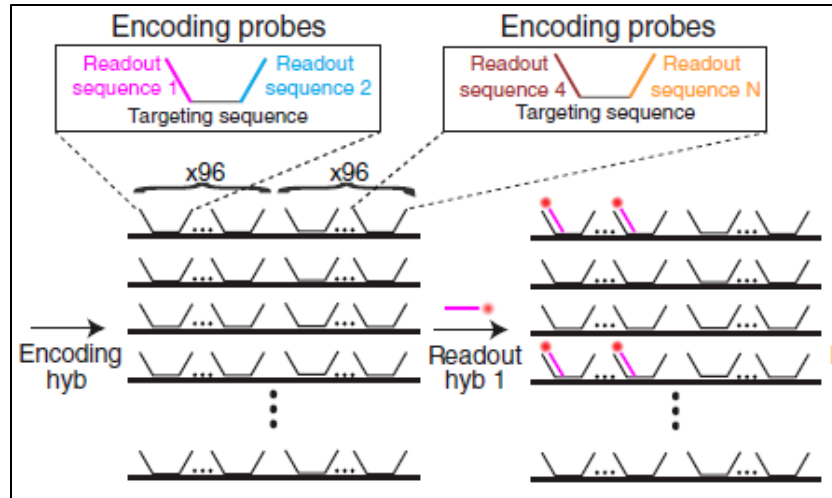
EX2002, ¶38. Zhuang depicted this first labeling step in Figure 1E, referred to as “Encoding hyb”:



EX1003, FIG. 1.

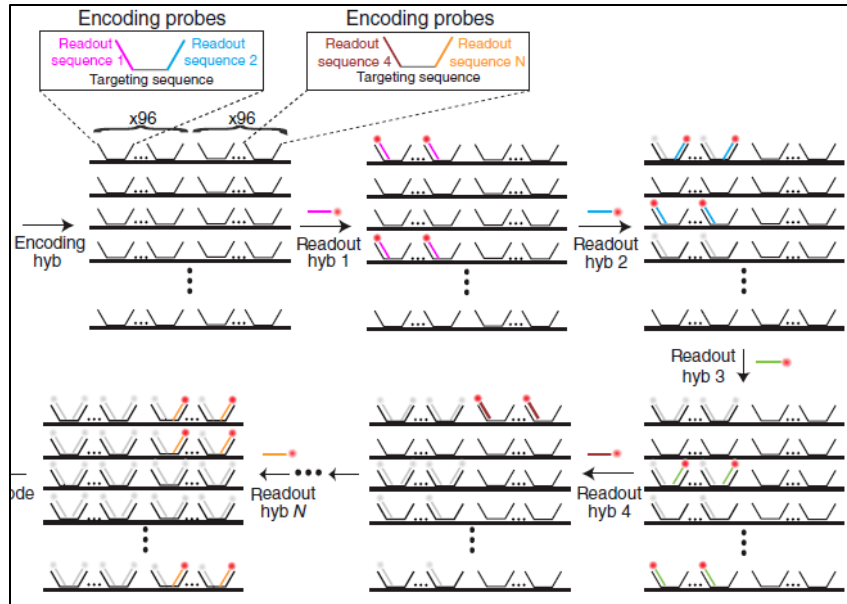
Zhuang explained that the encoding probe labeling step “convert[s] the RNA into a specific combination of readout sequences (Encoding hyb).” EX1003, 003, FIG. 1; EX2002, ¶38.

Next, Zhuang disclosed adding fluorescently labeled “readout probes,” which hybridize to specific readout sequences in the RNA-bound encoding probes. EX1003, 003, FIG. 1; EX2002, ¶39. This was shown in Figure 1E, excerpted below:



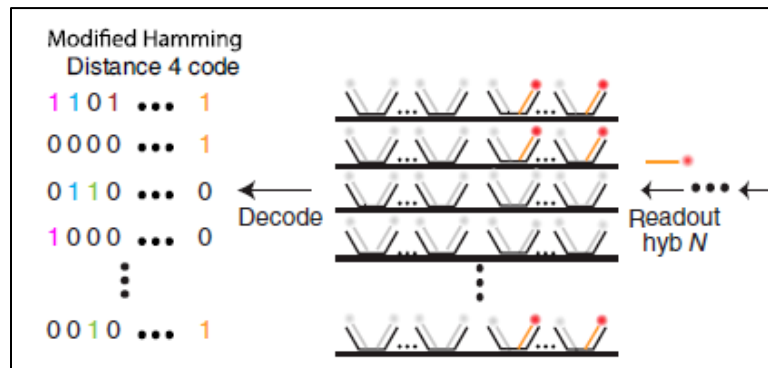
EX1003, FIG. 1.

After the fluorescent readout probes were bound, Zhuang disclosed imaging the now fluorescently labeled RNAs, stating that “[a]fter each round of hybridization with the fluorescent readout probes, cells were imaged by means of conventional wide-field imaging with an oblique-incidence illumination geometry.” EX1003, 003, FIG.1; EX2002, ¶40. Zhuang disclosed that the first round of fluorescently labeled readout probes were “inactivated by photobleaching” after imaging, and the readout probe hybridization process was repeated with a second round of readout probes. *Id.* The process was repeated through several “successive rounds of hybridization and imaging, each with a different readout probe.” EX1003, 001, 003, FIG. 1; EX2002, ¶40. This was shown in Zhuang’s Figure 1E, which depicts “N rounds” of sequential hybridization:



EX1003, FIG. 1.

During the successive rounds of hybridization and imaging, Zhuang disclosed using the fluorescent signals to “construct[] binary words from the observed fluorescent spots based on their on-off patterns” across the successive rounds of hybridization. EX1003, 003; EX2002, ¶41. Zhuang’s construction of the binary codewords (made of “0” and “1”) is depicted in Zhuang’s Figure 1E:



EX1003, FIG. 1.

Zhuang disclosed that these binary codewords were then decoded by matching them to words in a codebook, which correspond to specific RNA species. EX1003, 003; EX2002, ¶41. Zhuang disclosed that its MERFISH method “allows the copy numbers and spatial localizations of thousands of RNA species to be determined in single cells.” EX1003, Abstract, 001; EX2002, ¶41.

Before November 3, 2015, a POSA would have understood that Zhuang’s disclosure of using MERFISH for “spatial localization” of RNA molecules was in reference to *two-dimensional, and not three-dimensional*, spatial localization of the RNA molecules. EX1003, 001-002, 011-012; EX2002, ¶¶42-44. This is clear from the express disclosures in Zhuang. For example, Zhuang disclosed using MERFISH to image human primary fibroblast cells plated on a coverslip. EX1003, 011; EX2002, ¶42. Because the fibroblast cells were “relatively large and flat” and were plated in a layer, a POSA would have understood that the majority of the relevant fluorescent signals from the labeled RNA molecules were detected in a single focal plane. EX2002, ¶42; EX1003, 011. Therefore the MERFISH methods for RNA imaging were performed “*without* the need for optical sectioning” and “*without* ... z-scanning.” EX1003, 011, 012 (emphasis added); EX2002, ¶42. Thus, a POSA would have understood that Zhuang’s MERFISH method only used a single focal plane (*i.e.*, imaging in two dimension) for determining RNA spatial localization. EX2002, ¶42.

A POSA would have further recognized that Zhuang's disclosure of RNA spatial localization was only in two-dimensions, because Zhuang disclosed applying "a uniform width of 167 nm" (about "1 pixel") to each fluorescent spot during image analysis. EX1003, 012; EX2002, ¶43. As Dr. Waller explains, a POSA would have understood Zhuang's use of only the "width" parameter during analysis showed that Zhuang's methods were limited to determining *lateral* positional coordinates (x- and y-axis), *i.e.*, two-dimensional spatial localization of the RNA molecules. EX2002, ¶43. Zhuang's use of the term "spatial" in the context of two-dimensional imaging analysis was consistent with the art, which commonly used "spatial" to indicate two-dimensional analysis. EX2002, ¶44; EX2001, Abstract; EX2003, 11:31-33. For example, Stahl discloses a "*spatial* transcriptomics" strategy for "visualization and quantitative analysis of the transcriptome with *spatial* resolution in individual tissue sections" that provides "RNA-sequencing data with maintained *two-dimensional* positional information" from the tissue. EX2001, Abstract (emphasis added). Similarly, Frisen discloses a method for "partial or global transcriptome analysis of a tissue sample with two-dimensional *spatial* resolution." EX2003, 11:31-33 (emphasis added).

Zhuang also disclosed performing a quality-control experiment to confirm its system needed to only image the cells in a single focal plane. EX1003, 012; EX2002, ¶¶45-46. Here, Zhuang imaged additional focal planes using optical

sectioning and z-scanning to determine the fraction (quantity) of labeled RNAs that might be “outside the axial range of [] imaging geometry,” *i.e.*, outside of the focal plane imaged in the MERFISH-based system (referred to as the “basal focal plane” in Zhuang). EX1003, 012; EX2002, ¶45. Zhuang disclosed finding that “only a small fraction” of RNA molecules resided “outside the imaging range of a fixed focal plane.” EX1003, 012; EX2002, ¶45. In other words, Zhuang confirmed that its system captured the majority of the RNA signals in a single focal plane, eliminating any need for optical sectioning and z-scanning. EX2002, ¶45; EX1003, 011, 012. A POSA would not have understood Zhuang’s quality control experiment to teach or suggest determining three-dimensional positional information of the RNAs at least because (i) the experiment only assessed the fraction (quantity) of RNAs in other focal planes; and (ii) the experiment did not determine any positional information of those RNAs. EX2002, ¶¶46-47; EX1003, 012.

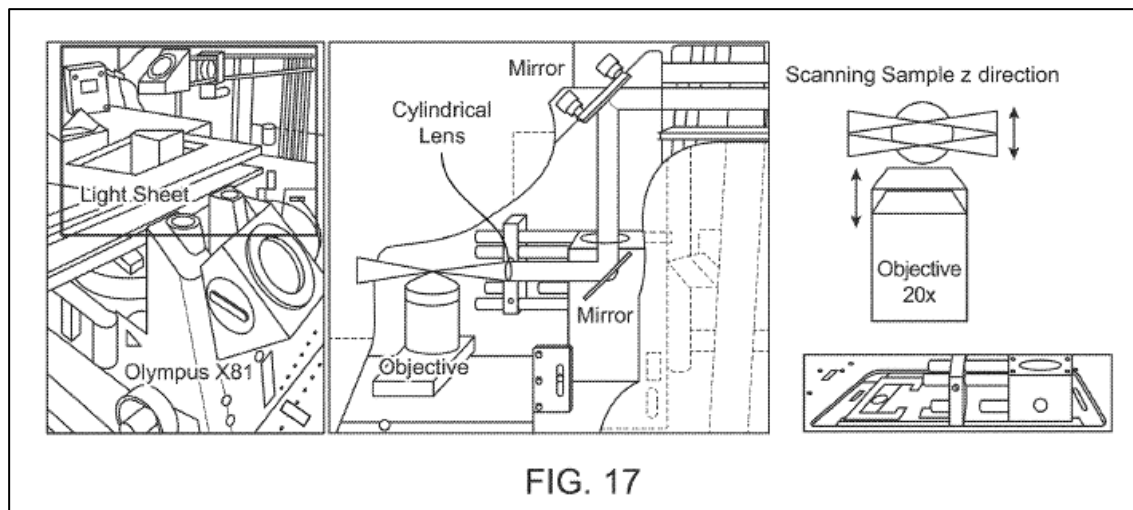
B. Petitioner’s relied-upon teachings in Cai did not disclose a system for determining three-dimensional positional information of nucleic acids in a sample

Cai (EX1004) disclosed “technologies for detecting and/or quantifying nucleic acids in cells, tissues, organs or organisms.” EX1004, Abstract; EX2002, ¶48. The Petition relies on an embodiment in Cai of using a light sheet microscope for imaging thick 100 μ M brain slices by “scanning the [brain] sample along [the]

z-axis.” Pet., 32-34, 42; EX1004, FIG. 17, 47:42-45, 47:48-50; EX2002, ¶48.

However, this disclosure of Cai did not teach determining three-dimensional, positional information of one or more nucleic acid molecules, as claimed. EX2002, ¶¶48-57.

Before November 3, 2015, a POSA would have known that light sheet microscopy uses a thin sheet of light to illuminate a sample. EX2002, ¶49. For example, Cai disclosed that “the present invention provides a light sheet microscope, wherein the sample is illuminated from the side.” EX1004, 47:31-33; EX2002, ¶49. Cai further disclosed that “[a]n exemplary setup of [a] light sheet microscope is illustrated in FIG. 17.” *Id.*, 47:36-37; EX2002, ¶49. Cai’s light sheet microscope in Figure 17 is copied below:



EX1004, FIG. 17.

Cai explained that the its light sheet microscope of Figure 17 utilized two mirrors and a cylindrical lens to create a “plane of light sheet,” which “illuminates

the sample from the side, and is perpendicular to the detection objective.” EX1004, 47:31-40; EX2002, ¶50. Cai further explained that this light sheet configuration permits the objective to move “synchronously with the illumination sheet, allowing scanning the sample along the z-axis.” EX1004, 47:40-47; EX2002, ¶50.

Before November 3, 2015, a POSA would have understood that this z-scanning ability of light sheet microscopy allowed the artisan to identify and select the optimal focal plane with the lowest out-of-focus background in the image. EX2002, ¶50. Accordingly, the art commonly referred to light sheet microscopy as “*selective plane* illumination microscopy,” or “SPIM.” EX1004, 46:49-53 (emphasis added); EX2002, ¶50. Indeed, Cai explained that its disclosure “utilize[s] imaging technologies that *minimize or prevent out-of-focus background*,” and “SPIM is used for *thicker slices* that have *higher out-of-focused background*.” EX1004, 47:15-18 (emphasis added); EX2002, ¶50.

Cai disclosed using its light sheet microscope system of Figure 17 to image β -actin mRNA in thick brain slices using “hybridization chain reaction” (HCR) probes. EX1004, 47:48-56, FIG. 18; EX2002, ¶51. Cai disclosed imaging 200 optical sections (200 focal planes) to image all of the β -actin mRNA in the thick brain slices. *Id.* Cai does not teach or suggest determining the three-dimensional positional information of the β -actin mRNA molecules. *Id.*; EX2002, ¶52. Rather, Cai only concluded that “[t]he β -actin mRNA is *highly expressed*, accounting for

the *large number* of dots in the cell bodies.” EX1004, 47:53-55 (emphasis added); EX2002, ¶52.

IV. PERSON OF ORDINARY SKILL IN THE ART

Solely for the purposes of this Preliminary Response, 10x has applied Petitioner’s definition of a POSA. *See* Pet., 13-14. 10x reserves the right to address the definition of a POSA should the IPR be instituted.

V. CLAIM CONSTRUCTION

For the limited purposes of this Preliminary Response, 10x does not believe that construction of any claim term is required. 10x reserves the right to address claim constructions should the IPR be instituted.

VI. PETITIONER FAILS TO ESTABLISH A REASONABLE LIKELIHOOD OF PREVAILING ON ANY OF ITS GROUNDS

For the Board to institute this proceeding, Petitioner must show that “there is a reasonable likelihood that [it] would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (stating that “the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable”).

The Petition includes 13 different grounds of unpatentability, comprising at least 16 different references cobbled together in an attempt to meet the challenged claim elements. *See* Pet., chart at 21-22. The Petition fails to, and indeed cannot,

meet its burden for several independent reasons, each of which alone is grounds for denial. When viewed together, the cumulative weight of the petition's defects, inaccuracies, and failure to comply with the Board's rules cannot be ignored. The Board should accordingly deny institution.

As demonstrated below and further supported by the declaration of Dr. Laura Waller (EX2002), Petitioner fails to establish a reasonable likelihood that (i) its asserted references disclose all the elements of the claimed system, and (ii) there was a reason to modify Zhuang's system with Cai's system to arrive at the claimed system with a reasonable expectation of success. EX2002, ¶¶54-88.

A. Petitioner fails to establish that the prior art teaches or suggests all the elements of the claimed system

The Petition is fundamentally defective in that it fails to show that its asserted art teaches or suggests all of the elements of the challenged claims. At a minimum, Petitioner fails to establish a reasonable likelihood that its applied art combination teaches or suggests all of the elements of independent claim 36. The remaining challenged claims 37-70 all depend directly or indirectly from claim 36, and therefore Petitioner's failures with respect to claim 36 alone are fatal to the petition in its entirety. The Board can and should deny institution based on this failure alone. *See, e.g., Floodbarrier, Inc. v. ILC Dover, LP*, IPR2019-01543, Paper 12, at 16 (P.T.A.B. Mar. 11, 2020) (rejecting Petitioner's obviousness ground and denying institution because "the Petition does not fully address each

element of the claims as issued in the [challenged] patent,” and thus “fails to satisfy the particularity requirement under 35 U.S.C. § 312(a)(3) and 37 C.F.R. § 42.104(b).”).

1. Petitioner fails to show that Zhuang teaches or suggests a system comprising a temperature control apparatus operatively coupled to the sample holder, as claimed

The Petition relies on the combination of Zhuang, Cai, and Shen for its challenge to independent claim 36. Pet., 22-42 (Ground 1). Claim element 36(a)(ii) requires “a temperature control apparatus operatively coupled to said sample holder.” EX1001, 33:33-34. Petitioner proffers two reasons for why the art allegedly discloses this claim element: (i) Zhuang’s system uses a Bioptechs FCS2 flow chamber that necessarily “includes temperature control capability,” and (ii) Zhuang’s system uses the Bioptechs objective heater that is “an additional temperature control system that becomes coupled to the ... sample holder.” Pet., 24-25. Both of Petitioner’s arguments fail to meet its burden in the Petition for the reasons discussed below.

a. The Bioptechs FCS2 flow chamber in Zhuang’s system does not necessarily include temperature control capability

Petitioner relies on Zhuang’s disclosure of a “Bioptech[s] FCS2 flow chamber” as purportedly meeting the claimed temperature control apparatus limitation. EX1003, 011; Pet., 24-25. According to Petitioner, a Bioptechs FCS2

flow chamber “is a system that includes temperature control capability.” Pet., 24.

But Petitioner does not—and cannot—point to any teaching in Zhuang that the FCS2 flow chamber disclosed therein is “operatively coupled” to a “temperature control apparatus,” as claimed. In fact, Zhuang has no disclosure at all regarding maintaining, regulating, or otherwise controlling the temperature in its FCS2 flow chamber. EX1003, 011.

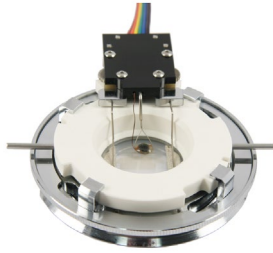
Unable to rely on Zhuang’s explicit disclosure, Petitioner resorts to an undeveloped *inherency* theory. Pet., 24. Specifically, Petitioner alleges that Zhuang’s Biopetechs FCS2 flow chamber *necessarily* “includes temperature control capability” merely because a different and completely unrelated reference (Sivaramakrishnan, EX1007²) purports to disclose maintaining a temperature of 37°C while using another Biopetechs FCS2 flow chamber. Pet., 24; EX1007, 2758.

² Petitioner cannot rely on Sivaramakrishnan to meet the expressly recited requirements of element 36(a)(ii) because Sivaramakrishnan is not part of the art combination of Ground 1 or any other Ground. *See, e.g., Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1002 (Fed. Cir. 2023) (“the Board is not permitted to entertain ‘shifting arguments’ but must, instead, reject any ‘entirely new theory of *prima facie* obviousness absent from the petition,’ if the petitioner attempts to inject such a theory into the proceeding post-petition.”) (citations omitted).

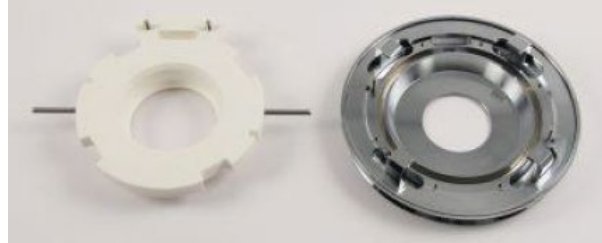
The law is clear that Petitioner must “meet a *high standard* in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis.” *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) (emphasis added). Indeed, Petitioner has the “burden to show *in the Petition* that the missing claim limitation ... was *inherent* in the prior art.” *Platinum Optics Tech. Inc. v. Viavi Solutions Inc.*, IPR2021-00424, Paper 11, at 9 (P.T.A.B. Dec. 6, 2021) (emphasis added). “[I]n order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue *necessarily must be present*, or the natural result of the combination of elements explicitly disclosed by the prior art.” *Par Pharm.*, 773 F.3d at 1195-96 (emphasis added). “Inherency ... *may not be established by probabilities or possibilities*.” *Id.* (emphasis added). Petitioner’s single, conclusory statement fails to meet this standard.

Petitioner’s inherency theory requires that Sivaramakrishnan’s Bioptechs FCS2 flow chamber and Zhuang’s Bioptechs FCS2 flow chamber *must necessarily* be of the same type. But Petitioner offers no such proof to meet its burden. In fact, Petitioner failed to address the fact that Bioptechs offers at least *two different types* of FCS2 flow chambers, one of which is a “No-Heat Flow Cell (FCS2)” described as “FCS2 without temperature control”:

FCS2 Chamber



No-Heat Flow Cell (FCS2)



See EX2004, 001; EX2005, 001. Thus, Sivaramakrishnan's disclosure of maintaining a certain temperature in its FCS2 flow chamber does not *necessarily* mean that Zhuang's system also used the same type of Bioprocess Systems FCS2 flow chamber, or that Zhuang's system included a temperature control apparatus as claimed. Indeed, Zhuang discloses nothing about maintaining, regulating, or otherwise controlling for any specific temperature in the FCS2 flow chamber. EX1003, 011.

The Petition also fails to address technical differences between the systems disclosed in Sivaramakrishnan and Zhuang. For example, Sivaramakrishnan discloses maintaining a Bioprocess Systems FCS2 flow chamber at 37°C for “*Live Cell Imaging*,” while Zhuang discloses using a Bioprocess Systems FCS2 flow chamber (again, with no mention of controlling its temperature) for imaging cells “*fixed ... in 4% paraformaldehyde*.” EX1007, 2758 (emphasis added); EX1003, 011. The Petition never reconciles these discrepancies in the references.

b. The Bioptechs objective heater in Zhuang’s system is not a temperature control system that is operatively coupled to a sample holder

The Petition also attempts to characterize Zhuang’s disclosure of a “Bioptechs objective heater” as an “additional temperature control system that becomes coupled to the ... sample holder.” Pet., 24-25. According to Petitioner, Zhuang’s objective heater meets the temperature control apparatus claim element because it heats *the objective* that is in “thermal contact with the stage holding the sample” via the immersion oil. *Id.* Petitioner’s arguments fail to meet its burden for several reasons.

First, Petitioner’s objective heater theory is contradicted by its own evidence. Exhibit 1006 expressly discloses that the Bioptechs objective heater “plugs into a *separate Temperature Controller* ... which regulates *the objective temperature*” EX1006, 6 (emphasis added). In other words, Exhibit 1006, which is Petitioner’s exhibit, discloses that the objective heater is operatively coupled to its own, separate temperature controller, and *not* to the sample holder, as claimed. *Id.*; EX1001, 33:33-34.

Second, Petitioner admits that Zhuang’s objective heater is, *at most*, only in “thermal contact” with (*i.e.*, touches) the sample holder. Pet., 24-25; EX1006, 6. Even if this were true, Zhuang’s objective heater is not a temperature control apparatus *operatively coupled* to the sample holder, as claimed, at least for the

reasons discussed above. Tellingly, Petitioner never argues that Zhuang’s objective heater is “*operatively* coupled” to the sample holder—only that it is “coupled” to the sample holder. Pet., 25.

In view of the above, Petitioner fails to show that its asserted art teaches or suggests at least claim element 36(a)(ii).

2. Petitioner fails to show that Zhuang teaches or suggests a system comprising a pump that provides fluid reagents from “one or more reservoirs” to a sample holder, as claimed

Claim element 36(b)(ii) requires “a fluid dispenser operationally coupled to a pump, which pump is configured to provide said one or more fluid reagents from said one or more reservoirs to said sample holder.” EX1001, 33:39-42.

Petitioner relies exclusively on Zhuang for this claim element. Pet., 27–28. The Petition, however, fails to show that Zhuang discloses a system comprising a pump that provides fluid reagents from “one or more reservoirs” to a sample holder. *Id.* In fact, the Petition does not even mention the word “reservoir” in relation to the element. *Id.*³ Instead, the Petition focuses only on Zhuang’s disclosure of a “peristaltic pump,” failing to address the requirement that a pump

³ As discussed below in Section VII.B, the Petition’s attempt to rely on an expert declaration to expand conclusory arguments in the Petition is an improper incorporation by reference. 37 C.F.R. § 42.6(a)(3); 37 C.F.R. § 42.104.

must provide fluid reagents from “one or more reservoirs” to the sample holder.

The PTAB has rejected other petitions for similar failures to address an express claim element, and should do the same here. *See e.g., Floodbarrier*, IPR2019-01543, at 14-16.

3. Petitioner fails to show that its asserted art teaches or suggests determining three-dimensional positional information of one or more nucleic acid molecules, as claimed

Claim element 36(e) requires “determining three-dimensional positional information of said one or more nucleic acid molecules.” EX1001, 34:15-16.

Petitioner argues in a single sentence that “Zhuang, by itself or in view of Cai, determines the 3D positional information of the RNA species.” Pet., 42. However, as explained below, Petitioner fails to meet its burden because neither Zhuang alone nor combined with Cai discloses or suggests a system for determining three-dimensional positional information of nucleic acid molecules. EX2002, ¶¶8-10, 54-81.

a. Zhuang does not teach or suggest determining three-dimensional positional information of one or more nucleic acid molecules

Zhuang discloses a MERFISH-based system that images many different RNA species to determine their two-dimensional positional information in cells, and explicitly states that its MERFISH methods are performed *without* any need for optical sectioning or z-scanning. EX1003, 001, 002, 011, 012; EX2002, ¶56.

Specifically, Zhuang discloses methods for imaging RNA molecules in a layer of human primary fibroblast cells plated on a coverslip, which Zhuang describes as being “relatively large and flat.” EX1003, 001, 011; EX2002, ¶56. Due to the “relatively large and flat” nature of the layer of fibroblast cells, a POSA would have understood that the fluorescently labeled RNA signals in the cells resided in *a single focal plane*, and there was no need to analyze signals in other focal planes. EX2002, ¶56; EX1003, 011, 012. Accordingly, Zhuang expressly discloses performing its MERFISH methods “*without* the need for optical sectioning” and “*without ... z-scanning.*” EX1003, 011, 012 (emphasis added); EX2002, ¶56. As discussed below, this explicit instruction in Zhuang *teaches away* from determining three-dimensional positional information because Zhuang expressly teaches that exploring other focal planes is *not* needed for the disclosed MERFISH imaging methods. *See* Section VI.B.1; EX2002, ¶60.

Zhuang’s two-dimensional methods are further evident from its disclosure of determining only the x- and y-axis positional coordinates (*not* the z-axis coordinates) of the RNA molecules in the cells. EX2002, ¶57; EX1003, 012. Specifically, Zhuang’s system analyzes fluorescent spots (each corresponding to an individual RNA molecule) in an image by inputting a “*width* of 167 nm” as the parameter in a computational algorithm to identify and localize the RNAs. EX1003, 012 (emphasis added); EX2002, ¶57.

As Dr. Waller explains, Zhuang’s disclosure of considering only “width”—not “height”—during image analysis is a direct indicator that Zhuang’s system addressed lateral (x-y axis) distance, but not axial (z-axis) distance. EX2002, ¶58; EX1003, 012. Consequently, Zhuang taught a system that determines only x- and y-axis positional coordinates, *i.e.*, *two-dimensional* positional information, of the RNA molecules in the cells. EX2002, ¶58. Thus, while Zhuang discloses using MERFISH to assess “spatial distribution” of RNA molecules in cells, that is a direct reference to determining two dimensional—not three dimensional—positional information of the RNA molecules. EX2002, ¶59; EX1003, 011, 012. Indeed, Zhuang’s use of the term “spatial” to indicate two-dimensional analysis consistent with its use in the art. EX2001, Abstract; EX2003, 11:31-33; EX2002, ¶59. For example, Frisen discloses a method for “partial or global transcriptome analysis of a tissue sample with two-dimensional *spatial* resolution.” EX2003, 11:31-33 (emphasis added).

Petitioner ignores these express disclosures in Zhuang, and instead takes an inapposite position that Zhuang “teaches” using MERFISH “to obtain the 3D spatial position.” Pet., 38. In doing so, Petitioner mischaracterizes Zhuang’s disclosure of “optically section[ing] ... cells by collecting stacks of images at different focal depths through the entire depth of the cells,” as a teaching or suggestion to determine three-dimensional positional information of one or more

nucleic acids. EX1003, 012; Pet., 38; EX1002, ¶¶128, 183; EX2002, ¶61.

However, this disclosure in Zhuang relates to a separate validation experiment (*i.e.*, quality-control experiment) using optical sectioning and z-scanning for *quantifying* RNAs—not for determining three-dimensional positional information (explained below). EX2002, ¶62. Indeed, Petitioner’s expert, Dr. Cyzmmek, admitted that Zhuang’s disclosure of optical sectioning and z-scanning was part of a “validation experiment[].” EX1002, ¶¶128 (“smFISH validation experiments”), 183 (“smFISH validation studies”); EX2002, ¶62.

Because Zhuang’s system imaged the cells “without optical sectioning and z-scanning,” Zhuang discloses using a conventional smFISH-based (*not* MERFISH-based) quality-control experiment for confirming that its system needed to only image the cells in a single focal plane. EX1003, 012; EX2002, ¶¶63-64. This quality-control experiment “*quantified the fraction*” of RNAs that might be “outside the axial range of [] imaging geometry,” *i.e.*, outside of the basal focal plane imaged. EX1003, 012 (emphasis added); EX2002, ¶64.

To perform this quality-control experiment, Zhuang “optically sectioned the[] cells by collecting stacks of images at different focal depths through the entire depth of the cells,” and then “aligned” the image stacks from “consecutive focal planes” to “compute[] for each cell the *fraction* of RNAs” in the collected stacks but not in the basal focal plane of the system. EX1003, 012 (emphasis added);

EX2002, ¶65. The analysis showed that “only a small *fraction*” of RNAs resided “outside the imaging range of a fixed focal plane,” confirming that optical sectioning and z-scanning *were not needed* for Zhuang’s system. EX1003, 012 (emphasis added); EX2002, ¶66. Thus, as Dr. Waller explains, a POSA would *not* have understood Zhuang’s quality control experiment to teach or suggest determining three-dimensional positional information of the RNAs at least because (i) the experiment only assessed the fraction (quantity) of RNAs in other focal planes; and (ii) the experiment did not determine any positional information of those RNAs, nor did Zhuang suggest doing so. EX2002, ¶¶63-66.

Additionally, mere disclosure of optical sectioning and/or z-scanning does not teach or suggest determining three-dimensional positional information of nucleic acid molecules, as claimed. EX2002, ¶67. As Dr. Waller explains, a POSA would have known that optical sectioning is a technique for acquiring images of thin slices (or “planes”) from a thick specimen by removing the contribution of out-of-focus light in each image plane. EX2002, ¶67; EX1012, 004 (disclosing that “optical sectioning” “removes out-of-focus blur and permits you to distinguish between the signals in thin ‘optical’ slices”). Dr. Waller further explains that this removal of unwanted light provides greater contrast and improves image quality. EX2002, ¶67.

Mere disclosure of “z-scanning” also does not teach determining three-

dimensional positional information of nucleic acid molecules. EX2002, ¶68. Z-scanning simply allows for imaging signals in different focal planes, which can then be analyzed in different ways, including *two-dimensional* imaging. *Id.* For example, Cai expressly discloses using z-scanning to create two-dimensional images of cells. *See* EX1004, FIG. 12, 10:56-63 (“Images were *2D maximum projections created from z stacks* of 11 images taken every 1.5 μ M.” (emphasis added)); EX2002, ¶68. Thus, Zhuang’s disclosure of optical sectioning and z-scanning as part of its smFISH validation experiment did not teach or suggest determining three-dimensional positional information of one or more nucleic acid molecules, as claimed. EX2002, ¶¶67-68.

Zhuang also discloses that “any optical sectioning technique could be used in MERFISH to allow the imaging of RNAs in thicker cells or tissues.” EX1003, 012; EX2002, ¶69. Petitioner never argues that this sentence teaches or suggests determining three-dimensional positional information of nucleic acids, as claimed—only that this sentence relates to imaging samples that have a “volume.” *Compare* Pet., 42 (addressing three-dimensional positional information claim element), *with* Pet., 24 (addressing sample having a volume claim element). Regardless, Zhuang’s reference to thicker cells or tissues would not have suggested to a POSA to determine three-dimensional positional information of nucleic acids. EX2002, ¶69. To the contrary, a POSA would have understood this statement in

Zhuang to simply suggest using optical sectioning to remove any unwanted light from the out-of-focus planes when imaging thicker cells or tissues (which typically have significant unwanted signals from the other focal planes) with Zhuang's MERFISH-based system. EX1003, 012; EX2002, ¶69.

Tellingly, subsequent publications by the same Zhuang research group (which post-date the 554 patent) reportedly “extended” the MERFISH technique to three-dimensional imaging and confirmed that the original MERFISH-based system relied on by Petitioner is limited to two-dimensional imaging. EX2002, ¶70. For example, Xiaowei Zhuang's 2023 *eLife* article (“Zhuang 2023,” EX2007) discloses a method for “three-dimensional (3D) single-cell transcriptome imaging of thick tissue specimens” by integrating MERFISH with confocal microscopy for optical sectioning. EX2007, Abstract. Zhuang 2023 explicitly states that while Zhuang EX1003 (referred to as “Chen et al., 2015” in Zhuang 2023) disclosed MERFISH for simultaneously imaging thousands of nucleic acids, the method was later “*extended to allow* spatially resolved 3D-genome imaging and epigenomic profiling of individual cells” in articles published *several years* after Zhuang EX1003. EX2007, 1 (emphasis added; citing EX2008 (Su 2020); EX2009 (Lu 2022)). By explaining that MERFISH was “extended” to allow spatially resolved 3D-genome imaging years after Zhuang EX1003 published, Zhuang 2023 confirms that the MERFISH-based system disclosed in Zhuang EX1003 did not determine

three-dimensional positional information of the RNA molecules in the cells. *Id.*; EX2002, ¶70.

Published statements from *eLife* peer reviewers of Zhuang 2023 (nearly *eight years* after Zhuang EX1003 published) further confirm that Zhuang EX1003's disclosures were in the context of two-dimensional spatial positioning only. EX2002, ¶¶70-71. For example, Reviewer #2 stated that the authors' new MERFISH 3D methods "present[] a *technical milestone*," and Reviewer #1 described Zhuang 2023's new MERFISH 3D methods as a "*major technical advance*." EX2007, 27-28 (emphasis added). The disclosures in Zhuang 2023, which are only further confirmed by the *eLife* reviewers' comments, make clear that Zhuang's 2015 publication did not teach using MERFISH for determining three-dimensional positional information of nucleic acids. EX2002, ¶¶70-71.

Further evidence is found in Petitioner's own expert's publication from 2022, entitled "Organizing your space: The potential for integrating spatial transcriptomics and 3D imaging data in plants." EX2010 ("Cyzmmek 2022"); EX2002, ¶72. In this review article, the authors (which include Dr. Cyzmmek) "review advances in [spatial transcriptomics] and 3D microscopy approaches and describe how these technologies could be combined to provide high resolution, spatially organized plant tissue transcript mapping." EX2010, Abstract; EX2002, ¶72. When discussing Zhuang's MERFISH-based system (referred to as "Chen et

al., 2015b”) and other spatial transcriptomics approaches, the authors first note MERFISH’s limitations on the number of genes that can be analyzed, and then discuss the potential to *now* generate those data in three dimension:

Targeted methods such as single molecule, fluorescent in situ hybridization (smFISH), yield precise and spatial gene expression data at a subcellular resolution (*Chen et al., 2015b, 2018; Merritt et al., 2020*). However, these methods are limited in the number of genes that can be analyzed per experiment ... Excitingly, there is also *potential to generate these data in 3D*, which requires reassembling the tissue from a serial array of 2D optical or physical tissue sections.

EX2010, 704 (emphasis added).

The authors’ explanation that there is *now* (seven years after Zhuang EX1003) a “potential” to generate three-dimensional images using MERFISH further confirms that Zhuang’s original MERFISH disclosures back in 2015 did not teach or suggest determining three-dimensional positional information of nucleic acid molecules, as claimed. *Id.*; EX2002, ¶¶73-74.

Additionally, a 2019 report by Ghani and Isogai entitled, “Optimisation of MERFISH Data Analysis and Visualisation,” provides even further confirmation that Zhuang’s MERFISH-based system was only in 2D. EX2011; EX2002, ¶75.

Ghani’s 2019 report disclosed using MERFISH to study “the cellular diversity of

hypothalamic tissue.” EX2011, Abstract; EX2002, ¶75. Ghani characterized Zhuang’s MERFISH-based system as a method of “sequential labelling and stripping of fluorophores to a fixed sample,” stating that Zhuang’s MERFISH-based system “exploits principles of digital communications to do robust quantification of gene expression.” EX2011, 1; EX2002, ¶75. Ghani expressly stated that MERFISH at the time (in 2019) had only been used *in 2D* and that the authors had *now* (in 2019) developed methods to “accelerate” using 3D MERFISH:

MERFISH analysis is currently done in 2D, where the z-data is discarded after generating maximum intensity projections to decrease computation time at the cost of sub-optimal single molecule localisation. We hypothesized that using machine learning techniques and GPU-computing would minimise this trade-off and accelerate 3D MERFISH analysis.

EX2011, 2 (emphasis added).

The Federal Circuit and its predecessor court have long held that later publications can provide evidence of an earlier state of the art. *See In re Hogan*, 559 F.2d 595, 605 (C.C.P.A. 1977) (noting that the CCPA “approved use of later publications as evidence of [an earlier] state of art”); *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (finding that “the district court properly used later reports as evidence of the state of the art”). The Board has also recognized this well-known principle. *See e.g., POSCO v.*

ArcelorMittal, IPR2019-01275, Paper 7, at 14 (P.T.A.B. Jan. 8, 2020) (“[The Board] may properly rely on post-filing date publications as evidence of the state of the art.”); *Coherus Biosci., Inc. v. AbbVie Biotech. Ltd.*, IPR2017-01008, Paper 11, at 21-22 (P.T.A.B. Sept. 7, 2017) (relying on a later publication for evidence of an earlier state of the art). Thus, later publications like Ghani, Czymmek 2022, and Zhuang 2023 are further evidence that Zhuang disclosed applying its MERFISH methods for determining two-dimensional positional information, not three-dimensional. EX2002, ¶¶70-76.

Petitioner fails to grapple with Zhuang’s explicit disclosures that its MERFISH was a two-dimensional analysis, nor does it recognize the fact that later publications consistently refer back to Zhuang’s original MERFISH disclosures in the context of two-dimensional imaging. Accordingly, Petitioner fails to show that Zhuang teaches or suggests determining three-dimensional positional information of one or more nucleic acid molecules, as required by claim element 36(e).

b. Petitioner fails to show that Cai teaches or suggests determining three-dimensional positional information of nucleic acid molecules

No doubt recognizing Zhuang’s deficiencies regarding (among others) claim 36’s determining step, the Petition argues in the alternative that the combination of Zhuang and Cai “determines the 3D positional information of the RNA species.” Pet., 42. This fallback argument also fails to meet the Petitioner’s burden. EX2002,

¶¶77-81.

First, the Petition’s Zhuang and Cai combination argument for this claim element is presented as a single, conclusory sentence: “Zhuang, by itself or in view of Cai, determines the 3D positional information of the RNA species.” Pet., 42. Rather than attempt to present a developed argument and explanation for this claim limitation, the Petition provides this single sentence and then refers back to another section of the Petition (“*See supra* X.A.1.e.i”) and four paragraphs of the Czymmek declaration (“¶¶ 216–219”). Pet., 42. As discussed below in Section VII.A, this format of nested, cross-referenced arguments is improper and should not be accepted by the Board. *See e.g., Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00450, Paper 9, at 8 (P.T.A.B. June 29, 2015) (“*Apple II*”) (finding that “[t]he pervasive use of internal cross-references within the Petition and the supporting [expert] Declaration obfuscates the evidentiary support for the Petition’s assertions.”).

To the extent the Board decides to “go on a treasure hunt for the evidence and the invalidity theory” (*see Samsung Elecs. Co., Ltd. v. Mojo Mobility, Inc.*, IPR2023-01091, Paper 11, at 33–34 (P.T.A.B. Jan. 8, 2024)), the Petition’s cross-referenced arguments nonetheless still fail to show that Cai teaches or suggests determining three-dimensional positional information. In fact, the Petition never explains how or why Cai supposedly teaches or suggests the determining step

claim element at all. Rather, the cross-cited section of the Petition only alleges that Cai teaches “the claimed Z-axis motion control system,” which, according to the Petition, “enables 3D interrogation.” Pet., 39.

When arguing that Cai “enables 3D interrogation,” Petitioner again cross-references to yet another section of the Petition (“*See supra* Section X.A.1.d.”). Pet., 39. But in that section of the Petition, Petitioner only argues that Cai teaches a “Z-axis motion control system,” with no explanation or argument regarding determining three-dimensional positional information. Pet., 32-33. Further still, the Petition relies upon two disclosures in Cai for its Z-axis motion control argument, neither of which teaches or suggests a system for determining three-dimensional positional information.

The Petition first cites Cai’s Figure 17 and disclosures at column 47:43–45. Pet., 33; EX1004, FIG. 17, 47:43–45. As Dr. Waller explains, these disclosures related to using a light sheet microscope for imaging thick 100 μ M brain slices by “scanning the [brain] sample along [the] z-axis,” and do not teach or suggest determining three-dimensional positional information of nucleic acids. EX1004, FIGs. 17-18, 11:25-32, 46:49-53, 47:42-45, 47:48-50; EX2002, ¶¶77-81. As explained above, mere z-scanning (*i.e.*, scanning along the z-axis) does not determine three-dimensional positional information of nucleic acid molecules, as claimed. EX2002, ¶79; *see* Section VI.A.3.a. And as Dr. Waller explains, Cai’s

light sheet microscope's purported z-axis motion control system would simply move the objective along the z-axis to *adjust the focal plane* for imaging. EX2002, ¶79. Thus, even if, *arguendo*, Cai's light sheet microscope had a z-axis motion control apparatus, that apparatus would not have determined three-dimensional positional information of nucleic acid molecules, as claimed. *Id.* Neither Petitioner nor Dr. Czymmek provides any explanation how a POSA would have purportedly used a z-axis motion control system to determine three-dimensional positional information. *Id.*

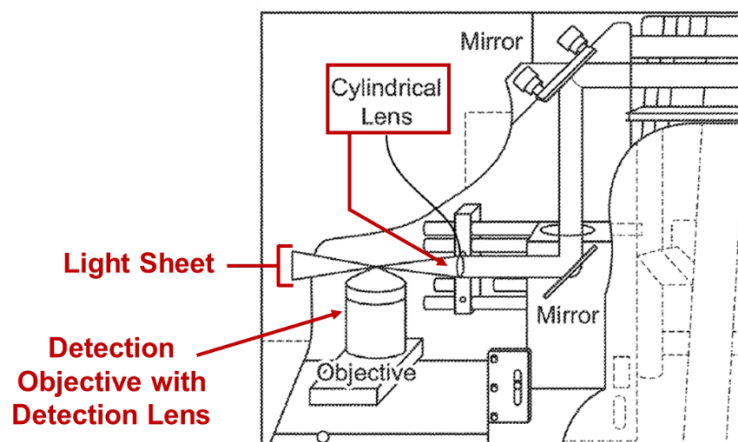
The Petition also cites a single sentence in Cai that states, “[i]n some embodiments, an imaging step provides three-dimensional spatial information of a target.” Pet., 34, 39; EX1004, 21:50-51. But Cai provides no further disclosure beyond this mere wish, and Petitioner certainly cites none. *Id.* “To render a claim obvious, the prior art, taken as a whole, *must enable* a skilled artisan to make and use the claimed invention.” *Raytheon Techs. Corp. v. General Electric Co.*, 993 F.3d 1374, 1380-1381 (Fed. Cir. 2021) (emphasis added). When there is no supporting evidence to establish enablement in the primary reference or general knowledge in the art—such as the case here—“the reference must necessarily enable the relied-upon portion of its own disclosure.” *Id.* at 1381. This is the “same standard applied to anticipatory references.” *Id.* (citing *In re Antor Media Corp.*, 689 F.3d 1282, 1290 (Fed. Cir. 2012)). The Petition provides no explanation

how a POSA would have purportedly determined three-dimensional positional information of nucleic acids with Zhuang's MERFISH-based system alone or combined with Cai's light sheet microscope approach. These critical deficiencies render the Petition's grounds for unpatentability untenable. EX2002, ¶80.

Indeed, the Petition fails to reconcile fundamental differences in Cai's and Zhuang's systems when arguing that a POSA would have allegedly combined these different systems. EX2002, ¶¶82-87. For example, Zhuang discloses that its MERFISH-based system uses a high-resolution, "1.45 NA, 100x oil immersion" objective. EX1003, 011; EX2002, ¶83. Before November 3, 2015, a POSA would have known that the "NA" (Numerical Aperture) of a lens in a microscope objective impacts the working distance (the space between the sample and lens) of the microscope. EX2002, ¶83; EX1012, 10. For example, Petitioner's EX1012 discloses that a "high NA also comes at the expense of reduced working distance (how far the objective lens can focus into your sample)". *See also* EX1019, 002 (stating that "longer working distances for objective lenses ... comes at the cost of lowering the numerical aperture"); EX2002, ¶83. Thus, a POSA would have known that Zhuang's disclosure of a 1.45 NA objective lens (a high NA) was a disclosure of an optical system with a small working distance. EX1003, 011-012; EX2002, ¶83.

Meanwhile, Cai discloses that its system images brain sections using a light

sheet microscope with a low-resolution “20x water immersion objective.” EX1004, 47:30-56, FIGs. 17, 18; EX2002, ¶84. Cai discloses that its light sheet microscope “illuminates the sample from the side” using a plane of light (called a “light sheet”) that is “perpendicular to the detection objective.” EX1004, 47:36-40, FIG. 17; EX2002, ¶84. Thus, a POSA would have understood that Cai’s light sheet system includes two optical setups. EX2002, ¶84; EX1004, FIG. 17. The first optical setup is *perpendicular* to the sample and comprises a low-resolution “20x water immersion” *detection objective* (containing a *detection lens*) for imaging the sample. EX1004, FIG. 17; 47:30-56; EX2002, ¶84. The second optical setup is *parallel* to the sample and the detection objective, comprising a “*cylindrical lens*” (commonly referred to as an *illumination lens*) for focusing a light sheet to illuminate the sample. EX2002, ¶84; EX1003, FIG. 17. Dr. Waller’s annotation of Cai’s Figure 17 is presented below:



EX2002, ¶84; EX1004, FIG. 17 (annotated).

As Dr. Waller explains, a POSA would have generally known that light sheet microscopes like Cai's microscope in Figure 17 utilize larger working distances and lower NA to account for the optical machinery and physical geometry needed for the light sheet, as well as spacing to accommodate the typically larger specimens being imaged. EX2002, ¶85. For example, Fisher *et al.* (Petitioner's own exhibit) discloses that light-sheet microscopy "forces the use of *long working distance* [and] somewhat *low NA* (typically 1.0 or less) objective lenses." EX1019, 007 (emphasis added); EX2002, ¶85. Indeed, Cai described using "20x *low NA objectives*," and expressly discloses using a light sheet microscope in (*e.g.*, Figure 17) with a 20x water immersion objective to image "100 μ m brain slices." EX1004, 44:34-35, 47:30-56, FIGs. 17, 18 (emphasis added); EX2002, ¶85. Thus, a POSA reading Cai would have known that Cai's light sheet microscope system uses a low NA detection lens and a low NA cylindrical lens, both of which use a large working distance. EX2002, ¶85.

Despite these clear and unmistakable differences in the design and function of these two very different systems, neither the Petition nor Dr. Czymmek explains in any detail how a POSA would have modified and combined them to arrive at the claimed determining step with a reasonable expectation of success. Pet., 42; EX2002, ¶¶86-88. Instead, the Petition focuses on alleged disclosure of claim elements in disparate portions of art combinations, underscoring Petitioner's use of

hindsight to make its obviousness case. Accordingly, the Petition fails to show that Zhuang alone, or Zhuang combined with Cai, teaches or suggests determining three-dimensional positional information of one or more nucleic acid molecules, as required by element 36(e).

4. Petitioner repeatedly fails to meet the legal standards for inherency throughout the Petition

Petitioner further fails to meet its burden because the Petition repeatedly relies on inherency theories to identify missing claim elements in its asserted art, yet makes no attempt to explain how the alleged claim elements “*necessarily must be present*” in the prior art. *Par Pharm.*, 773 F.3d at 1196 (emphasis added); *see also Platinum Optics*, IPR2021-00424, at 9 (“[I]t was *Petitioner’s* burden to show in the Petition that the missing claim limitation ... was inherent in the prior art.” (emphasis added)).

Petitioner relies on inherency for multiple elements of independent claim 36, as well as dependent claims 46, 61, and 63. For example, as explained above in Section VI.A.1, Petitioner fails to show that Zhuang *necessarily* discloses a Bioptechs FCS2 flow chamber that is operatively coupled to a temperature control apparatus. This defect in the Petition applies not only to Petitioner’s failure to meet its burden on claim 36, but also to dependent claim 63. For claim 63, Petitioner argues that “a POSA would have understood that Zhuang’s system including a temperature control apparatus and thermal control system would have *necessarily*

included a temperature sensor in the temperature control apparatus.” Pet., 49 (emphasis added). Petitioner relies only on EX1006, which fails to account for other FCS2 flow cells that do not contain a temperature control system (*e.g.*, the FCS2 “No-Heat Flow Cell”). EX2004, 001.

Petitioner attempts similarly undeveloped inherency arguments for other elements of independent claim 36. For claim element 36(b)(i) (reciting a fluidics system component comprising “one or more reservoirs ...”), Petitioner argues that “given that fluid reagents are repeatedly introduced to the sample in the flow chamber, Zhuang teaches the fluidic system includes reservoirs for holding these fluids.” Pet., 27; *see also* EX1002, ¶159 (“A POSA would have understood Zhuang’s automated system to *necessarily comprise* one or more reservoirs capable of holding fluid.”) (emphasis added). But neither the Petition nor the Czymmek Declaration explains why or how Zhuang’s system *necessarily* comprises one or more reservoirs and how those same one or more reservoirs are configured to the pump of claim 36(b)(ii).

Petitioner again relies on inherency when discussing claim element 36(c)(ii) (referring to “two or more light sources” configured to “emit two or more colors of light”). Here, Petitioner states in conclusory fashion, “[a]s Dr. Czymmek explains, Cai’s disclosure of different color fluorophores teaches using different colors of excitation light.” Pet., 30 (citing EX1002, ¶172). Putting aside Petitioner’s

conclusory statement and improper incorporation by reference (*see infra*, Section VII.B), a closer look at the relied upon testimony in the Czymmek Declaration shows yet another failed inherency argument. Dr. Czymmek testifies that “the detection of different fluorophores as described in Cai *would have required* using different colors of excitation.” EX1002, ¶172 (emphasis added). Yet absent from Dr. Czymmek’s testimony is *any* underlying evidence to support his conclusory statement that this is *necessarily* so. *Id.*; 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”).

Petitioner also fails to meet its burden when addressing claim element 36(c)(iii) (referring to “one or more detectors”). Petitioner argues only that “Zhuang teaches the use of an EMCCD camera to detect light signals from the sample volume.” Pet., 30. Petitioner provides no explanation as to how Zhuang’s disclosure of an EMCCD (electron-multiplying charge coupled device) camera meets the claimed “one or more detectors” element. *Id.* Dr. Czymmek again provides no underlying evidence to support his conclusory statement that “a POSA would recognize an EMCCD camera as a detector configured to receive light signals from the volume.” EX1002, ¶178 (citing no evidence); 37 C.F.R. § 42.65(a).

Petitioner’s argument addressing claim element 36(d) (referring to the “Z-

axis motion control system” component) likewise fails to prove inherency.

Petitioner argues that “to maintain a constant focus throughout an imaging process, a person of skill would understand that a Z-axis motion control system for adjusting the focal plane *would be necessary*.” Pet., 31 (emphasis added). The Petition provides no explanation or evidence showing *why* this would be “necessary.” *Id.* Dr. Czymmek’s testimony is equally deficient as he again provides no underlying evidence in the two paragraphs of his declaration relied upon by the Petition. *See* EX1002, ¶¶182–183; Pet., 31.

Finally, Petitioner also fails to meet the required standard for inherency when addressing dependent claims 46, 61, and 63 (claim 63 is discussed above). For claim 46 (referring to the “fluidics system” component further comprising one or more valves downstream of the one or more reservoirs and upstream of a fluid dispenser), Petitioner relies on the Czymmek declaration for its single statement that Zhuang’s system “*requir[es]* the use of valves that would *necessarily* be downstream of the reservoir and upstream of the dispenser.” Pet., 44 (emphasis added; citing EX1002, ¶239). Lacking in the Petition or Czymmek declaration, however, is any evidence demonstrating why or how Zhuang’s valves must *necessarily* be downstream of reservoirs and upstream of a dispenser. *Id.*

Petitioner’s argument for claim 61 (referring to a “vibration control rigid foundation”) is also defective. Petitioner argues that Zhuang’s system was “built

around the Olympus IX-71 microscope,” that “the Olympus IX-71 included a vibration control rigid foundation,” and thus, “a POSA would have understood that Zhuang’s microscope *would have included* a vibration control rigid foundation.” Pet., 64 (emphasis added). Petitioner mischaracterizes the disclosure in Zhuang and again fails to prove inherency. Zhuang does not disclose that its microscope was “built around the Olympus IX-71 *microscope*” as Petitioner contends; rather, Zhuang only discloses that its homebuilt microscope was “constructed around an Olympus IX-71 *body*.” EX1003, 011 (emphasis added). Petitioner fails to explain why a microscope merely constructed around the *body* of an Olympus IX-71 must *necessarily* have the vibration control rigid foundation of a complete Olympus IX-71 *microscope*. Zhuang made several modifications to the imaging system and the mere *possibility*, or even *probability*, of Zhuang’s system having a vibration control rigid foundation is insufficient to prove inherency.

The Federal Circuit explained in *Par Pharmaceutical* that “[i]nherency ... *may not be established by probabilities or possibilities*. The mere fact that a certain thing *may* result from a given set of circumstances is *not sufficient*.” *Par Pharm.*, 773 F.3d at 1195 (emphasis added; citations omitted). As shown above, Petitioner’s conclusory inherency arguments lack evidentiary support, and even if considered, the Petition at best relies on probabilities or possibilities. Thus, for these additional reasons, the Board should deny institution. *See, e.g.,*

GlaxoSmithKline LLC v. Fibrogen, Inc., IPR2016-01318, Paper 13, at 21 (P.T.A.B.

Jan. 11, 2017) (rejecting Petitioner’s inherency arguments because “Petitioner makes too many tenuous and unsupported connections that are not necessarily so” and the Petitioner “does not provide sufficient support that this is *necessarily* so.” (emphasis in original)).

B. Petitioner fails to establish a reason to modify Zhuang’s system to arrive at the claimed system with a reasonable expectation of success

Petitioner’s failure to show that its asserted art combinations teach or suggest all of the elements of the challenged claims is fatal to the Petition, as it cannot show a reasonable likelihood of prevailing on any of its grounds. Should the Board need additional reasons to deny institution, it need only look to the Petition’s failure to explain why or how a POSA would have modified Zhuang’s MERFISH-based system with Cai’s light sheet microscope system to arrive at the claimed system with a reasonable expectation of success. EX2002, ¶¶82-88.

The Petition argues that, “[t]o the extent that Zhuang is deemed to not disclose the claimed 3D feature, it would have been obvious to modify Zhuang in view of Cai to include this feature.” Pet., 39. The Petition’s thin rationale is based on (i) Cai’s single sentence wish for providing “three-dimensional spatial information” (EX1004, 21:49-51) and (ii) Cai’s alleged disclosure of a “Z-axis motion control system” (EX1004, 47:43-45). Pet., 39. As discussed above, Cai’s

wish for providing three-dimensional positional information is devoid of any explanation how to achieve it, and even if Cai did disclose a “Z-axis motion control system,” that in no way teaches or suggests a system for determining three-dimensional positional information of one or more nucleic acid molecules. *See supra*, Section VI.A.3.b; EX2002, ¶¶77-81.

Moreover, as discussed below, the Petition fails to address Zhuang’s *teaching away* from determining three-dimensional positional information of one or more nucleic acid molecules. EX2002, ¶60. And, even if the artisan had a reason to combine Zhuang’s MERFISH-based system with Cai’s light sheet microscope system, the Petition fails to grapple with significant differences in these two systems, providing no explanation or details as to how the POSA would have allegedly modified the systems to arrive at the claimed system. EX2002, ¶¶82-88.

1. Zhuang teaches away from determining three-dimensional positional information of RNA molecules in its system

“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be *discouraged* from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *Polaris Industries, Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (emphasis added)).

Zhuang discloses using a MERFISH-based system to image fluorescent

signals from cellular RNA molecules in a single focal plane, and it explicitly teaches that the system imaged cells “without the need for optical sectioning” and “z-scanning.” EX1003, 011, 012; EX2002, ¶¶42-45, 60; *see also*, Sections III.A and VI.A.3.a, *supra*. In fact, Zhuang discloses performing a quality-control test using conventional smFISH (not MERFISH) that *confirmed* the MERFISH-based system generates accurate and reliable data without any need for optical sectioning and z-scanning. EX1003, 012; EX2002, ¶¶62-66. Thus, a POSA reading Zhuang would have been “led in a direction divergent from” determining three-dimensional positional information because Zhuang explicitly confirmed there is no need to explore other focal planes in its MERFISH-based system. EX1003, 011, 012; EX2002, ¶¶60-66; *Polaris*, 882 F.3d at 1069. Accordingly, Zhuang teaches away from determining three-dimensional positional information of the RNAs in its system. The Petition fails to address this issue entirely.

Moreover, even if Zhuang is not found to teach away, “its statements regarding preferences” for two-dimensional imaging and analysis are “relevant to a finding regarding whether a skilled artisan would be motivated to combine” Zhuang with Cai. *Polaris*, 882 F.3d at 1069 (citation omitted).

2. Petitioner fails to explain why or how a POSA would have combined and modified Zhuang’s MERFISH-based system with Cai’s light sheet microscope system with a reasonable expectation of success

According to Petitioner, “it would have been obvious to modify Zhuang in

view of Cai to include [‘the claimed 3D’] feature.” Pet., 39. The Petition never explains what modifications the POSA would have made or how to make them – *e.g.*, which parts of Cai’s system are substituted into Zhuang’s system, or *vice versa*, and how those components are compatible between the two systems to provide the POSA with a reasonable expectation of success. EX2002, ¶¶82-88.

As already discussed above, the Petition’s relied upon embodiments in Cai and Zhuang have several significant differences left unaddressed in the Petition. *See* Section VI.A.3.b; EX2002, ¶¶82-88. Cai discloses using a light sheet microscope system (“Olympus X81”) with a low-resolution, large working distance, “20x water immersion objective,” while Zhuang’s MERFISH-based system is constructed around an “Olympus IX-71 body” and uses a high-resolution, small working distance, “1.45 NA, 100x oil immersion” objective. EX1004, 47:30-56, FIG. 17; EX1003, 011; EX2002, ¶¶83-85. Neither the Petition nor Dr. Czymmek addresses why or how a POSA would have combined these two different microscopes with different resolution systems and physical geometries to arrive at the claimed system. EX2002, ¶86.

For example, absent from the Petition and Dr. Czymmek’s Declaration is any explanation of how a POSA would have modified Zhuang’s system with a light sheet microscope to arrive at a system that has (i) a high NA detection lens (like Zhuang’s system) and (ii) a high-resolution illumination lens (for the light

sheet system)—each with corresponding small working distances—all while maintaining sufficient physical space to fit all of the necessary optical parts (such as, the detection objective, condenser, cylindrical lens) and other parts (e.g., stage, sample holder) in the small space between the sample and the two lenses. EX2002, ¶87. Additionally, a POSA would have known that significant physical modifications to a microscope’s geometry can negatively affect its performance. *Id.* For example, as one of Dr. Czymmek’s own exhibits states when discussing an Olympus IX-71 microscope, “[t]he *working distance can be increased* by removing the condenser CV,” but in making such a modification, the “illumination becomes *inappropriate*.” EX1005, 028; EX2002, ¶87.

The later publications regarding MERFISH and 3D imaging well after the 554 patent’s priority date further evince the strained nature of the Petition’s reasonable expectation of success argument. As discussed above in Section VI.A.3.a, these publications show that (1) it took *several years* after Zhuang’s original disclosure of MERFISH in 2015 for others to apply the MERFISH method in a system for determining three-dimensional positional information, and (2) the eventual application of MERFISH for three-dimensional imaging was lauded in the art as a “technical milestone.” EX2002, ¶¶70-76; EX2007, 1, 27-28; EX2010, 704; EX2011, 1-2; *see also* Section VI.A.3.a.

As shown above, “Petitioner’s arguments are *not well-developed* and rely on

too many speculations.” E-One, Inc. v. Oshkosh Corp., IPR2019-00162, Paper 16, at 17 (P.T.A.B. June 5, 2019) (emphasis added; citations omitted). In *E-One*, the Board denied institution due to the Petitioner’s “rel[iance] on hindsight and speculation,” concluding that “instituting a trial would be an inefficient use of Board resources.” *Id.* at 17, 20. The Petition suffers from the same deficiencies, and the Board should deny institution here as it did in *E-One*.

VII. THE PETITION SHOULD BE DENIED FOR FAILING TO COMPLY WITH 35 U.S.C. § 312 AND 37 C.F.R. §§ 42.22(a)(2) AND 42.104

In addition to the Petitioner’s failure to meet its burden on the merits, it also fails to comply with the Board’s explicit rules requiring particularity in the Petition and forbidding incorporation by reference. “In an IPR, the petitioner has the burden from the onset to *show with particularity* why the patent it challenges is unpatentable.” *Harmonic Inc.*, 815 F.3d at 1363 (emphasis added); 35 U.S.C. § 312(a)(3). The Board’s rules require that the Petition “must specify where each element of the claim is found in the prior art” and “identify[] specific portions of the evidence that support the challenge.” 37 C.F.R. §§ 42.104(b)(4)-(5). Similarly, the petition must “provide a sufficiently detailed explanation of the significance of the citations.” *Apple II*, IPR2015-00450, Paper 9, at 11; 37 C.F.R. § 42.22(a)(2). Further, the “[a]rguments must not be incorporated by reference from one document into another document.” 37 C.F.R. § 42.6(a)(3). Petitioner’s failure to satisfy these basic requirements further confirms that the Petition has not and

cannot meet its burden of showing a reasonable likelihood of prevailing on at least one challenged claims.

A. The Petition improperly cross-references its other sections without providing explanations

The Petition relies on repeated use of cross-referencing to other sections of the Petition, which further include additional cross-references to still other sections, in contravention with 35 U.S.C. § 312(a)(3) and 37 C.F.R. §§ 42.22(a)(2) and 42.104. *See, e.g.,* Pet., Sections X.A.1.e.iii (cross-referencing section X.A.1.e.ii, which in turn cross-references sections “X.A.c.ii” and “X.1.c.ii” that do not appear in the Petition), X.A.1.e.iv (cross-referencing section X.A.1.e.i, which in turn cross-references section X.A.1.d), X.J (cross-referencing section X.A.1.c.ii), X.Q (cross-referencing sections “X.1.c.ii” and “X.1.e.ii” that do not appear in the Petition), X.R (cross-referencing sections X.A.1.c.ii and X.A.1.e.ii).

The Board has criticized argument formatting like that used by Petitioner “obfuscates the evidentiary support for the Petition’s assertions.” *Apple II*, IPR2015-00450, Paper 9, at 8. According to the Board, such “practice results in multiple levels of abstraction, obscuring Petitioner’s position regarding which reference, and which portion of which reference, teaches or suggests the claim limitations.” *Id.* at 7.

As the Board stated in its Informative *Adaptics Ltd. v. Perfect Company* Decision, “[t]he statutory requirement for particularity in a petition for IPR takes

on heightened importance when considered in conjunction with *SAS*'s 'all-or-nothing' approach. Because the Board's practice, in light of *SAS*, is to institute on all grounds asserted in a petition, the Board may consider whether a lack of particularly [sic] as to one or more of the asserted grounds *justifies denial of an entire petition.*" IPR2018-01596, Paper 20, at 17 (P.T.A.B. Mar. 6, 2019) (informative) (emphasis added). The egregious amount of cross-referencing and nested citations in the Petition warrants denial. *See, e.g., EiKO Global, LLC v. Blackbird Tech LLC*, IPR2017-00980, Paper 16, at 22-23 (P.T.A.B. Sept. 1, 2017) (denying institution in part because "[t]he Petition's substantive analysis as to how [the prior art] allegedly discloses the [claim] limitation amounts to a single sentence," and such "conclusory analysis ... falls far below the particularity and specificity that [the Board's] governing statute and rules require of arguments and evidence in a petition.").

For example, Petitioner's argument in Section X.A.1.e.iii for claim element 36(e)(iii) amounts to a single, conclusory sentence: "Zhuang decodes the identity of the RNA species based on the optically-encoded signals," followed by a citation to another section of the petition ("See *supra* X.A.1.e.ii") and two paragraphs (¶¶214-215) of the Cyzmmek Declaration. Pet., 41. The cross-referenced section X.A.1.e.ii comprises nearly two pages of argument and in turn cross-references yet other sections of the Petition (sections "X.A.c.ii" and "X.1.c.ii" that do not appear

in the Petition) and four paragraphs (§§210-213) of the Cyzmmek Declaration.

Similarly, the Petition in Section X.A.1.e.iv includes a single sentence to address claim element 36(e)(iv): “Zhuang, by itself or in view of Cai, determines the 3D positional information of the RNA species” followed by a cross-reference to another section of the Petition and expert declaration (“*See supra* X.A.1.e.i; EX1002 §§ 216-219”). Pet., 42. The cross-referenced section X.A.1.e.i comprises four pages of argument and further cross-references another section of the Petition (“*See supra* Section X.A.1.d”) comprising another four pages of argument and twelve paragraphs (§§180-183, and 185-192) of the Cyzmmek Declaration.

As shown in the exemplary table below, the Petition’s improper cross-reference tactics are also found throughout its arguments addressing the dependent claims.

Challenged Claim	Petition’s argument	Cross-reference
56 (Section X.J)	“Zhuang discloses this limitation,” without any explanation or underlying evidence. Pet., 45.	Section X.A.1.c.ii
67 (Section X.Q)	“Disclosed,” without any explanation or underlying evidence. Pet., 51	Sections “X.1.c.ii” and “X.1.e.ii,” which do not appear in the Petition
68 (Section X.R)	“Disclosed,” followed by a single conclusory sentence. Pet., 52.	Sections X.A.1.c.ii. and X.A.1.e.ii

The Petition’s pervasive use of internal cross-referencing “improperly shifts the burden of deciphering Petitioner’s arguments onto Patent Owner[s] and the

Board, which ... is contrary to the statutory and regulatory provisions governing *inter partes* review proceedings, as well as the best practices outlined in the Office Patent Trial Practice Guide.” *Whole Space Industries Ltd. v. Zipshade Industrial (B.V.I.) Corp.*, IPR2015-00488, Paper 14, at 18 (P.T.A.B. July 24, 2015); *see also Apple*, IPR2015-00355, Paper 9, at 11 (denying institution in part because the petitioner “leaves it to the Board to ascertain what gaps to fill, and then presents vague statements regarding what the prior art suggests”); *EiKO Global*, IPR2017-00980, Paper 16, at 22-23. The Board should accordingly reject the Petition and deny institution. 35 U.S.C. § 312; 37 C.F.R. §§ 42.22(a)(2) and 42.104.

B. The Petition relies on improper incorporation by reference of its expert declaration to expand conclusory statements

In addition its use of improper cross-reference practice, the Petition repeatedly cites to broad sections of the Cyzmmek Declaration to support its conclusory arguments and reasoning. *See, e.g.*, Pet., 27 (claim element 36(b)(i)), 30 (claim element 36(c)(iii)), 42 (claim element 36(e)(iv) and claim 38), 45 (claims 47 and 56), 46 (claim 59), 50 (claim 64), 51 (claim 67), 52 (claim 68), and 56–57 (claim 48).

The Board prohibits “[a]rguments ... incorporated by reference from one document into another document.” 37 C.F.R. § 42.6(a)(3); *Apple II*, IPR2015-00450, Paper 9, at 8. Indeed, Petitioner’s “practice of citing the Declaration to support conclusory statements that are not otherwise supported in the Petition ...

amounts to incorporation by reference.” *Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12, at 9 (P.T.A.B. Aug. 29, 2014) (informative); *EiKO Global*, IPR2017-00980, Paper 16, at 23 (“Arguments that are not presented and developed in the Petition, and instead are incorporated by reference to [the expert’s] declaration, are not entitled to consideration.”).

For example, the Petition’s argument for claim element 36(b)(i) (“one or more reservoirs”) is a single sentence that Zhuang necessarily “teaches the fluidic system includes reservoirs” because Zhuang “repeatedly introduced [fluid reagents] to the sample in the flow chamber.” Pet., 27. Rather than explain *why* this is so, the Petition cites to two paragraphs of the Czymmek Declaration to incorporate Dr. Czymmek’s arguments by reference. *Id.* (citing EX1002, ¶¶158-159).

The Petition repeats this tactic when addressing claim element 36(c)(iii) (“one or more detectors”). The Petition argues that Zhuang allegedly discloses this claim element because Zhuang discloses “use of an EMCCD camera,” with no explanation in the Petition why a POSA would have understood that an “EMCCD camera” satisfies “one or more detectors configured to receive light signals from said volume,” as claimed. Pet., 30-31. Again, the Petition relies on incorporated testimony from Dr. Czymmek to expand the thin and conclusory statement in the Petition. *Id.*, 31 (citing EX1002, ¶¶ 176-178).

The Petition also resorts to incorporation by reference when addressing claim elements 36(e)(iii) (“identifying said one or more nucleic acid molecules based on said plurality of optically-encoded signals”) and 36(e)(iv) (“determining three-dimensional positional information of said one or more nucleic acid molecules”). Pet., 41-42. For each of these claim elements, the Petition provides a single sentence of argument, followed by a cross-reference to other portions of the Petition and incorporation of the Czymmek Declaration. *See* Pet., 41 (citing Petition Section X.A.1.e.ii and EX1002, ¶¶ 214-215), 42 (citing Petition Section X.A.1.e.i and EX1002, ¶¶ 216-219).

As shown in the exemplary table below, the Petition’s improper incorporation by reference tactics are also found throughout its arguments addressing the dependent claims.

Challenged Claim	Petition’s argument	Incorporation by reference
38	“A POSA would have known,” with no explanation or underlying evidence. Pet., 42.	EX1002, ¶¶ 222-224
47	“a POSA would have known,” with no explanation or underlying evidence. Pet., 45.	EX1002, ¶¶ 240-242
48	“A POSA would have had a reasonable expectation of success,” with no explanation or underlying evidence. Pet., 57.	EX1002, ¶¶ 311-312
56	“Zhuang discloses this limitation,” with no explanation or underlying evidence. Pet., 45.	EX1002, ¶¶ 248-250.
64	“A POSA would know,” with no	EX1002, ¶¶ 262-264

	explanation or underlying evidence. Pet., 50.	
67	“Disclosed,” with no explanation or underlying evidence. Pet., 51.	EX1002, ¶¶ 273-274.

Simply put, “the Petition generally does not stand on its own, and its arguments often are incomprehensible without reviewing broad portions of the [Cyzmmek] Declaration, the length of which exceeds the relevant discussion in the Petition by multitudes.” *Apple II*, IPR2015-00450, Paper 9, at 9-10. The Petition’s practice of repeatedly relying on the Czymmek Declaration “to support conclusory statements” and “expand its thin analysis and reasoning” is unquestionably an incorporation by reference and violation of the Board’s rules against incorporation by reference and rules requiring particularity and specificity *in the petition*. *Id.*; 37 C.F.R. § 42.6(a)(3); *Cisco*, IPR2014-00454, Paper 12, at 7-10. The Petition’s incorporation by reference “serves to circumvent the [word] limits imposed on petitions for *inter partes* review, while imposing on [the Board’s] time by asking [the Board] to sift through [the expert] Declaration ... to locate the specific arguments corresponding to the numerous paragraphs cited to support Petitioner’s assertions.” *Cisco*, IPR2014-00454, Paper 12, at 10. As the Board held in its Informative *Cisco* Decision, “we will not consider arguments that are not made in the Petition, but are instead incorporated by reference to the cited paragraphs” of the expert declaration. *Id.*; *see also EiKO Global*, IPR2017-00980, Paper 16, at 23.

The Board should follow *Cisco* and *EiKO* and do the same here.

The Petition's incorporation by reference also runs afoul of the governing statute and rules requiring particularity and specificity in the Petition. *See* 35 U.S.C. § 312(a)(3); 37 C.F.R. §§ 42.22(a)(2), 42.104(b)(4)–(5); *Adaptics*, IPR2018-01596, Paper 20, at 24 (informative) (determining that “the entire petition should be denied” due to the Petition's “fail[ure] to meet the particularity requirement of 35 U.S.C. § 312(a)(3).”).

The totality of issues addressed above create an incomprehensible web of internal cross-references throughout the Petition and Czymmek Declaration, leaving the Board and Patent Owner “to play archeologist with the record.” *Cisco* IPR2014-00454, Paper 12, at 10. For these additional reasons, the Board should deny institution.

VIII. THE PETITION CANNOT MEET THE COMPELLING MERITS STANDARD OF A FINTIV ANALYSIS

As shown above, the Petition fails to establish a reasonable likelihood of prevailing on the merits and should be denied. Petitioner has not submitted a *Sotera* stipulation. To the extent the Board assesses the *Fintiv* factors and determines that *Fintiv* Factors 1-5 weigh against institution, the Board should analyze *Fintiv* Factor 6 under the “compelling merits standard.” *CommScope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23, at 3-5 (P.T.A.B. Feb. 27, 2023) (precedential); *OpenSky Indus., LLC v. VLSI Tech. LLC*, IPR2021-

01064, Paper 102, at 49 (P.T.A.B. Oct. 4, 2022) (precedential). Because the Petition fails to even meet the “reasonable likelihood” standard for the numerous reasons discussed above, it cannot meet the even-higher standard of “compelling merits.” *CommScope*, IPR2022-01242, Paper 23, at 3 (stating that “the compelling merits standard is a higher standard than the [reasonable likelihood] standard for institution set by statute”) (citing *OpenSky*, IPR2021-01064, Paper 102, at 49).

IX. CONCLUSION

As demonstrated in this Preliminary Response, Petitioner fails on numerous levels to demonstrate that it is reasonably likely to prevail on its obviousness grounds for any challenged claim. In view of the cumulative defects throughout the Petition’s grounds and improper argument formatting, Petitioner has not and cannot meet its burden in the Petition. The Board should deny institution of *inter partes* review.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. The undersigned certifies that this Patent Owner's Preliminary Response is 12,415 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing.

2. This Response complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

Respectfully submitted,

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PATENT OWNER'S PRELIMINARY RESPONSE** and associated **Exhibits 2001-2012** were served in their entirety on May 28, 2024, upon the following parties via email:

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