

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BRUKER SPATIAL BIOLOGY, INC.,
Petitioner,

v.

PRESIDENT AND FELLOWS OF HARVARD COLLEGE and 10X
GENOMICS, INC.,
Patent Owner

Case IPR2024-00526
Patent 11,542,554

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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EX1001	U.S. Patent No. 11,542,554 (“the ’554 Patent”)
EX1002	Declaration of Dr. Kirk Czymmek, Ph.D. under 37 C.F.R. § 1.68
EX1003	Kok Hao Chen et al., <i>Spatially resolved, highly multiplexed RNA profiling in single cells</i> , 348(6233) Science 412 (Research Article Summary) – aaa6090-1 - aaa6090-14 (2015) (“Zhuang”)
EX1004	U.S. Patent No. 10,457,980 to Long Cai et al. (“Cai”)
EX1005	Olympus Lifescience, <i>Instructions IX71/IX51 Inverted Research Microscope/Inverted Basic Microscope</i> , (2005) at https://www.ucc.ie/en/media/academic/anatomy/imagingcentre/icdocuments/OLYMPUSIX71_manual.pdf (“Olympus Manual”)
EX1006	Biopetechs, <i>FCS2 (Focht Live-Cell Chamber System) Instructions</i> , 1-6 (2007) at http://www.biopetechs.com/Instructions/FCS2_i/fcs2-3_i.htm (“FCS2 Instructions”)
EX1007	Sivaraj Sivaramakrishnan et al., <i>Shear Stress Induced Reorganization of the Keratin Intermediate Filament Network Requires Phosphorylation by Protein Kinase Cζ</i> , 20 Molecular Biology of the Cell 2755-2765 (2009) (“Sivaramakrishnan”)
EX1008	Chatarina Larsson et al., <i>In situ detection and genotyping of individual mRNA molecules</i> , 7 Nature Methods 395-397 (2010) (“Larsson”)
EX1009	Emmanuelle Querido and Pascal Chartrand, “Chapter 12 Using Fluorescent Proteins to Study mRNA Trafficking in Living Cells,” 85 <i>Methods In Cell Biology</i> , Elsevier Inc. 273-292 (2008) (“Querido”)
EX1010	Andrea M. Femino et al., “[13] Visualization of Single Molecules of mRNA in Situ,” 361 <i>Methods in Enzymology</i> , Elsevier Science (USA) 245-304 (2003) (“Femino”)
EX1011	Evan P. Perillo et al., <i>Enhanced 3D localization of individual RNA transcripts via astigmatic imaging</i> , 8950 SPIE 895003-1-895003-11 (2014) downloaded from https://www.researchgate.net/publication/263033754_Enhanced_3D_localization_of_individual_RNA_transcripts_via_astigmatic_imaging (“Perillo”)
EX1012	Alison J. North, <i>Seeing is believing? A beginners’ guide to practical pitfalls in image acquisition</i> , 172 The Journal of Cell Biology 9-18 (2006) (“North”)
EX1013	US Patent Application Publication No. US 2015/0267251 A1 to Long Cai et al. (“Cai reference”)
EX1014	Paul James, <i>Water Objectives A personal exploration.....all is not what it seems</i> , Microscopy UK 1-8 (2004) at www.microscopy-uk.org.uk/mag/indexmag.html?http://www.microscopy-uk.org.uk/mag/artoct04/pjwater.html (“James”)
EX1015	David L. Spector et al., “[75] Observation of Live Cells in the Light Microscope,” <i>Cells A Laboratory Manual Volume 2: Light Microscopy and Cell Structure</i> , Cold Spring Harbor Laboratory Press, 75.1-75.13 (1998) (“Spector”)

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EX1016	Hamilton, <i>HVXM 8-5 Valve Laboratory Products</i> , (November 7, 2023) at https://www.hamiltoncompany.com/laboratory-products/valves/36766 (“Hamilton website”)
EX1017	Clare O’Connor, <i>Fluorescence In Situ Hybridization (FISH)</i> , 1(1):171 Nature Education (2008) at https://www.nature.com/scitable/topicpage/fluorescence-in-situ-hybridization-fish-327/ (“O’Connor”)
EX1018	Derek Toomre and Joerg Bewersdorf, <i>A New Wave of Cellular Imaging</i> , 26 Annu. Rev. Cell Dev. Biol. 285-287 (2010) (“Toomre”)
EX1019	Robert S. Fischer et al., <i>Microscopy in 3D: a biologist’s toolbox</i> , 21(12) Trends Cell Biol. 682-691 (2011) at https://pubmed.ncbi.nlm.nih.gov/22047760/ (“Fischer”)
EX1020	Sheel Shah et al., <i>Dynamics and spatial genomics of the nascent transcriptome by intron seqFISH</i> , 174(2) Cell 363-376 (2018) at https://pubmed.ncbi.nlm.nih.gov/29887381/ (“Shah”)
EX1021	Jeffrey R. Moffitt and Xiaowei Zhuang, <i>RNA Imaging with Multiplexed Error Robust Fluorescence in situ Hybridization</i> , 572 Methods Enzymol 1-49 (2016) at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5023431/ (“Moffitt”)
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EX1024	Erlend Hodneland et al., <i>CellSegm – a MATLAB toolbox for high-throughput 3D cell segmentation</i> , 8:16 Source Code for Biology and Medicine 1-24 (2013) (“Hodneland”)
EX1025	Emilie A. Delaune et al., <i>Single-Cell-Resolution Imaging of the Impact of Notch Signaling and Mitosis on Segmentation Clock Dynamics</i> , 23 Developmental Cell, Elsevier Inc. 995-1005 (2012) (“Delaune”)
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EX1027	Jie Xiao, “Single-Molecule Imaging in Live Cells,” <i>Handbook of Single-Molecule Biophysics</i> , Springer 43-93 (2009) (“Xiao”)
EX1028	Allen Ehrlicher et al., “Chapter 21 Optical Neuronal Guidance,” 83 <i>Methods in Cell Biology</i> , Elsevier Inc. 495-520 (2007) (“Ehrlicher”)
EX1029	Christopher Fang-Yen et al., <i>Video-rate tomographic phase microscopy</i> , 16(1) Journal of Biomedical Optics 011005-1 – 011005-5 (2011) (“Fang-Yen”)
EX1030	Marc J.P. Richard et al., <i>Cellular mechanisms by which lipoic acid confers protection during the early stages of cerebral ischemia: A possible role for calcium</i> , 69 Neuroscience Research 299-307 (2011) (“Richard”)
EX1031	Harvard Apparatus, <i>PHD 22/2000 Syringe Pump Series User’s Manual</i> , (1996) at https://www.harvardapparatus.com/media/harvard/pdf/702000_Syringe_Pumps_Manual.pdf (“Harvard Apparatus Manual”)
EX1032	Feimo Shen et al., “[32] Digital Autofocus Methods for Automated Microscopy,” 414 <i>Methods in Enzymology</i> , Elsevier Inc. 620-632 (2006) (“Shen”)

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EX1043	Nikon MicroscopyU, <i>Culture Chambers for Live-Cell Imaging</i> (August 2015) at https://web.archive.org/web/20150810165805/http://www.microscopyu.com:80/articles/livecellimaging/culturechambers.html . ("Nikon")
EX1044	Cassandra S. Niman et al., <i>Controlled microfluidic switching in arbitrary time sequences with low drag[†]</i> , 13 Lab Chip 2389-2396 ("Niman")
EX1045	Thermo Fischer Scientific, <i>Fluorescence SpectraViewer</i> , at https://thermofischer.com/order/fluorescence-spectraviewer/#/
EX1046	Gregory B. Sands et al., <i>Automated Imaging of Extended Tissue Volumes Using Confocal Microscopy</i> , 67 Microscopy Research and Technique 227-239 (2005) ("Sands")
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EX1048	Peder Skafte-Pedersen et al., <i>A self-contained, programmable microfluidic cell culture system with real-time microscopy access</i> , 14 Biomed Microdevices 385-399 (2012) ("Skafte-Pedersen")

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EX1050	Johannes T. Wessels et al., <i>Light-Emitting Diodes in Modern Microscopy—From David to Goliath?</i> , 81A Cytometry Part A 188-197 (2012) downloaded at https://onlinelibrary.wiley.com/doi/10.1002/cyto.a.22023 (“Wessels”)
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EX1052	Patrick JM Zessin et al., <i>A hydrophilic gel matrix for single-molecule super-resolution microscopy</i> , 2:4 Optical Nanoscopy 1-8 (2013) (“Zessin”)
EX1053	Olympus Lifescience, <i>Research Inverted System Microscope IX71/IX81 IX2 Series</i> , (2005) at https://www.olympus-lifescience.com/data/olympusmicro/brochures/pdfs/ix71.pdf?rev=EABE
EX1054	Ilja Gerhardt et al., <i>Detection of Single Molecules Illuminated by a Light-Emitting Diode</i> , 11 Sensors 905-916 (2011) (“Gerhardt”)
EX1055	Akifumi Hattori et al., <i>Single-molecule Imaging with an Inexpensive UV-LED Light Source</i> , 38 Chemistry Letters 234-235 (2009) (“Hattori”)
EX1056	Jason S. Kuo et al., <i>High-power blue/UV light-emitting diodes as excitation sources for sensitive detection</i> , 25 Electrophoresis 3796-3804 (2004) (“Kuo”)
EX1057	Thermo Fischer Scientific, <i>FluoSpheres™ Carboxylate-Modified Microspheres</i> , (January 9, 2024) at https://www.thermofisher.com/order/catalog/product/F8809
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EX1074	Tatjana Trcek et al., <i>mRNA quantification using single-molecule FISH in Drosophila embryos</i> , 12 Nature Protocols 1326-48 (2017)
EX1075	Andrew G. York, et al., <i>Confined activation and subdiffractional localization enables whole-cell PALM with genetically expressed probes</i> , Nature Methods (2011)
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Exhibit #	Description
EX1086	Reply Declaration of Dr. Kirk Czymmek, Ph.D. under 37 C.F.R. § 1.68

I. INTRODUCTION

The record following institution has cemented Petitioner's *prima facie* case of obviousness, as shown by the testimony of Patent Owner's ("PO's") own expert, Dr. Hari Shroff, who could not even answer the most basic question in this case:

- Q. What, if anything, is there that you contend is novel or inventive in any of the claims of the '554 patent?
- A. Sir, it's not really what I think is important or inventive, it's really about Dr. Czymmek's erroneous assertion that one can combine these prior art in order to come up with what is described in claim 36.

EX1082 at 73:2-74:20. He was given four opportunities to answer this question but dodged it every time. *See id.* If there is anyone who should have been able to persuasively state what is inventive about the claims, it is Dr. Shroff, who is PO's highly-paid expert that ostensibly spent hours investigating this issue.

He took the same tack when asked the equally fundamental question of whether any claim elements were in the prior art:

- Q. If there's any particular step in many of the claims of the '554 patent that you contend is not in the prior art, please identify that now.
- A. I'd have to do a thorough analysis on that, sir. I couldn't give you an immediate answer there.

Id. at 72:16-73:1. Of course, the reason Dr. Shroff ducked these sorts of questions is not because he failed to perform an analysis, but because there is nothing non-obvious or inventive in the '554 patent.

As documented below, this only becomes clearer upon considering the specifics of PO's response to the Petition.

II. RESPONSE TO PO'S ARGUMENTS

PO's response to the Petition reflects an improper attempt to narrow the claims and apply an unduly stringent standard for obviousness. PO did not even properly advise its expert on the correct standards for claim construction or obviousness, thus enabling skewed opinions that do not stand up to scrutiny. *See* EX1082 at 54:1-60:17, 75:10-77:19, 79:19-82:6. As proven below, each of PO's rebuttals fails.

A. PO's Interpretation Of "Temperature Control" Is Erroneous

PO first seeks to evade the prior art by construing "temperature control" to narrowly to require the "ability to actively heat and actively cool in an apparatus." POR at 27. This construction, however, is contrary to the intrinsic record. Tellingly, PO never sought this construction in district court. *See* POR at 29 n.3.

Nothing in the claim language requires "temperature control" to include both active heating *and* active cooling. On its face, the term "temperature control" is broader and encompasses merely adjusting or controlling temperature. *See* EX1086 ¶¶ 18-20. PO's own expert directly confirmed that the plain meaning of "temperature control" is not as narrow as PO contends and encompasses heating alone or cooling alone. *See*

EX1082 at 103:7-14, 105:2-8. He likewise confirmed that PO’s construction would exclude from the claims several processes that maintain samples at specific temperatures, a result that makes no sense. *Id.* at 108:4-14, 112:12-113:10, 114:3-115:15.

To the extent PO points to anything in the claim language, it is only dependent claim 43, which recites a “heat sink or Peltier element.” PO alleges that this supports its interpretation because a Peltier element is a type of active cooling system. POR at 27. But just because *part* of a dependent claim refers to a particular type of active cooling system does not mean that “temperature control” in independent claim 36 *always* requires active cooling. *See* EX1086 ¶ 21.

PO’s construction finds no support in the specification either. PO admits that “temperature control” is not “expressly defined” and does not contend there was disclaimer or disavowal. *Id.*; *see also* EX1082 at 78:9-14, 79:8-18. Its expert had never even heard of disavowal or disclaimer. *See* EX1082 at 81:16-82:6. The very most PO points to in the specification are mere examples that supposedly include both active heating and cooling. *See* POR at 28. But mere examples do not limit claim scope. *See, e.g., Littelfuse v. Mersen USA EP Corp*, 29 F.4th 1376, 1381 (Fed. Cir. 2022). And, if anything, the specification is permissive in its description of “temperature control,” teaching that the “stage may include a heating *or* cooling apparatus where the stage may be heated *or* cooled (such as through thermoelectric

cooling using Peltier elements).” EX1001 at 18:5-7. Stating that the stage “may” include heating “or” cooling, the specification is clear that there is no requirement for *both* heating and cooling. *See also id.* at 30:32-35; EX1086 ¶¶ 22-24.

Finally, PO notes that during prosecution the claims were amended from reciting “a heating or cooling apparatus” to a “temperature control apparatus.” POR at 28. This proves nothing. In fact, the claims originally recited a “a heating or cooling apparatus programmable for a time and temperature parameter.” EX2006 at 671. Nothing suggests that changing this language to “temperature control apparatus” was for any reason other than brevity and simplicity.

B. The Combination of Chen,¹ Cai, & Shen Renders The Claims Obvious

1. The Cited Prior Art Teaches “Temperature Control”

PO contends there is “no direct evidence” that the FCS2 flow chamber in Chen has “temperature control.” As Dr. Czymmek explained, however, the Bioptechs FCS2 flow cell in Chen includes extensive “temperature control.” *See, e.g.*, EX1002 ¶¶ 142-43, 236; EX1086 ¶¶ 28-29. Any suggestion otherwise is put to rest by a 2020 publication by Su et al.—which was submitted by PO—and provides the serial number for the Bioptechs FCS2 flow cell system used in Chen. *See* EX2009. As

¹ The Petition originally referred to this reference as “Zhuang.” Petitioner now refers to it as “Chen” to be consistent with the POR.

Dr. Czymmek explains, this serial number corresponds to the very Bioprotech FCS2 system that was relied upon in the Petition and that undeniably includes temperature control. *See* EX1086 ¶ 28.

Petitioner further contends that the Bioprotech FCS2 flow cell does not include “temperature control” because it lacks active cooling. POR at 33. Yet, as proven above, “temperature control” does not require this. *See supra* Part II.A. PO’s expert acknowledged that “the ‘FCS2 instruction document’ discloses an FCS2 controller exclusively capable of raising temperature and ***maintaining the temperature.***” EX2024 ¶ 71; *see also* POR at 33-34. Because the FCS2 system is capable of “maintaining the temperature,” it has “temperature control.” *See* EX1086 ¶ 30.

As if this were not enough, the Petition established that the objective heater in Chen provides temperature control. *See* Petition at 24-25. While PO again contends that the objective heater is not “temperature control” because it lacks active cooling, *see* POR at 34, this relies upon an erroneous construction of “temperature control.” PO’s contention that the objective heater is not “operatively coupled to the sample holder” similarly fails because its own expert confirmed that the oil immersion lens that is being heated is coupled to the sample holder via an oil droplet:

Q. Is it accurate that in those lenses, an oil droplet is placed in the front of the lens and it's moved to contact the cover slip for the sample?

A. Yeah. That is accurate, sir.

EX1082 at 82:7-14; *see also* EX1086 ¶ 31.

Finally, even if PO's construction is adopted, it does not help PO because the Petition established that a Peltier element, which provides active temperature control, is obvious. *See* Petition at 43; EX1002 ¶ 233; EX1082 at 86:8-12, 97:17-98:3, 99:11-20. Patent Owner's expert presented no rebuttal. Rather, when asked about this, he confirmed obviousness by repeatedly testifying that a Peltier element was well-known. *See* EX1082 at 96:11-17 ("Q. Why, in 2015, would a person of skill in the art have used heat sink or a Peltier element? A. A person skilled in the art would have known, in 2015, that a heat sink or Peltier element could be an element of temperature control."); *see also id.* at 89:1-8, 90:7-91:6, 93:9-96:10, 99:5-10, 100:13-101:19.

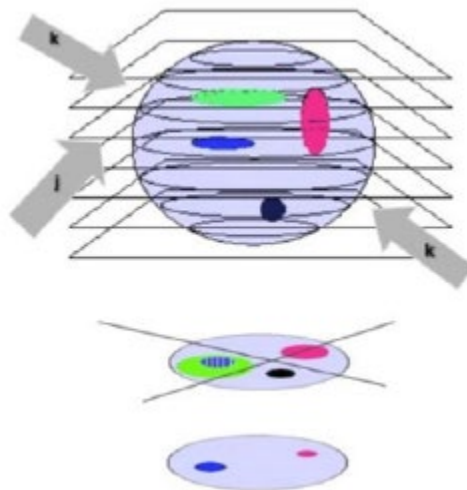
2. The Cited Prior Art Contemplates 3D Imaging

According to Petitioner, "Chen never suggested modifying its 2D MERFISH methods to somehow arrive at 3D MERFISH." POR at 42. This is dead wrong. *See, e.g.*, EX1002 ¶¶ 128, 183, 189, 204; EX1086 ¶¶ 32-39.

The authors of Chen acknowledged that their initial experiments involved only 2D data, which may have caused them to miss some targets. *See* EX1003.012.

To remedy this, Chen suggested 3D imaging, explaining that “because a fraction of the cell could be outside the imaging area or focal depth,” “[t]iling images of adjacent areas and adjacent focal planes could be used to improve the counting accuracy.” *Id.* The Petition relied upon this very disclosure, *see* Petition at 34, but both PO and its expert ignored it.

PO cannot credibly deny that Chen’s disclosure of tiling adjacent focal planes is a disclosure of 3D imaging given its own exhibits and expert witness testimony. Specifically, PO’s expert relies on Figure 17 from EX2078 showing the tiling approach:



EX2024 ¶ 36 (citing EX2078 at 25). This figure appears in a section entitled “Three-dimensional optical sectioning” and explains that a “set of 2D images is acquired at various focus positions along the z-axis, Fig. 17. The result of such e collection can be arranged in separate views or in a single view that considers all the information collected in the 3D volume, Fig. 18.” EX2078 at 24. Dr. Shroff confirmed that this

tiling approach was used for 3D imaging and that it was known in 2015. As he explained “in general, the idea of taking a stack to acquire a volume was known.” See EX1082 at 121:8-13; see also *id.* at 225:15-226:10, 227:17-228:3, 228:4-14; EX1086 ¶¶ 9-11, 38.

This approach for 3D imaging based on “tiling” or “optical sectioning” is not just mentioned once in Chen. As PO acknowledges, and as the Petition explains, Chen further states that “[f]rom an imaging perspective, any optical sectioning technique could be used in MERFISH to allow the imaging of RNAs in thicker cells or tissues.” EX1003, 012; EX2024 ¶ 89. PO, through its expert, contends that this is referring to nothing but the removal of background fluorescence. See EX2024 ¶ 89. The full text of the relevant passage in Chen puts any such reading to rest:

Because we imaged cells using wide-field imaging with oblique-incidence illumination, without optical sectioning and z-scanning, we quantified the fraction of individual RNA species that was outside the axial range of our imaging geometry for six different RNA species using conventional smFISH....We found that only a small fraction, $15 \pm 1\%$ (mean $\pm$ SEM across six different RNA species) of RNA molecules were outside the imaging range of a fixed focal plane without z-scanning. These measurements also confirmed that our excitation geometry illuminated the full depth of our cells. *From an imaging perspective, any optical sectioning technique could be used in MERFISH to allow the imaging of RNAs in thicker cells or tissues.*

EX1003.012. Here, the authors of Chen explain that for their 2D experiments, a smattering of targets were outside the 2D plane they imaged. The subject of the passage is thus how to ensure that all targets in the sample are imaged. With thicker samples, Chen explains, one can use “any optical sectioning technique.” This is not, as PO contends, about using optical sectioning to remove background fluorescence, but about how to image the full volume of a sample (*i.e.*, how to do 3D imaging). *See* EX1086 ¶¶ 35-37.

To try to support their arguments about how MERFISH is not for 3D imaging, Dr. Shroff cites patents directed to MERFISH that Chen and co-workers applied for. *See* EX2024 ¶ 49. He states the “reason I cited these patent applications, sir, is that I’m trying to make an argument that MERFISH is directed towards multiplexity.” EX1082 at 21:1-4; *see also id.* at 18:19-19:14, 21:14-19, 22:7-17. PO thus must agree that is reasonable to look to Chen’s patents to understand how MERFISH can be used. Unsurprisingly—and consistent with Chen’s scientific publication—Chen’s patents teach using MERFISH for 3D imaging, stating “the determination may also be spatial, e.g., the position of the nucleic acid within the cell or other sample may be determined in two or three dimensions.” EX1073 at 14:34-40; *see also id.* at 18:44-58, 22:49-62; EX1086 ¶¶ 52-53.

While Chen’s MERFISH publication and patents teach 3D imaging, so too does Cai, which teaches scanning along the Z-axis to provide “three dimensional

spatial information of a target.” EX1032.004; EX1004 at 21:50-51; EX1002 ¶ 191. PO discounts this disclosure as a “single sentence.” *See* POR at 3. But, in fact, Cai includes extensive actual 3D imaging data across multiple figures, as PO’s own expert confirmed. *See* EX1082 at 261:20-262:5, 262:11-14, 263:13-15, 264:13-22; EX1086 ¶ 39.

Given the foregoing disclosure in Chen and Cai, PO’s assertions that the Petition is based on hindsight should be rejected.

3. A POSA Would Have Successfully Adapted MERFISH For 3D Imaging

As detailed in the Petition, a POSA would have wanted to adapt Chen’s MERFISH method for 3D and had no trouble doing so. *See, e.g.*, Petition at 33-34, 39. As documented above, Chen expressly contemplates MERFISH for 3D, and PO does not dispute that a POSA would have had the extensive skills and competencies set forth in Petitioner’s definition of the level of ordinary skill, which would have easily enabled a POSA to make the minor adaptation. *See supra* Part II.B.2; Petition § IV; EX1002 ¶¶ 68-70; EX1082 at 120:17-22; EX1086 ¶¶ 5-15. As is undisputed, the Chen reference even presents 3D smFISH validation experiments using the same apparatus. *See* EX1086 ¶ 40; EX2024 ¶ 88. Against this backdrop, PO presents no persuasive rebuttal to Petitioner’s *prima facie* obviousness showing.

**a. Prior Art Need Not Be Bodily Combined Nor Does
The Petition Proposing Doing So**

PO argues that a POSA would not have combined Chen with Cai because “Cai’s imaging setup is in stark contrast with Chen’s 2D MERFISH imaging setup” and identifies differences in the details of how the systems operate. *See* POR at 44-45. Yet, this argument fails as a matter of law because the “test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.” *In re Keller*, 642 F.2d 413, 425 (C.C.P.A. 1981). Indeed, a “person of ordinary skill is also a person of ordinary creativity, not an automaton.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

PO’s contention that the myriad of features in Chen, Cai, and Shen do not fit together is likewise irrelevant as a factual matter because Petitioner is not seeking to make an indiscriminate chimera of Chen, Cai, and Shen that smooshes all their features together. Petitioner is proposing to apply specific discrete features from Cai and Shen to Chen in a rational way.

Most important, with respect to 3D imaging, the Petition explains that if Chen “is deemed to not disclose the claimed Z-axis motion control system, it would have been obvious to modify [Chen] in view of Cai to include such a feature.” Petition at 32; EX1086 ¶¶ 41-43, 48. The Petition explains that a “POSA would have been motivated to include the Z-axis motion control system of Cai...because it would have enabled one to more effectively scan the sample in three dimensions at different

focal planes.” Petition at 33; *see also id.* at 39 (“Specifically, as documented above, Cai teaches the claimed Z axis motion control system, which enables 3D interrogation.”). Thus, the theory of the Petition is not that Cai’s array of features should be jammed into Chen’s MERFISH, but simply that Cai’s z-axis motion control should be applied to Chen to enable stacking of focal planes and hence 3D imaging.

PO’s own expert confirms that there would be no impediments to this straightforward modification, even considering that Chen uses a widefield microscope while Cai uses a light sheet microscope. This is because, as PO’s expert confirmed, with widefield microscopy one can use z-axis control to generate a series of images from different focal planes to generate a 3D image, just as was done using light sheet microscopy in Cai:

Q. Now, this tiling method, where you tile the adjacent areas and the adjacent focal points, is that something that can be done using widefield microscopy?

A. Well, the success of that procedure will depend on how much out-of-focus light there is in the sample, sir.

Q. But it could be done depending on the sample type, correct?

A. Depending on the sample type, it could be done.

EX1082 at 228:4-14; *see also id.* at 212:17-20 (“Q. Now, with widefield imaging, is that ever used with this concept of making Z stacks? A. Widefield imaging can be used in the context of taking a Z stack.”). As Dr. Shroff confirmed, in November

2015 widefield microscopy was used for 3D imaging. *See id.* at 133:16-21. It is thus without merit to suggest that a POSA would not apply Cai's z-axis motion control to Chen's MERFISH method simply because Cai and Chen use different microscopy modalities. *See* EX1086 ¶¶ 9-15, 41-48. As noted above, Chen even used its apparatus to do 3D smFISH validation studies. *See* EX2024 ¶ 88.

Notably, to the extent the claims recite any specific microscopy modality, it is only widefield microscopy in claims 34 and 69. This is the precise approach used in Chen's MERFISH method. But, as Dr. Shroff confirmed, there is no disclosure in the '554 patent of any *new* improvements to widefield microscopy to make it any more suitable for 3D imaging for use with the alleged invention. *Id.* at 203:9-205:10. At most, the '554 patent refers to known prior art widefield microscopy methods. *Id.* In fact, Dr. Shroff confirmed that the '554 patent described no improvements whatsoever to address all the challenges associated with 3D imaging that allegedly would have dissuaded a POSA from adapting MERFISH for 3D. *See* EX1082 at 193:4-195:20.

This leaves no doubt that it would be natural to adapt Chen's 2D MERFISH approach based on widefield microscopy for 3D. Indeed, it was known that widefield could be used for 3D microscopy (including through the tiling of focal planes by z-axis control) and the '554 patent acknowledges that no new developments would be required. *See* EX1086 ¶¶ 40-47.

b. Chen's Alleged Goals Are Not Contrary To 3D Imaging

According to PO, Chen's goal was to simultaneously analyze many targets and adapting Chen for 3D "would *reduce the ability to multiplex* due to decreases in resolution, SBR, and SNR and increases in data complexity and requisite computing power." POR at 56. Thus, in PO's view, a POSA would not have bothered to adapt MERFISH to 3D because this would supposedly be too hard for large numbers of targets.

This argument, however, fails for the simple reason that there is no requirement in the claims to analyze large numbers of targets. In fact, the claims require only the detection of "*one* or more" nucleic acid molecules. *See* EX1001 at claim 36. Because the claims require detecting only "one" nucleic acid molecule, Petitioner's argument that the claims are not obvious because one of Chen's goals is high multiplexicity is irrelevant and entitled to no weight. *See* EX1086 ¶ 51.

Tellingly, when asked whether there were a *minimum* number of targets that could be analyzed with MERFISH, PO's expert repeatedly dodged the question. *See* EX1082 at 170:4-173:11. In fact, there is nothing about MERFISH that would preclude analyzing a small number of targets, nor would a POSA deem this unnecessary or uninteresting. *See* EX1086 ¶ 49-50. In 2014, for instance, Dr. Shroff himself was performing 3D imaging in a single cell of four different nucleic acid targets. *See* EX1082 at 248:12-251:16; EX1076. As Petitioner's expert explains, a

“POSA would not be so unreasonable as to believe it is pointless to adapt MERFISH to 3D because one might not be able to analyze as many targets as is possible when one is performing pure 2D imaging.” EX1086 ¶ 50.

Even assuming *arguendo* that a POSA would strangely think it is pointless to consider a 3D version of MERFISH unless one can analyze a large number of targets, PO identifies no true impediment to using MERFISH for this purpose. PO identifies nothing more than routine issues with 3D imaging that had long been addressed by standard solutions. *See* EX1086 ¶¶ 11-15, 54. The law is clear, however, that for obviousness, the expectation of success in modifying the prior art “need only be reasonable, not absolute.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). PO ignores this principle, as detailed below.

PO and its expert argue foremost that “axial resolution (z-axis) is more difficult...than lateral resolution.” POR at 10; EX2024 ¶ 20-32. They allege, for instance, that because “thicker cells or tissues than the flat fibroblast cell layer of Chen would encounter illumination of several additional planes, the fluorescent signals generated when imaging thicker cells or tissues would have higher out-of-focus fluorescent signals in the 2D focal plane, increasing the background and noise, and thus decreasing the SNR and SBR.” POR at 42; *see also* EX2024 ¶ 31. For such reasons, PO argues, a POSA would not bother with 3D MERFISH.

Yet, even if it were somewhat more difficult to optically probe a thick sample,² the claims are not limited to any particular sample thickness. As Dr. Shroff confirmed, “I don’t recall seeing any statement about minimal sample thickness.” EX1082 at 220:3-14. In fact, Dr. Shroff confirmed that 3D imaging of thin samples—including even a *single cell*—is within the scope of the ’554 patent claims.

Q. You agree that 3D imaging of a single cell, that's within scope of the claims of the '554 patent, right?

A. 3D imaging in a single cell within the scope of the '554 patent?

Yes, I agree with that.

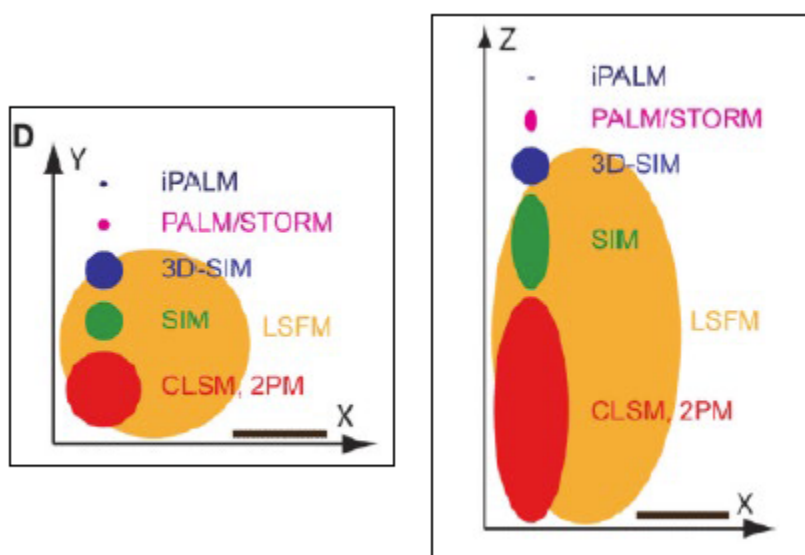
Id. at 180:8-13; *see also id.* at 222:17-22.

Such experiments on thin samples or single cells were not esoteric or unimportant. *See* EX1086 ¶ 14. As early as 2011, Dr. Shroff himself was performing 3D imaging in samples that had a thickness of roughly 8 microns, which, according to Dr. Shroff, “is about the thickness of a single cell.” *Id.* at 242:5-243:16. Three years later, Dr. Shroff himself was performing 3D imaging of multiple nucleic acid particles in a single cell. *See id.* at 248:12-251:16. In November 2015, researchers were thus interested and motivated to perform 3D imaging of nucleic acids in not just thick samples, but also samples as thin as a single cell. As

² Patent Owner never contends it would be impossible, just that it might be more difficult.

Petitioner's expert explains, "[a]ny perceived difficulties with 3D imaging of thick samples would not have wholly dissuaded the POSA from attempting to adapt MERFISH to a 3D experiment, but would have simply guided the research to focus on numerous use cases with thinner or smaller samples, such as single cells or thin FFPE prepared tissue slices." EX1086 ¶ 14.

PO nonetheless argues that the point spread function ("PSF") is elongated in the z-axis relative to the lateral axes and that this would have impacted resolution. POR at 10-15. PO's own evidence, however, confirms that there are multiple microscopy modalities that have narrow point spread functions in the z-direction. *Id.* at 11-12. PO, for instance, presents the figure below, which shows that while LSFM microscopy (shown as an orange oval) has a relatively broad PSF in the z-direction, there are several modalities that have substantially narrower PSFs in the z-direction, including SIM, 3D-SIM, PALM/STORM, and iPALM:



POR at 12 (citing EX1019, FIG. 1D); EX1086 ¶ 13.

Dr. Shroff further confirmed that a POSA would have known of techniques improving resolution over a standard point spread function:

A. You're asking if a person would have known that there are methods to improve resolution over a standard point spread function?

Q. Yes.

A. A POSA would have known that there are methods that, in some contexts, can provide better resolution than what is available under a standard point spread function.

Id. at 141:2-142:5. He confirmed that as of 2015, there were “a broad class of methods called super-resolution microscopy methods that a POSA would have known existed.” *Id.* at 142:6-12. These methods included SIM, IPALM, PALM, STORM, and 3D SIM, as shown in the image above. *See id.* at 142:20-143:18. If a POSA were concerned about the PSF, he or she could have simply selected a microscopy modality with a sufficiently low PSF. *See* EX1086 ¶ 13

Beyond this, Dr. Shroff confirmed that in 2015 POSAs would have been aware of deconvolution methods to increase resolution that relied upon modeling the PSF. *See* EX1082 at 145:7-22, 146:1-7, 167:10-17, 168:15-169:16. In fact, there was publicly available commercial software for this purpose, such as the Huygens package. *See id.* at 168:15-169:16. As yet another example, Dr. Shroff confirmed that expansion microscopy was available to improve resolution. *See id.* at 146:1-7.

Although Dr. Shroff purported to be unaware of whether this was available in 2015, POSAs were, in fact, well-aware of the method. *See* EX1086 ¶ 11.

PO and its expert further contend that “the signal density of a 3D multiplexed sample” creates “challenges with computational complexity.” EX2024 ¶ 112; *see also* POR at 50-51. But Dr. Shroff at most contends that this alleged complexity would “diminish” the expectation successfully adapting MERFISH for 3D imaging; he never opines that this would have made it impossible or overwhelming. *Id.* ¶ 112. PO’s vague worries about “computational complexity” thus cannot undermine obviousness. As Petitioner’s expert explains, the “Chen paper described results with 2D MERFISH, and extending this to 3D would have only required a linear increase in the required dataset size for computation due to the need to analyze images in multiple focal planes. In other words, the needed computation power would simply scale linearly with the number of focal planes, and in 2015 there was more than sufficient computational power that was readily available to address this.” EX1086 ¶ 54.

The foregoing shows that even if there were issues adapting MERFISH to 3D, there were well-known techniques for overcoming these issues that would have been within the basic competencies of the POSA. If it were truly so unreasonable or challenging to adapt MERFISH for 3D, Chen never would have expressly suggested

this nor would its authors have taught this in their contemporaneous patent filings.
See supra Part II.B.2.

c. That The Prior Art Is “Homebuilt” Is Irrelevant

PO emphasizes that Chen and other prior art allegedly describe so-called “homebuilt” systems. The POR refers to “homebuilt” 26 times, alleging that such systems were “unwieldy and unsuitable for mass production or commercial development.” POR at 9; *see also* EX2024 ¶¶ 20-21.

Such arguments, however, are irrelevant because there is nothing in the claims that excludes systems that are “unwieldy” or “homebuilt.” PO’s emphasis on the prior art being “homebuilt” is odd because there is no basis in fact or law to contend that a “homebuilt” system is any less significant as a prior art reference. While Dr. Shroff emphasized Chen’s “homebuilt” qualities, he had no opinion that there was any sort of connection between a system being “homebuilt” and obviousness:

Q. Okay. So homebuilt, to you, weighs against obviousness in this case?

A. Sir, I don't have any expressed opinions about homebuilt and obviousness. Nowhere in this do I say anything about that.

EX1082 at 61:13-17; *see also id.* at 61:18-63:5.

In fact, the claims here cover so-called “homebuilt” systems. Dr. Shroff confirmed that “I wouldn’t say that claim 36 excludes homebuilt systems because nowhere in that – nowhere in those claims do we have any language about that one

way or the other.” *Id.* at 63:22-64:3; *see also id.* at 65:11-14. PO’s arguments about homebuilt systems supposedly being “unwieldy” and “sprawling” are irrelevant and entitled to no weight. *See* EX1086 ¶ 12.

C. PO’s Objective Indicia Are Without Merit

For objective indicia, PO relies upon commercial success, long-felt need, and industry praise in connection with two commercial products: PO’s Xenium product and Petitioner’s CosMx product. *See* POR at 58-69. PO, however, has failed to prove nexus and otherwise argues about irrelevant features unconnected to the claims.

1. PO Has Not Shown Nexus

For nexus, PO attempts to show that CosMx and Xenium embody claim 36. PO has not met its burden.

As to the CosMx product, PO and its expert presented nothing to show that it meets the “temperature control” apparatus requirement in claim 36. *See* EX2024 ¶ 120-23. Dr. Shroff confirmed this point-blank. *See* EX1082 at 276:10-21. Thus, as to CosMx, Patent has not shown nexus. *See* EX1086 ¶ 57.

The same is true of Xenium. Claim 36 of the ’554 patent requires “two or more light sources.” PO’s expert opines that “multiple channels of the Xenium system indicate that multiple sources of light are used in the system, for which at least one detector would be needed to detect said light channels.” EX2024 ¶ 124.

Thus, Dr. Shroff assumes that because there are “multiple channels” there must be multiple light sources. This, however, is wrong. A single light source can be used to generate multiple optical channels, as Dr. Shroff confirmed. *See* EX1082 117:1-119:1; EX1086 ¶ 58.

Accordingly, PO has not shown the required nexus for objective indicia, and the Board should give them no weight. The defects in PO’s objective indicia contentions only become clearer upon closer inspection.

2. Commercial Success Of CosMx And Xenium Does Not Show Non-Obviousness

PO’s reliance on commercial success of CosMx and Xenium is perplexing because its own expert could not even say why these products are successful:

Q. Do you know what features of CosMx made CosMx commercially successful?

A. Sir, I wouldn't be able to speculate on what features made it commercially successfully.

Q. Do you know what features made Xenium commercially successfully?

A. Same answer, sir, I don’t know what features exactly makes it commercially successful.

Id. at 44:15-45:2. PO also submitted a declaration from, Julie Davis, an economics expert. But she also had no idea what made these products successful. *See* EX1083 at 42:10-43:14; *see also id.* at 31:4-13. If there was anything about the claims driving

the commercial success of CosMx or Xenium, at least one of PO's experts would have said so. Dr. Shroff, however, could not even identify a novel aspect of the claims or a single claim element that was not in the prior art. *See supra* Part I.

Against this backdrop, it is unsurprising that when PO and Petitioner promote Xenium and CosMx, they do not mention anything connected to the claims of the '554 patent. Consider, for instance, EX1080, which is promotional literature for the CosMx product. This document promotes features such as analyzing a large number of targets, analyzing proteins, certain specific applications, specific *in situ* hybridization chemistry, a cloud-based computing system, an integrated data viewer, specific gene panels, FFPE and FF compatibility, cell segmentation, sample preparation methods, compatibility with different sample types, and a grant support package. *See generally* EX1080. None of these features that Bruker promotes are part of the claims of the '554 patent, a point Dr. Shroff confirmed. *See generally* EX1082 at 279:11-302:13; EX1086 ¶¶ 59-61.

Likewise, as to the Xenium product, consider EX1081, which promotes features such as the DAPI nuclear stain, analyzing many targets, profiling protein expression, compatibility with desktop tools and downstream third-party tools, chemistry that uses padlock probes, short sequencing time, and onboard data processing. *See* EX1081. Dr. Shroff again confirmed that these features were not part of the claims. *See* EX1082 at 302:21-310:15. As with CosMx, if Xenium is

commercially successful, it is not because of features in the claims of the '554 patent, which are all part of the prior art, but rather sundry features that are not in the claims and that 10x promotes to its customers. *See* EX1086 ¶ 62.

3. Long-Felt Need For Xenium And CosMx Does Not Show Nonobviousness

As to long-felt need, PO contends that, before CosMx and Xenium, labs were forced to rely upon “homebuilt arrangements made from piecemeal compilations of components, which were laborious to construct and not achievable outside of specialized labs.” POR at 66. As shown above, however, the claims cover homebuilt systems and include no language excluding “piecemeal” components that are “laborious” to make. *See supra* Part II.B.3.c. As PO’s expert affirmed, “Sir, I don’t have any expressed opinions about homebuilt and obviousness. Nowhere in this do I say anything about that.” EX1082 at 61:13-17.

4. Industry Praise For Xenium Does Not Suggest Nonobviousness

PO’s reliance on praise for Xenium suffers from the exact same defects as its arguments about commercial success and long felt need. *See* EX1086 ¶¶ 63-64. Dr. Shroff opines, for instance, that Xenium has been praised for “the breadth of the system’s sequencing ability, the smooth workflow provided by the integrated system, and the ability of the platform to provide high-resolution spatial data for

nucleic acid molecules.” *Id.* None of these features are in the claims, as Dr. Shroff confirmed. *See* EX1082 at 65:11-14, 215:16-216:2, 217:2-4.

As another example, PO notes that a researcher said “[t]he intuitive design of [Xenium’s] bench workflow and post-run analysis software may be the most valuable aspect of this high-throughput in situ technology to accelerate science.” POR at 66. Yet, intuitive bench workflow and post-run analysis software again have nothing to do with the claims. Given that this commentary about Xenium characterizes features having nothing to do with the claims as “most valuable,” it is perplexing that PO contends it supports non-obviousness.

III. CONCLUSION

The Board should cancel all challenged claims.

Dated: March 18, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 5,588 words as calculated by the “Word Count” feature of Microsoft Word for Microsoft 365, the word processing program used to create it.

Dated: March 18, 2025

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I hereby certify that on March 18, 2025, copies of the foregoing
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