

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

10X GENOMICS, INC.,
Patent Owner

Case IPR2023-00958
Patent 10,697,013

PATENT OWNER'S SUR-REPLY

LIST OF EXHIBITS

Exhibit	Description
EX2001	File History of U.S. App. No. 15/677,957
EX2002	File History of U.S. App. No. 13/859,450
EX2003	Dictionary of Microbiology and Molecular Biology (2d ed. 1987)
EX2004	File History of U.S. App. No. 14/792,094
EX2005	File History of U.S. App. No. 13/387,343
EX2006	U.S. Patent Pub. No. 2007/0238113
EX2007	Laird <i>et al.</i> , <i>Hairpin-bisulfite PCR: assessing epigenetic methylation patterns on complementary strands of individual DNA molecules</i> , 101 PNAS 204-09 (Dec. 12, 2003)
EX2008	Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00876, Pap.1 (May 25, 2023)
EX2009	File History of U.S. App. No. 14/172,694
EX2010	Declaration of Sayem Osman
EX2011	Declaration of Sayem Osman
EX2012	<i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00876, EX1002 (Apr. 20, 2023) (Declaration of Gregory Cooper, Ph.D.)
EX2013	Declaration of Dr. John Quackenbush
EX2014	Bruce Alberts, et al., <i>Molecular Biology of the Cell</i> , Garland Science (4th ed. 2002)
EX2015	S. Guan, A. Blanchard, P. Zhang, & Z. Zhu, <i>Alteration of Sequence Specificity of the Type IIS Restriction Endonuclease BtsI</i> , (July 26, 2010)
EX2016	Piovesan <i>et al.</i> , <i>On the length, weight, and GT content of the human genome</i> , BMC Res. Notes 12:106 (2019) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6391780/#:~:text=Considering%20a%20mean%20weight%20in,units%2Fcarat.htm)
EX2017	T. Chauhan, <i>T4 DNA Ligase: Introduction, Functions, Applications, and Protocol</i> , (available at https://geneticeducation.co.in/t4-dna-ligase/)
EX2018	IPR2023-00876 Deposition Transcript of Gregory Cooper, Ph.D.
EX2019	INTENTIONALLY OMITTED
EX2020	IPR2023-00958 Deposition Transcript of Gregory Cooper, Ph.D.
EX2021	Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00955, Pap.1 (May 25, 2023)

Exhibit	Description
EX2022	<i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00955, EX1002 (Apr. 20, 2023) (Declaration of Gregory Cooper, Ph.D.)
EX2023	Excerpt of <i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, D.I. 001 (D. Del. Aug. 24, 2022) (Complaint)
EX2024	Excerpt of <i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00878, Pap.1 (Apr. 20, 2023)
EX2025	Excerpt of <i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00955, Pap.1 (May 25, 2023)
EX2026	Excerpt of <i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-01030, Pap.1 (June 06, 2023)
EX2027	Excerpt of <i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-01033, Pap.1 (June 06, 2023)
EX2028	INTENTIONALLY OMITTED
EX2029	INTENTIONALLY OMITTED
EX2030	<i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, D.I. 121 (D. Del. Dec. 21, 2023) (Order Denying Motion to Stay)
EX2031	Excerpt of <i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00955, Pap.8 (Jan. 02, 2024) (Rehearing Request)
EX2032	<i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, D.I. 048 (D. Del. Mar. 07, 2023) (Scheduling Order)
EX2033	INTENTIONALLY OMITTED
EX2034	<i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, D.I. 164 (D. Del. Feb. 20, 2024) (Order Denying Parse Renewed Motion to Stay)
EX2035	Excerpt of <i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, D.I. 229 (D. Del. June 12, 2024) (Parse's Opposition to 10x Ltr. re Motion to Strike Portions of Cooper Report; Ex. A: Sept. 19, 2023 Parse First Amended Invalidity Contention; Ex. B: Apr. 16, 2024 Parse Second Amended Invalidity Contention)
EX2036	Excerpt of <i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, D.I. 218 (D. Del. May 30) (10x Ltr. re Motion to Strike Portions of Cooper Report; Ex. A: May 17, 2024 Expert Report of Dr. Gregory Cooper Regarding Invalidity (Excerpted))
EX2037	<i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, May 21, 2024 Email from J. Reich to D. Walter re Cooper Report

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EX2038	<i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, May 28, 2024 Email from D. Walter to J. Reich re Cooper Report
EX2039	<i>10x Genomics, Inc. et al. v. Parse Biosciences, Inc.</i> , No. 22-1117-JHS, D.I. 224 (D. Del. June 06, 2024) (Parse Ltr. Requesting New Trial Date)
EX2040	IPR2023-00955 September 3, 2024 Deposition Transcript of Gregory Cooper, Ph.D.
EX2041 – EX2101	INTENTIONALLY OMITTED
EX2102	C. Wansgasnuwat <i>et al</i> , <i>Efficient and cost-effective bacterial mRNA sequencing from low input samples through ribosomal RNA depletion</i> , BMC Genomics (2020) 21:717 (marked as EX2102 in Dr. Cooper’s September 3, 2024 deposition (EX2040))
EX2103	V. Llorens-Rico <i>et al</i> , <i>Single-cell approaches in human microbiome research</i> , Cell (2022) 185:2725 (marked as EX2103 in Dr. Cooper’s September 3, 2024 deposition (EX2040))

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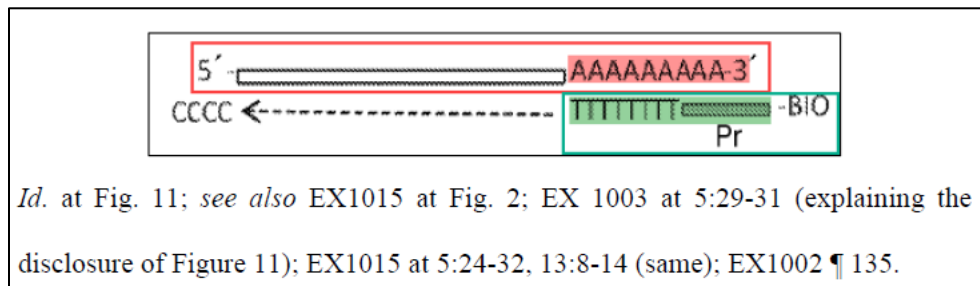
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Faced with PO's evidence and Petitioner's own expert contradicting its Petition, Petitioner abandons its original theories and starts over. For example, despite including biotin as part of its mapping, drawing a green box around the CDS's biotin in Fig.11, Petitioner now argues biotin is "optional." Pet.32; Rep.17-18.



A Reply isn't a mulligan; the Petition governs and "guide[s] the life of" Petitioner's IPR "***through to conclusion.***"¹ *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1353, 1355-57 (2018). Petitioner's belated new positions are meritless and prohibited. Indeed, Petitioner's overwhelming reliance on improper new arguments supports *ignoring the entire Reply*. *E.g.*, *Consolidated Trial Practice Guide* (PTAB, Nov. 2019), 74 ("indications that a new issue has been raised include...newly raised rationale to combine... not expressed in the petition";

¹ Unless stated, statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates, internal citations omitted, emphases/annotations are added, and abbreviations are from the POR.

“improper...to ‘gap-fill’” with “newly cited” art); *Sirius XM Radio Inc. v. Fraunhofer-Gesellschaft Zur Forderung Der Angewandten Forschung E.V.*, IPR2018-00690, Pap.63, 13-15 (July 23, 2020) (“Once the Board identifies new issues presented for the first time in reply,’ the Board ‘will not attempt to sort proper from improper portions...’ ***We do not consider the Reply.***”). Petitioner’s attempts to distract from its Petition’s failings—*e.g.*, (1) complaining PO didn’t ask deposition questions to enable Petitioner’s expert to volunteer new opinions, (2) criticizing PO’s expert for not opining on-the-fly on out-of-scope questions about arguments Petitioner never raised until Reply, (3) mischaracterizing PO’s court opinions,² and (4) quoting PO’s statements about concepts *in other*

² Petitioner mischaracterizes Quackenbush’s litigation report to incorrectly assert that dual-tagging was known. Rep.1. His report and the two referenced patents (EX1086-EX1087 (both incorporated by reference into ’013’s specification)), confirm neither discloses using both claimed tags—EX1086 discloses a source tag, and EX1087 discloses a polynucleotide-specific tag. EX1086, 12:60-64 (“sequence tokens... ***to enable identification of the source of any particular nucleic acids...***”); EX1087, 1:17-18 (“***identifying such polynucleotides by detection of the attached tag.***”); EX1084, ¶316 (identifying the tag disclosed in each patent).

patents—cannot change Petitioner’s failure to meet its burden.³

I. Ground 1: Petitioner Failed To Meet Its Burden To Establish Obviousness

Petitioner’s improper new Reply arguments are too late and, like Petitioner’s other gap-filling attempts, don’t save its failed theories.

A. Petitioner’s Conclusory Ligation Combination Fails

Petitioner mistakes basic patent law. That “ligation” is conventional doesn’t mean ligation is automatically trivial or would be compatible with every aspect of any reference—including Linnarsson (particularly without the specific explanation obviousness arguments require). Petitioner’s improper new Reply theories on how its original proposed combination might be *further modified* to accommodate ligation (Rep.11-13) confirm ligation fails in Petitioner’s originally-proposed combination.

1. Petitioner’s New CDS And TSO Modifications Are Late

Petitioner doesn’t dispute that, if the CDS is biotinylated or the second tag is ligated to the TSO (as in Petitioner’s expressly-relied-on Fig.11 embodiments), ligation fails. Rep.11-13. Instead, Petitioner argues (1) Linnarsson doesn’t require biotin and fragmentation, (2) “bodily incorporat[ion]” isn’t required, and (3)

³ The Fodor Patents are not prior art to ’013, and are unrelated to ’013, Linnarsson, or McCloskey. Pet.12-14 (citing EX1016, 10-12); Rep.1-2.

additional modifications would allow ligation to work. Rep.11-13.

Argument (1) is new and wrong (§I.C.1.a). Indeed, the Petition *expressly and repeatedly relied on Fig.11’s embodiment employing biotin and fragmentation*, and never explained how Linnarsson’s method would work without biotin or fragmentation. §I.C.1.b. Additionally, Petitioner’s reliance on the statement that “[a]rbitrary sequence[s] can be *inserted* at the 5’ end of the TSO...” is misplaced. Rep.12. This disclosure (about “insert[ing]”) is *not* about adding sequences *by ligation* (EX1003, 25:1-2), and is thus irrelevant to Petitioner’s arguments about *ligating* a sequence to the *end* (Pet.37-39).

Regarding (2), *PO’s REOS argument doesn’t assume “bodily incorporat[ion].”* POR.28-36. PO showed, instead, that without further modification *to Linnarsson*—and the required motivation and REOS for that modification—ligation fails. *Juniper Networks, Inc. v. Swarm Tech. LLC*, IPR2021-01445, Pap.62, 26-28 (Feb. 7, 2023) (no bodily incorporation simply in explaining why petitioner’s “proposed combination” *wouldn’t work*); *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 887-89 (Fed. Cir. 2024); *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367-68 (Fed. Cir. 2015) (affirming teachings of references “could not be combined because...[one’s] indexing (i.e., tagging) scheme could not be used with [other’s] restriction-

digestible amplification primers.”); *infra* p.25.

Lastly, regarding (3), Petitioner’s ***new biotin modifications*** (e.g., adding biotin after ligation) ***and cut site modifications*** (e.g., modifying its location) ***weren’t in the Petition***. Rep.13; *Juniper*, IPR2021-01445, Pap.62, 26-28 (rejecting improper new reply evidence); *Medtronic, Inc. v. Teleflex Innovations S.A.R.L.*, IPR2020-00127, Pap.107, 51-52 (June 17, 2021) (“[t]he extensive need to modify Kontos’s device in a way not suggested in the Petition supports [PO’s] argument that the proposed modifications are based on a hindsight desire to recreate the claimed invention...”), *aff’d* 70 F.4th 1331 (Fed. Cir. 2023); *Dynaenergetics Eur. Gmbh v. Swm Int’l, LLC*, IPR2022-01372, Pap.27, 49-50 (Feb. 5, 2024) (rejecting “meaningfully distinct” reply argument). And if considered, Petitioner fails even to argue POSITA would have been ***motivated*** to modify Linnarsson in this manner, or to explain why POSITA would have had ***REOS***. Rep.13; POR.36-38. Further, as PO explained (POR.23-28), POSITA would not have been motivated to complicate Linnarsson’s approach to achieve what Petitioner argues is “an equivalent method.” POR.23-28 (citing *In re Schweickert*); *Taiwan Semiconductor Mfg. Co. v. Godo Kaisha IP Bridge I*, IPR2016-01442, Pap.7, 20 (Jan. 27, 2017) (rejecting obviousness where same

problem already solved).

2. Petitioner Does Not Contest Ligation Adds Steps And Complexities To Linnarsson's Method

While Petitioner devotes pages to ligation's "conventional[ity]" (Rep.19-23), this doesn't mean POSITA would've been motivated to add steps to add a tag by ligation (as Cooper admitted was necessary (EX2040, 63:1-20)) or would have expected to succeed *in the context of Linnarsson*. *Virtek*, 97 F.4th at 886-87 ("KSR did not do away with the requirement that there must exist a motivation to combine various prior art references..."). "It does not suffice to meet the motivation to combine requirement to recognize that two alternative arrangements...were both *known*." *Id.* at 886-88.

Petitioner's citation to *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) supports PO. Rep.8. Petitioner failed to prove "anticipated success" using ligation in Petitioner's original combination—a requisite for "obvious to try." *KSR*, 550 U.S. at 421; POR.28-36. Petitioner's other cases fail for similar reasons. In *I/P Engine, Inc. v. AOL Inc.*, 576 F. App'x 982, 987 (Fed. Cir. 2014) the patent acknowledged the exact limitation used in the combination was routine and conventional. That is not the case here, and '013 doesn't say ligation to a biotinylated nucleic acid, as in Linnarsson, was routine and conventional. EX2040, 66:5-67:10. For the same reason, *McCoy v. Heal Systems, LLC*, 850 F.

App’x 785, 789 (Fed. Cir. 2021) (nonprecedential) is inapposite. And unlike *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 274 (Fed. Cir. 2022), where expert testimony established POSITA “would not have expected any incompatibilities,” here Petitioner never explained why there would be no incompatibilities (there plainly would be (POR.28-36)). Lastly, unlike here, in *Ball Aerosol & Specialty Container, Inc. v. Ltd. Brands, Inc.*, 555 F.3d 984, 992-93 (Fed. Cir. 2009) there was no REOS dispute.

Petitioner’s argued motivation to use ligation was because it offered “flexibility” *over* “***the method already disclosed by Linnarsson.***” Pet.39. Thus, Petitioner needed to demonstrate that POSITA would have been motivated to ligate the second tag despite the added steps and complexity introduced as compared to Linnarsson’s disclosed method. Petitioner didn’t do so. Petitioner again points to Cooper’s vague argument that “flexibility” motivates ligation, but improperly flips the burden away from Petitioner, arguing *PO* could have cross-examined Cooper for details. Rep.8-9; §316(e). And even after Cooper submitted a *second* declaration, his supposed “flexibility” benefit fails as unclear and conclusory. Rep.8-9; *Virtek*, 97 F.4th at 889 (reversing Board’s obviousness conclusion resting on “conclusory testimony” for motivation to combine). Cooper argues, *e.g.*, that one needing to tag a small number of molecules could use shorter barcodes. EX1070, ¶77. But Petitioner doesn’t explain how such “***added*** flexibility” is

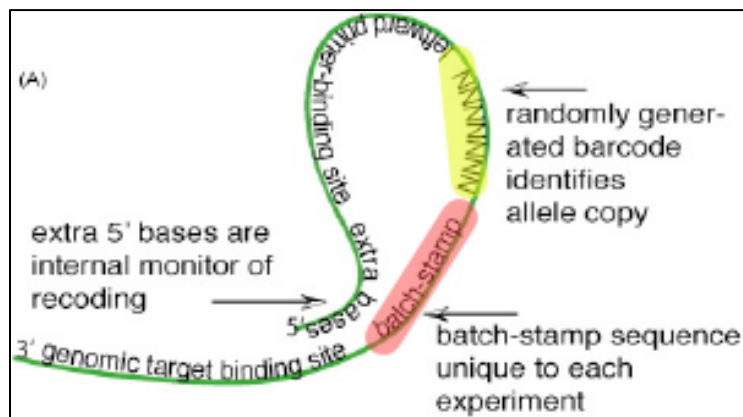
specifically achieved *by ligation* (as opposed to, *e.g.*, providing both tags through Linnarsson's STRT approach). Moreover, Cooper does not explain how POSITA would *know at the outset* whether only a small number of endogenous molecules are present: the claimed method's purpose is to *determine that number of molecules in the sample*. EX1070, ¶77; EX1001, Cl.1.

3. Petitioner's New "Ligate To The Sample Sequence" Theory Is Late, And Fails

Petitioner's original ligation theory was clear that the second tag is ligated *"to the CDS or TSO."* Pet.37-39; Rep.13. But on Reply, instead of ligating to the CDS or TSO, Cooper now claims his theory was to ligate *to the sample sequence after extension*. EX1070, ¶86. This is new and improper—and, even if considered, fails to explain how those modifications would work.

B. Petitioner's Motivation To Combine Still Fails

In the Petition, Petitioner mapped McCloskey's "barcode" without any further discussion or modification.



Pet.34-35 (“a ‘barcode’ (highlighted in yellow...)”). While PO properly noted the ambiguity in Petitioner’s mapping (POR.49 n.26), to the extent, *arguendo*, the “barcode” mapping means anything, it must refer to the 7-nucleotide barcode McCloskey actually disclosed because Petitioner proposed ***no modifications to the McCloskey barcode for this Ground***. EX1004, 3; Pet.34-35. Indeed, the fact that Petitioner didn’t modify McCloskey’s barcode and didn’t invoke McCloskey’s “4ⁿ” disclosure in Ground 1 is confirmed by the fact that ***Petitioner did so affirmatively, and for the first time, in its Ground 2 arguments***. Pet.60-64 (Ground 2); EX1002, ¶¶254-258 (Ground 2). Petitioner knew how to do so, ***but did not in Ground 1***.

1. Petitioner Never Relied on “Yeast” or “Bacterial” RNA; Petitioner’s Combination Lacks Sufficient Tags For Either

The Petition (and Cooper) ***repeatedly*** relied on eukaryotic cells, including Linnarsson Fig.1’s “***tissue*** of interest” (Pet.27-28, 32-33; EX1002, ¶¶61, 116-117, 121-122 (discussing Fig.1 and citing EX1003, 22:22-23), and opining “step B requires selecting a plurality of single cells ***from the dissected tissue of interest***” (emphasis original)), and Figs.2-4 and 11 from Exs.I-II, which analyzed ***eukaryotic (mouse) cells*** (although without acknowledging Linnarsson’s two-“Example” framework). *See also* EX1003, 10:12, 23:20, 31:7 (“tissues”), 37:16 (“mouse cell types”). On Reply, Petitioner instead argues ***bacteria*** and ***yeast*** have fewer mRNA molecules than the “50,000-300,000” expected per mammalian cell. Rep.22-23.

But *neither Petitioner nor Cooper ever mentioned bacteria or yeast* or made this argument in the Petition or opening testimony. *See generally*, Pet. & EX1002. Instead, Petitioner’s approach is improper “new evidence [and] argument in reply that [Petitioner] could have presented earlier...to make out a prima facie case of unpatentability.” *Juniper Networks, Inc. v. Swarm Tech. LLC*, IPR2021-01445, Pap.64, 12-13 (Apr. 20, 2023) (denying rehearing and affirming FWD’s refusal to consider improper new reply evidence and argument); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016) (affirming Board’s refusal to consider improper reply evidence, noting petitioner’s “obligation...to make their case in their petition”); *Carrier Fire & Sec. Ams. Corp. v. SentiLock, LLC*, IPR2021-00664, Pap.34, 29-21 (Sept. 14, 2022) (refusing to consider “a theory of configuration” presented in reply); *Apple Inc. v. e-Watch, Inc.*, IPR2015-00412, Pap.50, 43-44 (May 6, 2016) (Accepting...belatedly presented new arguments would be unjust to the Patent Owner...”).

Even if considered, Petitioner’s yeast argument fails for the same reasons its original arguments failed. POR.49 n.26; EX2013, ¶¶87-94. Petitioner doesn’t (and can’t) deny it expressly stated POSITA would need *many times more* tags than the expected number of molecules to tag each uniquely (Pet.60-61)—indeed, Cooper and the Petition argued “*100 times more*” to “ensure each sample polynucleotide... would be tagged.” Rep.23-26; Pet.61; EX1002, ¶256; *see also*

infra §I.A.2. Cooper admits yeast cells have 15,000-60,000 mRNA molecules, meaning POSITA (by Cooper’s own arguments) would have needed far more than the 16,348 tags McCloskey’s seven-nucleotide barcode could provide. EX1070, ¶134.

Petitioner’s parallel bacteria argument fares no better. Petitioner’s original mappings relied exclusively on annealing a CDS’s thymine sequence *to the mRNA’s poly-A tail (and only the poly-A tail)*. Pet.31-33 ([1D]), 39-42 ([1F]). But Cooper admits “in general, *the rule for bacteria is that they’re not polyadenylated*.” EX1081, 72:10-75:8 (only “small percentage of the transcripts within any given bacteria” have poly-A tail); EX2040, 23:5-24:21; EX2102, 1. Thus—although Petitioner’s motivation to combine *expressly required it (infra*, §I.B.2)—“each”/“every”/“substantially all” bacterial mRNA could *not* be tagged by Petitioner’s identified CDSs because they lack a poly-A tail.⁴ And for the few bacterial mRNA that *are* polyadenylated, the *functionality is different* from eukaryotic organisms. *E.g.*, EX1081, 74:18-76:3, 64:16-71:14, esp.64:16-65:1 (“I

⁴ Petitioner complains PO “argued for the first time on sur-reply [in IPR2023-00876] that McCloskey’s barcode cannot tag mRNA molecules in bacteria” (Rep.23 n.8) but ignores that there (as here) *Petitioner* improperly raised its new bacteria theory only in Reply.

don't think [polyadenylation in prokaryotes is] used in quite the same way or has the...*same functionality*”), 65:8-21 (doesn't know, one way or the other, whether “mRNA polyadenylation is absent in prokaryotic mRNAs except in transcripts bound for degradation”), 66:5-69:20 (same); EX2040, 15:15-16:11, 17:1-20:16 (admitting EX2103 was published in “reputable journal,” Cell), 24:16-25:11; EX2103, 4 (“polyadenylation is absent in prokaryotic mRNAs except in transcripts bound for degradation”).

Petitioner's bacteria argument also fails because *Petitioner's numbers confirm there wouldn't be enough unique tags*. See Pet.60-61; EX1002, ¶¶255-257; see also *infra*, §I.A.2. Cooper's only (new) estimate for bacterial mRNA molecules is 1,380 (EX1070, ¶134)—and based on his own reasoning (EX1002, ¶¶255-257) tagging each requires 138,000 tags (POR.49 n.26; EX2013, ¶¶87-94), meaning McCloskey's 16,348 are insufficient.

2. Petitioner's Theory Is That “Each” Polynucleotide Would Be Tagged

Petitioner's “second” new argument is that the claims “do not require tagging *all* the mRNA.” Rep.23. While the *claims don't* require “tagging all the mRNA molecules” (Rep.23), *Petitioner's stated theory does* to motivate combining with McCloskey. POR.48-49.

The Petition's arguments *expressly require uniquely tagging every* mRNA in the cell: Petitioner argued POSITA would've been motivated to tag “each

sample polynucleotide” to “‘solve’ amplification bias.” EX1002, ¶¶173-174; Pet.36-37. And, arguing coverage for a claim in the related ’197 patent, Cooper testified POSITA would understand *Linnarsson’s “sample polynucleotides”* as “*substantially all mRNA molecules of said cell*”:

A POSA would understand that because the mRNA is indiscriminately released from each single cell, and because Linnarsson does not describe any additional elimination or filtration, *the released mRNA sample comprise substantially all mRNA molecules of said cell*. As discussed above, *Linnarsson’s method then tags these sample polynucleotides* for the purpose of gene expression analysis. A POSA would understand that *the purpose of such a method would be to analyze substantially all mRNA molecules of a cell—therefore, this method would provide associating a tag with substantially every sample mRNA molecule*.

EX2022, ¶222; *see also* EX1002, ¶¶124 (equating “plurality of sample polynucleotides” with the mRNA released from lysed cells); 125 (similar), 129 (equating the “released plurality of the mRNA molecules” to the sample polynucleotides); Rep.23-24; EX2021, 70-71. This *isn’t merely* what “Linnarsson’s design is *capable of*” (Rep.24); *this is how Cooper opined POSITA*

would understand Linnarsson’s unaltered method operated. EX2022, ¶222.⁵

For this same reason, it’s irrelevant the claims don’t require tagging all mRNA molecules of a cell—the issue here is *how Petitioner mapped Linnarsson and argued POSITA would understand Linnarsson’s disclosures on which it actually relied.* Cooper confirms Linnarsson would be understood to disclose tagging “substantially all mRNA molecules of a given cell.” *Intelligent Bio-Sys.*, 821 F.3d at 1369. And Petitioner argued “solv[ing]”⁶ amplification bias (its asserted motivation to combine) required tagging “[e]very sample and the polynucleotides within every given sample... uniquely... before being amplified.” EX1002, ¶¶87, 171-174; Pet.36-37 (“exact solution”); POR.49 n.26; EX2013, ¶¶87-94. Petitioner was master of its Petition and never argued modifying Linnarsson to tag *less than*

⁵ Cooper’s late discussion of *other* Linnarsson disclosures to argue a *new combination* in which less than all mRNA are tagged is improper reply evidence. *Supra*, §I.B.1.

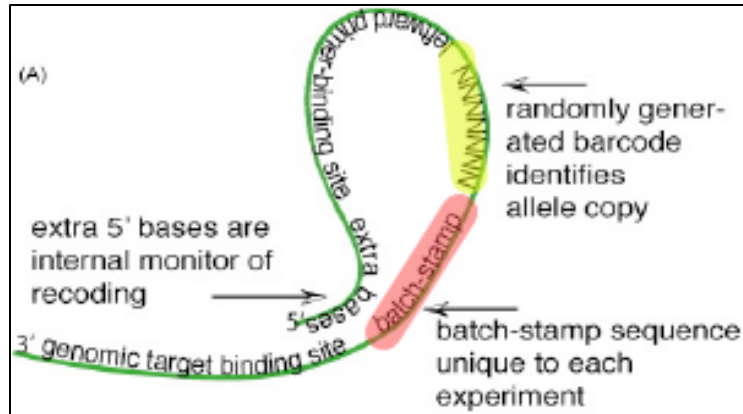
⁶ Petitioner cannot recast its motivation from “*solv[ing]*” amplification bias (Pet.36-37) to simply “*reduc[ing]*” it. Rep.24. Petitioner’s motivation was premised on Linnarsson “*only ‘reduc[ing]’ amplification bias,*” “[but] *not actually solv[ing] the problem....*” EX1002, ¶¶173-174. In contrast, Petitioner argued McCloskey “provides the *exact solution.*” Pet.36-37.

“substantially all mRNA molecules” in the cell—instead Petitioner *explicitly relied on embodiments that indiscriminately tagged mRNA using a poly-dT RCS.*

Supra, §I.B.1. It cannot about-face now. *Supra*, §I.B.1; *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1367 (Fed. Cir. 2023).

3. Petitioner Relied Only On McCloskey’s Seven-Nucleotide Barcode

Petitioner’s “third” new argument is that “McCloskey’s disclosure is not limited to 16,384 barcodes.” Rep.25. As discussed above, (supra, pp.8-9), Petitioner still *cannot identify any statement in its Petition or Cooper’s opening testimony about changing the length of McCloskey’s unmodified 7-nucleotide barcode* for Ground 1. POR.48-49 & n.26. to the contrary, Petitioner asserts it “cite[d] to McCloskey’s exemplary molecular tag, which is ‘seven nucleotides’” and that PO “acknowledge[d] that Petitioner cites to an exemplary 7-nucleotide barcode from McCloskey,” but Petitioner now jettisons that argument in favor of a barcode of *any* length (which it also allegedly “cite[d] to.”). Rep.21-22. To the extent Petitioner is credited with actually identifying a barcode from McCloskey, it can *only* be the barcode actually used in McCloskey—which Petitioner acknowledges is “seven nucleotides.” Rep.21.



Pet.34-35 (“As shown above, McCloskey’s encoding oligonucleotide comprises... a ‘barcode’ (highlighted in yellow, above)...”).

Petitioner’s attempt now to rely on a formula identifying the number of possible barcode sequences for a tag of a particular length **other than 7** as the “barcode” is new and improper: the Petition argued this **only** for Ground 2, **never** for Ground 1. Rep.21. If Petitioner wished to argue this, it knew how—and this theory should have been “presented earlier...to make out a *prima facie* case of unpatentability.” *Juniper*, IPR2021-01445, Pap.62, 28-29 (refusing to consider new theory where petition didn’t “mention or describe [its] use” or how it would be incorporated into combination); *Juniper*, IPR2021-01445, Pap.64, 12-13 (“the ability to respond does not give Petitioner free reign to expand and revise its arguments by adding new features and configurations”); *Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017) (rejecting reply’s attempt to cure petition by relying on “new theory,” “[r]ather than explaining how its original petition was correct”) (citation omitted); *Intelligent Bio-Sys.*, 821 F.3d

at 1370 (similar). And *had this actually been Petitioner’s theory, Petitioner would have said so*: only in **Ground 2** did the Petition *first mention the “4ⁿ” formula* and first *rely on an additional reference, McCloskey II, to modify Petitioner’s Ground 1 Linnarsson-McCloskey combination* and provide a longer barcode to cover claim 13. Pet.61-62; EX1002, ¶¶255-257. But the Petition *never mentioned “4ⁿ” or included McCloskey II* for Ground 1 (claims 1-12 and 19-28), as the Reply now improperly attempts. Cf. EX1070, ¶140, 146 (citing EX1002, ¶¶255-258 (located within Cooper’s **Ground 2** opinions)); Rep.25 (arguing Ground1 but citing Petition at 60-62, 64 (Ground 2) and EX1002, ¶¶254-258 (same)). See *Renesas Elecs. Corp. v. Lone Star Silicon Innovations, LLC*, IPR2017-01869, Pap.33, 43-45 (Mar. 25, 2019) (improperly relying on newly-cited exhibits in reply).

C. Petitioner’s Sequencing Arguments Fail

1. Petitioner Failed to Support Petitioner’s Argument that Linnarsson’s Entire Tagged Polynucleotide Is Sequenced

The Petition argued Linnarsson disclosed “sequencing” based on Linnarsson’s sequencing of the “tagged polynucleotide,” which Petitioner equated to *the full-length “double-stranded cDNA molecules” generated by reverse transcription*. Pet.30, 44. While Petitioner’s Reply runs from Petitioner’s own argument and concocts a non-existent claim construction dispute as cover to

rewrite Petitioner’s Linnarsson mapping (Rep.13-14), PO never argued construction. Instead, PO called out *Petitioner’s failure to support Petitioner’s sole argument for disclosure of the sequencing limitation*—that Linnarsson disclosed sequencing *the entire tagged polynucleotide*.⁷ “Linnarsson teaches that after generating *the tagged polynucleotides*, ‘sequencing is performed’ thereon.” Compare Pet.44 with POR.43. And Petitioner is foreclosed from starting over now with improper *new* arguments for mapping this limitation.

(a) Linnarsson’s STRT Method Consistently Discloses Fragmentation and Capture

Petitioner again asserts, on Reply, that Linnarsson discloses sequencing the entire tagged polynucleotide, but makes the new argument (contradicting its Petition mapping) that “Linnarsson cannot possibly require fragmentation as in Figure 11,” and Figs.3-4 “include neither a biotin nor a restriction enzyme cut site.” Rep.17-18. But Linnarsson’s fragmentation-and-capture STRT method employs *both* biotin and a restriction enzyme cut site (EX1003, 23:1-37:32;

⁷ The Petition included no further explanation, or even an expert citation, to explain its mapping. Pet.44.

EX2013, ¶¶36-37, 47)—including in Linnarsson’s only two examples:⁸ **Ex.I**, which **introduces Figs.2-4** (EX1003, 23:9-25:6; EX2040, 25:21-31:9 (agreeing “both Examples 1 and 2 of Linnarsson disclose fragmentation and capture”)), and **Ex.II**, which **introduces Fig.11** (EX1003, 37:31-32).

Petitioner’s Cooper *agrees* Ex.I discloses fragmentation-and-capture, **which requires biotin and a restriction enzyme cut site** (EX2040, 25:21-31:9), and that Figs.3-4 are disclosed in, and “not inconsistent” with, Ex.I (and that the only other place they’re disclosed is in Linnarsson’s list of figures). EX2040, 25:21-31:9. Cooper further agrees POSITA reading Linnarsson *would know to use biotin* with Fig.4’s CDS in Ex.I. EX2040, 74:10-75:19. And while Cooper argues a *BtsCI* cut site isn’t present in Figs.3-4, he doesn’t dispute *another restriction enzyme cut site (CGAGTG) is present in Figs.3-4*, and agrees POSITA would *not* interpret Linnarsson as *limited to using only BtsCI*. EX1070, ¶¶55-56; EX2015, 1;⁹ EX2040, 37:16-21 (agreeing other restriction enzymes within Linnarsson’s

⁸ Exs.I-II employ a biotinylated CDS, and a TSO with a cut site on the cell-tag’s 5’ end. POR.29-30; EX2013, ¶¶33, 36-37, 45-47, 97; EX1003, 23:9-19, 31:3-32:27; EX1081, 96:12-97:11, 118:5-8; EX2040, 25:21-31:9.

⁹ Cooper previously testified Figs.3-4 “do not contain *any* restriction enzyme cut site” (e.g., EX1081, 118:14-130:5, 133:19-137:10; EX1070, ¶¶36-59, 114-117,

scope); EX1081, 123:11-124:21, 125:5-22, 133:19-137:10; Rep.18 n.7.¹⁰ Given these admissions and Linnarsson’s consistent disclosures of using biotin and fragmentation,¹¹ Petitioner failed to show Figs.3-4 teach anything other than polynucleotide sequences for a compatible CDS (to which a biotin molecule would be added) and TSO for Ex.I’s method. Petitioner certainly provided no basis to credit Cooper’s assertion that Fig.4 would be understood as disclosing a CDS to be used *without* biotin. Compare EX2013, ¶¶33, 36-37, 47, 97, with EX2040, 74:10-

esp. 117, 48). Cooper thus contradicted his prior testimony *about the same reference* and his testimony should be given little or no weight. *Applied Materials, Inc. v. Demaray LLC*, IPR2021-00104, Pap.54, 29-33 (June 29, 2022) (rejecting petitioner’s reliance on expert’s testimony that was “belied by [the expert’s] own testimony”).

¹⁰ Petitioner’s implication that Figure 11 *cannot possibly use a different restriction enzyme* because “Linnarsson calls out BtsCI, but *never* BtsI” is thus irrelevant. Rep.18 n.7 (emphasis original).

¹¹ As Petitioner admits, a cut site as in Figs.3-4 “[is] part and parcel of the fragmentation method” also used in Linnarsson’s Fig.11. Rep.17; EX1070, ¶37.

75:19.¹² And there is no basis to credit Petitioner’s unsupported assertion that including a BtsI cut site *in both Figs.3-4* was “mere coincidence.” Rep.18 n.7.

That Linnarsson’s cDNA library is *fragmented* is confirmed by Linnarsson’s “cDNA library” definition: “a collection of cloned complementary DNA (cDNA) *fragments*....” EX1003, 12:4-8; POR.44; EX2013, ¶¶33, 47, 83-84. This is consistent with Linnarsson’s reference to, *e.g.*, “3’ *fragments*,” “internal *fragments*,” and “5’ *fragments*” (EX1003 6:5-9, 26:22-25, 35:17-31 (“Amplified cDNA was fragmented,” resulting in, *inter alia*, “3’ and 5’ fragments”)), and Petitioner identified nothing in Linnarsson referring to the cDNA, before fragmentation, as a “fragment.” Cooper’s reply assertion that “fragment” in Linnarsson’s “cDNA library” definition “is merely stating that the cDNA will necessarily be a fragment of DNA since the RNA is itself just a fragment of

¹² Cooper similarly argues Fig.2—which depicts only the poly-T and poly-G sequences of the CDS and TSO, respectively, and a black line at the end of each—wouldn’t include “the BtsCI cut site or biotin.” EX1070, ¶54. But like Figs.3-4, Fig.2 is discussed only within Ex.I, which includes biotin and fragmentation. EX1003, 23:1-24:20; EX2013, ¶¶36-37, 47. And Cooper himself characterized Fig.2 as “explaining Figure 11,” which he agrees illustrates fragmentation-and-capture. EX1002, ¶108; EX1070, ¶¶36-48.

nucleic acid” (EX1070, ¶104) would render Linnarsson’s use of “fragments” in the definition superfluous. *Id.*; *see also* EX2040, 32:17-35:1; EX1081, 107:16-111:3.

Petitioner’s final (new) argument for reading fragmentation out of Linnarsson involves Linnarsson’s Claims 1 and 27. Rep.18-19 (citing EX1070, ¶¶59, 127); EX1003, 48:9-10. Even if these belated arguments were considered, they fail: “The scope of a patent’s claims determines what infringes the patent; it is no measure of what it discloses.” *In re Benno*, 768 F.2d 1340, 1345-46 (Fed. Cir. 1985); *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1262 (Fed. Cir. 1989). Claim 1 doesn’t ***exclude*** biotin or fragmentation: it’s simply ***silent*** on those features. EX1003, 46:3-12. Petitioner similarly argues Linnarsson Claim 27—requiring “the processing comprises fragmenting the cDNA library”—means Claim 1 doesn’t require fragmentation as part of *creating* the library. Rep.18-19 (citing EX1070, ¶¶59, 127); EX1003, 48:9-10. But Claim 27’s plain language involves processing *the cDNA library itself*—and merely confirms *additional* fragmentation (*e.g.*, after Fig.11’s fragmentation and *after* preparing the cDNA library (EX1081, 101:9-103:7; EX2040, 31:19-32:11)) may be used to prepare the cDNA library for, *e.g.*, next-generation sequencing (“NGS”). EX1081, 111:8-113:16; EX2040, 31:19-32:11. For example, Linnarsson generates 200-300 base-pair cDNA fragments in Fig.11 through DNase digestion. EX1003, 6:3-4.

Cooper agreed it may be *necessary* to further fragment the cDNA to sequence it.¹³

EX1081, 97:17-101:22, 111:8-113:16; EX2040, 31:19-32:11. Lastly, Linnarsson discloses another reason to further fragment the library: shotgun sequencing.

EX1003, 22:5-21; EX1081, 103:8-19.

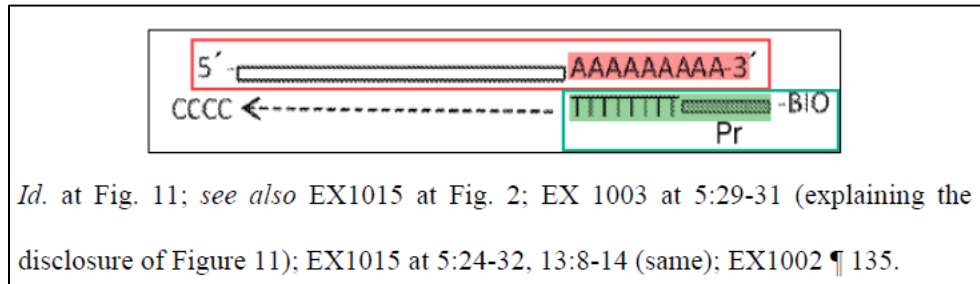
Petitioner's arguments that PO and Quackenbush "ignore[d]" Linnarsson's Figs.3-4 and dependent Claim 27 (Rep.19) disregards the citations in the POR (POR.9-10, 16-17) and Quackenbush's declaration (EX2013, ¶¶36-37, 45-47). Further, the Petition never mentioned Claim 27, and *neither the Petition nor Cooper argued biotin was optional* based on Figs.2-4 or dependent Claim 27.

(b) Petitioner Relied On Fragmentation And Biotin Examples

The Petition didn't explain how or why Fig.11's biotin and fragmentation would be compatible with or modified for Petitioner's mapping. Petitioner's new attempts to cast Linnarsson's fragmentation as "optional" shouldn't be credited *because the Petition affirmatively relied on Linnarsson's fragmentation-and-capture disclosures (including biotin)*. Petitioner's and Cooper's Ground 1 analysis, for example, *repeatedly relied on Fig.11* (reflecting Ex.II's method), which indisputably incorporates the fragmentation approach, and Cooper

¹³ Cooper identified NGS systems at the time that might read only "a few dozen" base pairs. EX1070, ¶8.

specifically included biotin in the green box he drew around what he called the CDS. Pet.32-33, 41-42 (mapping Fig.11 to [1D], 1[F]); EX1002, ¶¶135-140, 155-156 (same, to [1D], [1F]); Pet.32:



Petitioner and Cooper also *repeatedly equated Figs.2 and 11* (including the CDS in each), and *treated Figs.2-4 and 11 as a single, consistent embodiment*. Pet.31-33 (“As shown in Figures 2 and 11... Figure 11... *discloses the same*... As shown in Figure 2 below, a TSO... *Figure 11 discloses the same*... Figure 3... *similarly discloses* that the TSO...”), 45-47; EX1002, ¶¶135-140, 155-156. Petitioner’s new suggestion these are now separate, distinct embodiments (some using biotin/fragmenting, some purportedly not) is contradicted by Petitioner’s and Cooper’s initial mapping. It is also belied by Cooper’s admission that POSITA would biotinylate the sequence in Fig.4 to use it in Ex.I, where Fig.4 is introduced. EX2040, 74:10-75:19.

Cooper’s new optionality opinions lack a reasoned basis for deciding which parts of Fig.11 are “optional.” For example, Cooper admits the CDS, TSO, and amplification (panels A-C), are *required* (EX2040, 51:21-56:4), but now argues

fragmentation and capture (panels D-E) are optional. EX2040, 56:20-57:17.

Cooper provides no reasoning about why fragmentation and capture are any more “optional” than the CDS and TSO.

Further, even if Petitioner’s late distinguishing of Linnarsson “embodiments” were permitted, Petitioner never provided the required analysis about which elements from which embodiments are to be combined. *Markforged Inc. v. Continuous Composites, Inc.*, IPR2022-00679, Pap.24, 14-15 (Sept. 26, 2023) (“Pointing to disparate embodiments without providing a sufficient motivation to combine them is not enough to establish... obviousness...”); *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Cooper relied on what he now calls multiple embodiments, but never explained *how* or *why* POSITA would mix-and-match across them. EX1002, ¶¶135-140, 153-156; *see also* EX1081, 47:17-48:15 (arguing Linnarsson discloses “lots of optionality”), 76:13-78:19.

Even if, *arguendo*, POSITA would’ve interpreted Figs.2-4 as usable in a method *inconsistent* with Exs.I-II’s fragmentation-and-capture approach (*i.e.*, a method without a biotinylated CDS), Petitioner has identified no complete method (from tagging through sequencing) disclosing use of Figs.2-4 ***without*** those steps. Rep.17-19; Pet.44. As Quackenbush explained, Linnarsson’s biotin is critical, allowing tagged polynucleotides to be isolated: without such purification, tagged

and untagged polynucleotides (*e.g.*, DNA) would be sequenced and the information would be muddled. *See* EX2013, ¶¶45-47, 97; EX1003, 14:8-13.

2. Petitioner's New Reply Arguments Should Be Disregarded

Petitioner now argues Linnarsson meets this limitation for a *different* reason—*i.e.*, that it teaches sequencing a *portion* of the tagged polynucleotide. Rep.13-15.¹⁴ This new Reply theory should be rejected because it could've been presented in the Petition, but wasn't. *Supra* p.1; *Juniper*, IPR2021-01445, Pap.62, 28-29; *Wasica*, 853 F.3d at 1286; *Intelligent Bio-Sys.*, 821 F.3d at 1370. And Petitioner's attempt to conceal its failed disclosure theory by arguing, instead, about what the claims do or don't require, should also be disregarded. It was Petitioner's burden to establish that *Petitioner's* mapping—based here on Linnarsson's disclosure—would accomplish what Petitioner argued. *Intelligent Bio-Sys.*, 821 F.3d at 1369. Petitioner cannot propose a new combination with so-called biotin- and fragmentation-free approaches on Reply to avoid its failure to

¹⁴ Petitioner's arguments relying on improperly incorporated by reference arguments from Cooper's Reply Declaration should be disregarded. For example, Petitioner incorporates over **40 paragraphs** from Cooper to explain two sentences of argument. *See* Rep.14 (citing EX1070, ¶¶8-9, 23-30, 96-127); Rep.11 (citing EX1070, ¶¶31-59, 114-127); Rep.25 (citing EX1070, ¶¶61-71, 128-144).

show sequencing of the “tagged polynucleotide”—the cDNA generated in Linnarsson’s method—as argued in its Petition. Rep.15.

3. Petitioner’s Reply Arguments About Sequencing A Portion Of The Tagged Polynucleotide Fail To Meet Their Burden

Even if considered, Petitioner failed to establish that some undefined but “sufficient” portion of Linnarsson’s tagged polynucleotide was sequenced. Cooper testified sequence information would need to be generated *“for the two tag sequences and a portion of the sample sequence.”* EX1070, ¶104; EX2040, 8:17-11:11. But the Petition (and Reply) failed to address *how much* of the sample polynucleotide would “suffic[e],” or attempt to show Linnarsson’s methods would sequence a “sufficient” amount of it, let alone that the entirety of the tags would be sequenced. *See* POR.42-48.

II. Grounds 1 and 2: Petitioner’s Belated “McCloskey” Evidence Fails

Petitioner’s attempt to cure McCloskey’s evidentiary failings *on reply* fail. Rep.4-5. The Petition asserts only that McCloskey was published online in October 2007, citing EX1028. Pet.22. But EX1028, Hall-Ellis’s first declaration, *does not mention McCloskey*. *See generally*, EX1028. PO timely objected to both McCloskey and EX1028, but Petitioner *did nothing*. Pap.12, 1-2. Months after the POR, Petitioner belatedly included unauthorized declaration evidence pre-dating the Petition to cure this failing. Rep.4-5; EX1085. Petitioner’s self-help fails, and with it the entire Petition. *Sirius XM*, IPR2018-00690, Pap.63, 13-15

(refusing to consider reply evidence that reference was prior art where “Patent Owner’s Response simply pointed out the defect in the Petition”).

Sirius is on point: that patentee “simply pointed out the defect in the Petition”—failure to establish the reference was prior art—and the Board refused to consider improper reply evidence. *Id.* Petitioner’s reliance on *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Pap.29, 15 (Dec. 20, 2019) (precedential) (Rep.5) fails: EX1085 is not “responsive” to PO’s assertion. POR.18; *Sirius XM*, IPR2018-00690, Pap.63, 13-15.

Petitioner’s Reply arguments that McCloskey was published online in October 2007 (Rep.4 (citing Pet.22)) also fail to make a *prima facie* case that McCloskey was publicly accessible, and thus a printed publication. *Hulu*, IPR2018-01039, Pap.29, 10-11. The Board should follow *Medivis*: a copyright date “is not sufficient [even] at... institution... to demonstrate public accessibility”—the same evidence is deficient post-institution. *Medivis, Inc. v. Novarad Corp.*, IPR2023-00042, Pap.35, 27 (Mar. 6, 2024). Like *Medivis*, the only other record argument is an unsubstantiated assertion the reference appeared online; this is insufficient, particularly without evidence the reference was *accessible*. *Id.* at 28-30. Lastly, like *Medivis*, the Reply’s mere citation to the improper Hall-Ellis declaration ***without discussion*** is incorporation by reference, and shouldn’t be considered. *Id.*

III. Grounds 1 and 2: Petitioner's Improper New Analogous Art Arguments

Petitioner doesn't dispute the Petition failed to analyze whether its art was analogous to '013. Rep.27-28 (no Petition cites). Far from waiting for PO to raise analogousness, and then respond, the Petition here affirmatively argued analogousness—but between the prior art references, thus failing to carry Petitioner's burden of showing the art was analogous to '013. Pet.35. The POR noted that error without inviting a broadening reply. *Cf. Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1004-10 (Fed. Cir. 2023) (declining to find Board abused discretion in allowing argument responding to patentee's affirmative assertions against analogousness, noting, *inter alia*, “petitions were **ambiguous**; they did not make clear whether [petitioner] was stating [references] are in the same field... as the Challenged Patents or, instead, merely... one another”; petitioner “permitted to respond both by **bolstering** its field of endeavor argument and by adding” pertinent-to-the-problem argument); POR 68 (“Nowhere does Petitioner assert...”); *cf., e.g., Apple Inc. v. Corephotonics, Ltd.*, IPR2020-00861, Pap.14, 25

(March 2, 2021). The Board should not now permit Petitioner to rewrite its clearly-deficient Petition.

IV. Conclusion

Petitioner failed to meet its burden to show any Challenged Claim unpatentable.

Respectfully submitted: /Megan Raymond/ September 13, 2024

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S SUR-
REPLY complies with the type-volume limitation in 37 C.F.R. §42.24(b)(1).
According to the word-processing system's word count, the brief contains 5,549
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Dated: September 13, 2024

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER’S SUR-
REPLY has been served in its entirety by causing the aforementioned document to
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