

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

10X GENOMICS, INC.,
Patent Owner

Case IPR2023-00876
Patent 10,155,981

PATENT OWNER'S SUR-REPLY

LIST OF EXHIBITS

Exhibit	Description
EX2001	U.S. Patent Pub. No. 2007/0020640 A1
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., IPR2023-00958, Pap.1 (May 25, 2023)
EX2009	File History of U.S. App. No. 14/172,694
EX2010	Declaration of Sayem Osman
EX2011	Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00958, EX1002 (May 25, 2023) (Declaration of Gregory Cooper, Ph.D.)
EX2012	Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00958, EX1054 (May 25, 2023) (Georgi K. Marinov <i>et al.</i> , <i>From single-cell to cell-pool transcriptomes: Stochastically in gene expression and RNA splicing</i> , 24.3 Genome Research 496-510 (2014) (“Marinov”))
EX2013	Declaration of Dr. John Quackenbush
EX2014	Bruce Alberts, <i>et al.</i> , <i>Molecular Biology of the Cell</i> , Garland Science (4th ed. 2002)
EX2015	Declaration of Sayem Osman
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	Deposition Transcript of Gregory Cooper, Ph.D.
EX2019	Li <i>et al.</i> , <i>Amplification and analysis of DNA sequences in single human sperm and diploid cells</i> , Nature 335(6189):414-417 (1998)
EX2020	May 2, 2024 Deposition Transcript of Gregory Cooper, Ph.D.

Exhibit	Description
EX2021	<i>Parse Biosciences, Inc. v. 10x Genomics Inc.</i> , IPR2023-00955, Pap.1 (May 25, 2023)
EX2022	<i>Parse Biosciences, Inc. v. 10x Genomics, Inc.</i> IPR2023-00955, EX1002 (Apr. 20, 2023) (Declaration of Gregory Cooper, Ph.D.)
EX2101	S. Guan, A. Blanchard, P. Zhang, & Z. Zhu, <i>Alteration of Sequence Specificity of the Type IIS Restriction Endonuclease BtsI</i> , (July 26, 2010) (marked as EX2101 in Dr. Cooper's May 2, 2024 deposition (EX2020))
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 May 2, 2024 deposition (EX2020))
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 May 2, 2024 deposition (EX2020))
EX2104	N. Sarkar, <i>Polyadenylation of mRNA in Prokaryotes</i> , Annu. Rev. Biochem (1997) 66:173-97 (marked as EX1067 in Dr. Cooper's May 2, 2024 deposition (EX2020))
EX2105	S. Slomovic <i>et al.</i> , <i>RNA Polyadenylation in Prokaryotes and Organelles; Different Tails Tell Different Tales</i> , Critical Revs. In Plant Scis. (2006) 25:65-77 (marked as EX1068 in Dr. Cooper's May 2, 2024 deposition (EX2020))

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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. But a Reply is not a mulligan; the Petition governs and "guide[s] the life of" Petitioner's IPR **"through to conclusion."** *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1353, 1355-57 (2018). Petitioner's belated new positions are not only meritless—they're 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"; "It is also 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 of the reply.'...***We do not consider the Reply.***"). Petitioner's various 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, and (3)

quoting PO's statements about concepts *in other patents*—cannot change

Petitioner's failure to meet its burden.¹

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

A. Petitioner's Motivation To Combine Still Fails

Petitioner's improper new Reply arguments (*see, e.g.*, Pap.25) are too late and, like Petitioner's other gap-filling attempts, don't save its failed theories.

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

Petitioner's arguments that bacteria and yeast have fewer mRNA molecules than the “50,000-300,000” expected per mammalian cell (Rep.11-12) ignores, first, that these are improper Reply theories: *neither Petitioner nor Cooper ever mentioned bacteria or yeast* or made this argument in the Petition or opening testimony. EX2020, 71:5-9, 76:1-3. Instead, the Petition repeatedly relied on eukaryotic cells, including Linnarsson Fig.1's “tissue of interest” (EX1002, ¶¶120 (discussing Fig.1 and citing EX1003, 22:22-28), 213), and Figs.2-4 and 11 from Examples I and II, which analyzed eukaryotic (mouse) cells (albeit without ever

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.

acknowledging Linnarsson’s two-“Example” framework). Pet.37-39, 41-48; *see also* EX1003, 10:12, 23:20, 31:7 (“tissues”), 37:16 (“mouse cell types”); EX2020, 94:3-7. 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”).

Even if considered, Petitioner’s yeast argument fails for the same reasons its original arguments failed. POR.33-36. Petitioner doesn’t (and can’t) deny it asserted POSITA would need **many times more** tags than the expected number of molecules to tag each uniquely (EX2008, 76)—indeed, Cooper argued **100 times more** to “ensure each sample polynucleotide...would be tagged.” Rep.11-14; EX2011, ¶256; *see also infra* §I.A.2. For yeast cells, which Cooper admits have 15,000-60,000 mRNA molecules, POSITA (by Cooper’s own arguments) would have needed far more than the 16,348 tags McCloskey’s seven-nucleotide barcode could provide. EX1059, ¶87.

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.41-42 ([1C]), 44-47 ([1D]). But Cooper admits “in general, *the rule for bacteria is that they’re not polyadenylated*. EX2020, 72:10-75:8 (only “small percentage of the transcripts within any given bacteria” have poly-A tail); EX2102, 1. Thus—although Petitioner’s motivation to combine required it (*infra*, §I.A.2)—“each”/“every”/“substantially all” mRNA in bacteria could *not* be tagged by the CDSs it identified because they lack a poly-A tail. And for the few bacterial mRNA that *are* polyadenylated, the *functionality is different* from eukaryotic organisms. *E.g.*, EX2020, 74:18-76:3, 64:16-71:14, esp.64:16-65:1 (“I *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); EX2103, 4 (“polyadenylation is absent in prokaryotic mRNAs except in transcripts bound for degradation”).

Petitioner’s bacteria argument also fails because Petitioner’s own numbers confirm there wouldn’t be enough unique tags. *See* EX1002, ¶¶135-147; *see also infra*, §I.A.2. Cooper’s only (new) estimate for bacterial mRNA molecules is 1,380 (EX1059, ¶87)—and based on Cooper’s own reasoning (EX2011, ¶256)

tagging each would require 138,000 tags (POR.33-36), meaning McCloskey's 16,348 would be 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.12. While the *claims don't* require "tagging all the mRNA molecules" (Rep.12), *Petitioner's stated theory does* to motivate its combination with McCloskey. POR.33-36.

The Petition's arguments *rely on and require uniquely tagging every* mRNA in the cell: Petitioner argued POSITA would have been motivated to tag "*each*" sample polynucleotide to resolve amplification bias. Pet.53-55. Petitioner and its expert also represented that—before any modification—"Linnarsson describes a method which is designed to be applied to *substantially all mRNA molecules of a given cell.*" EX2022, ¶222 ('197's "sample polynucleotides" are thus "*substantially all* mRNA molecules of a given cell"); Rep.12 n.5; EX2021, 72. And Petitioner argued "solv[ing]"² amplification bias required tagging

² Petitioner also cannot recast its motivation from "*sol[ving]*" amplification bias (Pet.54) to simply "*reduc[ing]*" it. Rep.13-14. The Petition's motivation was premised on arguing that Linnarsson "notes a problem [of] potential amplification

“[e]very sample and the polynucleotides within every given sample... uniquely... before being amplified.” EX1002, ¶92; Pet.54 (“exact solution”); POR.33-36. Petitioner was master of its Petition and never argued modifying Linnarsson to tag *less than* “substantially all mRNA molecules” in the cell. It cannot about-face now. *Supra*, §I.A.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.13. While aspects of the Petition’s Linnarsson-McCloskey arguments were unclear (POR.19 n.8), Petitioner explicitly relied on a *7-nucleotide* barcode second tag, asserting “Linnarsson would be conceptually divided into two portions [including] one that codes for the unique molecule”—the latter being a “barcode [that] comprises *7 nucleotides*.” EX1002, ¶192; Pet.56 (citing EX1002, ¶192). Per Cooper, “a POSA could have... *use[d] th[os]e next 7 nucleotides to distinguish the tagged polynucleotide from other one from the*

bias” but “only *reduces amplification bias*, and it does not actually solve the problem.” Pet.54 (emphasis original). Petitioner argued McCloskey “provides the *exact solution*.” Pet.54-55.

same single cell.”³ EX1002, ¶192; EX2020, 37:9-47:15, 49:11-58:1, esp.57:8-58:1 (failing to identify any statement in EX1002 regarding barcode-length other than seven; the “only number I mention here specifically is 7”). But Petitioner now jettisons that argument in favor of a barcode of *any* length. Rep.13. This theory should have been “presented earlier...to make out a *prima facie* case of unpatentability.” *Juniper Networks, Inc. v. Swarm Tech. LLC*, IPR2021-01445, Pap.62, 28-29 (Feb. 7, 2023) (refusing to consider new “zone” theory where petition didn’t “mention or describe the[ir] use” or how they 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,” switching from the “common” frequency to the “modulating scheme” in its original reference, and then modified that scheme

³ Cooper’s emphasis (EX2020, 52:13-53:13) that he wrote “POSA could” (vs. “would”) doesn’t save Petitioner (this is its only obviousness mapping), but underscores Cooper’s failure to show obviousness. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015); *see also* EX1002, ¶242.

using other references “[r]ather than explaining how its original petition was correct”) (citation omitted); *Intelligent Bio-Sys.*, 821 F.3d at 1370 (similar).

Finally, unlike the ’197 proceeding, where Cooper’s opening declaration relied on “McCloskey II” for a longer barcode (EX2022, ¶¶251-255), the Petition and Cooper’s original declaration *never even mentioned* McCloskey II, which is not an exhibit here. EX2020, 58:2-22; *see also* EX1059, ¶85 (citing EX2011, ¶¶256-257). Nevertheless, Cooper *now improperly relies on McCloskey II to motivate lengthening the barcode*. EX1059, ¶85; *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). The same is true of additional opinions Cooper raised in that *other IPR but not here*, which Petitioner now complains *PO* failed to mention. Rep.14.

B. Petitioner’s Sequencing Arguments Fail

1. Petitioner Cannot Establish The Entire Tagged Polynucleotide Is Sequenced

(a) Petitioner’s Reply Arguments Should Not Be Considered

The Petition argued Linnarsson disclosed “sequencing” based on its sequencing of the “tagged polynucleotide,” which Petitioner equated to *the full-length cDNA molecules generated by reverse transcription*. Pet.44, 56-57. Far from “constru[ing]” the claims to require “sequencing the *entirety* of the ‘tagged

polynucleotide[s]’” (*cf.* Rep.3), the POR responded to ***Petitioner’s affirmative mapping of sequencing the entire polynucleotide.***⁴ “Linnarsson teaches that after generating ***the tagged polynucleotides, ‘sequencing is performed’ thereon.***” *Compare* Pet.57 with POR.22-23. Petitioner’s Reply now asserts Linnarsson discloses sequencing the entire “tagged polynucleotide” based on an improper new argument that Linnarssons’s fragmentation approach is *optional*. Rep.5. Petitioner’s new reply theory should be rejected. *Juniper*, IPR2021-01445, Pap.62, 28-29; *Wasica*, 853 F.3d at 1286; *Intelligent Bio-Sys.*, 821 F.3d at 1370. Even if considered, it fails.

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

Petitioner first argues, now, that “Linnarsson cannot possibly require fragmentation as in Figure 11” because Figs.3-4 “include neither a biotin nor a restriction enzyme cut site.” Rep.5-6. But Linnarsson indicates—including in its only two examples⁵ (Example I, which introduces Figs.2-4, EX1003, 23:9-25:6;

⁴ The Petition included no further explanation, or even an expert citation, to explain its mapping. Pet.56-57.

⁵ Examples I-II employ a biotinylated CDS, and a TSO with a restriction enzyme (Bts) cut site on the cell-tag’s 5’ end. POR.53; EX2013, ¶¶36, 89; EX1003, 23:9-19, 31:3-32:27; EX2020, 96:12-97:11, 118:5-8.

EX2020, 90:9-92:19, 94:8-97:11, 118:5-8 (Ex.I includes “fragmentation and capture”), and Example II, which introduces Fig.11, EX1003, 37:31-32)—that its STRT method includes both biotin and a restriction enzyme cut site (EX1003, 23:1-37:32).

Indeed, according to Linnarsson, Figs.3-4 show nucleotide sequences for a “typical” TSO and CDS and, consistent with Example I’s STRT disclosures, include, *inter alia*, a primer (APS), cell-tag, and Bts restriction site. EX1003, Figs.3-4; EX2101, 1. Cooper testified Figs.3-4 “do not contain **any** restriction enzyme cut site” (*e.g.*, EX1059, ¶¶66), and thus concluded these Figures show fragmentation is “optional.” EX1059, ¶¶33-44, 66. However, at deposition, he admitted that—although POSITA could—**he** did **no** investigation to see whether Figs.3-4 had any restriction enzyme cut site other than the specific example (for enzyme BtsCI) used in Fig.11 (which Cooper repeatedly argued was non-limiting). EX2020, 118:5-122:14; 123:11-124:21, 127:21-129:1 (no opinion whether Fig.11 works with other cut site), 133:19-137:10; EX1059, ¶¶33-44, 66. Ultimately, Cooper admitted that—although he’d “have to do more homework” to know, himself—an article with authors from an entity Cooper recognized as prolific in the field clearly identified **a restriction enzyme cut site (CGAGTG) that is present in Figs.3-4**. EX2020, 123:11-124:21, 125:5-22, 133:19-137:10 (“it’s from New England Biolabs, and that’s what they’re saying”); EX2101, 1. And 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. EX2020, 123:11-125:4, 129:2-7; Rep.5; EX1059, ¶31.

Cooper now also asserts Fig.2 does not employ fragmentation or biotin. EX2020, 76:13-77:9. But Fig.2, like Figs.3-4, is discussed only in the context of Example I, which includes biotin and fragmentation, and in no other embodiment of Linnarsson. EX1003, 23:1-24:20.

Petitioner’s final (new) argument regarding optionality of fragmentation involves Linnarsson’s dependent claim 27,⁶ which requires “the processing comprises fragmenting the cDNA library.” Rep.6; EX1003, 48:9-10. But even assuming, *arguendo*, this is a proper dependent claim narrowing the “***processing*** [of] the cDNA library to obtain a library suitable for sequencing” (EX1003, 48:7-8), this merely confirms that—as Cooper agreed would sometimes be required—

⁶ The only other disclosure Cooper identified—for the first time at deposition—as evidence of fragmentation’s supposed optionality was claim 1, which was cited only to argue written-description support for Linnarsson’s provisional. EX2020, 130:22-132:2, 132:7-133:15; *e.g.*, EX1002, ¶¶105-107. Even if considered, claim 1 does not exclude biotin or fragmentation: it is a “comprising” claim and simply silent on those features. EX1003, 46:3-12.

additional fragmentation (*e.g., after* preparation of the cDNA library, such as after Fig.11's fragmentation steps (EX2020, 101:9-103:7)) may be used to prepare the cDNA library for, *e.g.*, NGS. EX2020, 111:8-113:16. For example, Linnarsson uses DNase digestion generate 200-300 base-pair cDNA fragments in Fig.11. EX1003, 6:3-4. Cooper agreed POSITA would want optimally-sized polynucleotides for sequencing—and if that optimal size were under 200 base pairs,⁷ further fragmenting would have been needed. EX2020, 97:17-101:22, 111:8-113:16. Lastly, Linnarsson discloses another reason POSITA might further fragment the already-fragmented cDNA library—shotgun sequencing. EX1003, 22:5-21; EX2020, 103:8-19.

That Linnarsson fragments cDNA in preparing the cDNA library is confirmed by Linnarsson's "cDNA library" definition as "a collection of cloned complementary DNA (cDNA) *fragments*...." EX1003, 12:4-8; POR.23. Cooper's reply assertion that this "is merely stating that the cDNA will necessarily be a fragment of DNA since the RNA is itself just a fragment of nucleic acid" (EX1059, ¶71) would render Linnarsson's definition redundant: if cDNA is already "*necessarily [a] fragment*," Linnarsson's definition would refer to

⁷ Cooper identified NGS systems at the time that might read only "a few dozen" base pairs. EX2020, 97:17-98:20; EX1059, ¶8.

“complementary DNA (cDNA) [**fragments**] **fragments**.” And Cooper’s response that (plural) “fragments” merely stands-in for “molecules” to show the cDNA’s “numerosity” (EX2020, 108:17-111:3 (“at least two”)) is equally nonsensical: “molecules” and “fragments” are not synonymous in Linnarsson. *E.g.*, EX1003, 22:5-21 (“The *cDNA library* can be shotgun sequenced... In this method, the DNA to be sequenced is first shredded into *smaller* fragments which can be sequenced individually.”).

Petitioner’s arguments that PO and Quackenbush “ignore[d]” Figs.3-4 and dependent claim 27 (Rep.6-7) fail to acknowledge that the Petition did not mention claim 27, and *neither the Petition nor Cooper argued biotin was optional* based on those disclosures. The Petition did not even acknowledge that Fig.11 (which its mappings relied on, *infra* §I.B.1.a.ii.) employed biotin and fragmentation, let alone explain how or why those aspects of Fig.11 would be compatible with its proposed combination. Petitioner’s various citations to Quackenbush’s testimony (Rep.6; Rep.6 n.4) are, at best, misleading: Quackenbush *cited* Fig.4 (and Fig.3). EX2013, ¶¶37, 94-5; EX2020, 115:4-117:7 (Cooper backtracking from declaration position that Quackenbush “ignores Figures 3 and 4”: “if he did discuss them, he did not discuss them *to the degree that I felt they were warranting*”). And, Petitioner’s citation *cuts off* the rest of Quackenbush’s testimony confirming he considered and responded to Cooper’s Fig.4 arguments: “to the extent that Dr.

Cooper makes arguments about the cell tag appearing in the CDS, I discussed that in my response without necessarily explicitly calling out Figure 4.” EX1057, 138:1-25. Moreover, Quackenbush didn’t testify that Fig.4 was not part of Fig.11—he testified it was an alternate form of Fig.11’s CDS that could include the cell tag. *Id.*

These embodiments do not disclose other approaches, and thus, even if considered, Petitioner’s new evidence fails on the merits.

**(ii) Petitioner Relied On Examples Using
Fragmentation And Biotin**

Regardless of whether Figs.2-4 require fragmentation and capture, Petitioner cannot now cast Linnarsson’s fragmentation as “optional” *because its Petition affirmatively relied on Linnarsson’s fragmentation disclosures*. Petitioner’s and Cooper’s Ground 1 analysis, for example, *repeatedly relied on Fig.11* (reflecting Example II’s method), which indisputably incorporates the fragmentation approach. Pet.41-42, 45-47 (mapping Fig.11 to [1C], [1D]); EX1002, ¶¶139-141, 143, 153-156, 163-166 (same, to [1C], [1D], [1E]); EX2020, 59:1-64:2, 77:11-84:17 (admitting reliance on Fig.11 for [1C], [1D], [1E]); *see also* EX2020, 103:20-106:5 (mapping other fragmentation disclosures), 113:17-114:13. They both also *repeatedly equated Figs.2 and 11*, and *treated them and Figs.3-4 as a single embodiment*. Pet.26-29, 41-42 (“As shown in Figures 2 and 11... Figure 11... *discloses the same...*”), 42-43 (“As shown in Figure 2 below, a TSO...

Figure 11 discloses the same... Figure 3... similarly discloses that the TSO...”), 45-47; EX1002, ¶¶139-141, 143, 153-156, 163-166; EX2020, 82:7-84:17.

Moreover, both included the biotin molecule in their mapping callouts for Fig.11’s CDS. *E.g.*, Pet.41; EX2020, 77:11-78:20. Petitioner’s new suggestion that these are now separate, distinct embodiments (some using biotin/fragmenting, and some purportedly not) is contradicted by Petitioner’s and Cooper’s mapping. Further, Petitioner never provided the necessary explanation of which elements from which embodiments are to be combined.⁸

That Cooper “didn’t view [biotin (or fragmentation)] as germane to” his mapping does not mean reliance on these features were excluded, nor did Cooper assert they were. EX2020, 76:13-78:19. Even assuming Figs.2-4 do not require biotin or a cut site, Petitioner still identifies no complete method (from tagging

⁸ Cooper *conceded* he relied on what he considers multiple embodiments, but never explains how and why POSITA would mix-and-match across them. EX2020, 47:17-48:15 (arguing “lots of optionality”), 76:13-78:19, 84:11-90:1; *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...”).

through sequencing) using Figs.2-4 without those steps.⁹ Rep.6; Pet.56-57. As

Quackenbush explained, Linnarsson's biotin is critical, allowing for tagged polynucleotides to be isolated from untagged polynucleotides (*e.g.*, DNA).

EX2013, ¶90. Without such purification, tagged *and* untagged polynucleotides would be sequenced and the information would be muddled. *See* EX2013, ¶90;

Parse Biosciences, Inc. v. 10x Genomics, Inc., IPR2023-00955, EX2020, 15:8-13.

2. Petitioner's Reply Arguments About Sequencing A Portion Of The Tagged Polynucleotide Are Improper And Fail To Meet Their Burden

Petitioner's Reply arguments that this limitation is met by sequencing only a *portion* of the tagged polynucleotide should not be considered. *See* Rep.4-5; *supra* p.1.

Even if considered, Petitioner failed to establish that some (undefined) portion of the tagged polynucleotide was sequenced. First, Cooper testified that only *some portion* of a tag needs to be sequenced. EX2020, 15:7-17:2. But if only a *portion* of, *e.g.*, the second tag were sequenced, that sequencing would reflect far fewer than 16,348 unique tags (*e.g.*, if only the first five bases of two second tags, GTCCTA A and GTCCTT T, were sequenced), and thus could uniquely identify even *fewer* sample polynucleotides. *See supra*, §I.A.3. Further, Cooper admitted

⁹ *See* n.8.

that some of the tagged polynucleotide corresponding to the sample polynucleotide would need to be sequenced. EX2020, 17:4-15; EX1001, Cl.1(c)-(e). But the Petition (and Reply) failed to address how much of the sample polynucleotide would need to be sequenced, or attempt to show Linnarsson's methods would sequence enough of it. *See* POR.22-26.

Lastly, with respect to ligating to the CDS specifically, Petitioner admits Fig.11 does not sequence a CDS, but now first argues the "CDS... is sequenced" in Fig.4 because it "*can* include a cell tag." Rep.7-8 (emphasis original). The Petition never identified any embodiment disclosing sequencing of Fig.4, and Example I (the only example in which Fig.4 appears) does not sequence the CDS. Pet.56-57; EX1003, 13-19, 26:22-27:9; EX2013, ¶¶36, 41. Additionally, Petitioner's citation to Linnarsson "identif[ying]" cDNA using a cell tag does not establish *sequencing* it. Rep.7 (citing EX1003, 19:4-11). And Petitioner's second citation, which is about Fig.1, does not mention a CDS, let alone show it includes a tag that is sequenced. Rep.7 (citing EX1003, 22:22-28); *see also* POR.24 (citing EX003, 4:8-13 (describing Fig.1); EX2013, ¶58).

C. Petitioner's "First Tag" Theory Is Unclear

The Reply newly argues Petitioner's "first tag" analysis was "was based on Linnarsson...." Rep.8, 14. The Petition (and Institution Decision, at 21-22) relied on Cooper's theory that POSITA would have "conceptually divide[d]...

Linnarsson’s cell-tag sequence into two portions, *wherein the first portion performs the function of McCloskey’s batch-stamp....*” EX1002, ¶192. But Petitioner now disclaims that theory in Reply. Rep.9 (“Petitioner relies upon McCloskey for the ‘second tag sequence’”). This backtracking underscores the Petition’s failure to present its Grounds with particularity and is an independent reason to reject Petitioner’s invalidity arguments. POR.26-28, 43 n.15; *adidas AG v Nike, Inc.*, IPR2016-00922, Pap.31, 51-53 (Feb. 19, 2019) (“Judges are not like pigs, hunting for truffles buried in briefs.”) (quoting *U.S. v. Dunkel*, 927 F.2d 955, 956 (7th Cir. 1991)).

II. Ground 2: Petitioner’s Conclusory Ligation Combination Fails

Petitioner confuses elementary patent law. That “ligation” is a conventional technique does not mean any and all uses of ligation are automatically trivial or would work (particularly without specific explanation) in any and all approaches. Petitioner’s improper new reply theories on how its original proposed combination might be *further modified* to accommodate ligation simply confirm ligation doesn’t work in its original combination. Rep.24.

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

Petitioner does not 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 as explained in the POR. Rep.22-24. Instead, Petitioner argues (1)

Linnarsson does not require biotin and fragmentation, (2) “bodily incorporat[ion]” is not required, and (3) *additional modifications* would allow ligation to work.

Rep.22-24

Argument (1) is new, and is wrong for the reasons above (§I.B.1.a). Indeed, Petitioner and its expert *expressly relied on Fig.11’s embodiment employing biotin and fragmentation*, and Petitioner has not explained how Linnarsson’s method would work without biotin or fragmentation. *Supra*, pp.15-16.

Additionally, Petitioner’s reliance on the statement that “[a]rbitrary sequence[s] can be *inserted* at the 5’ end of the TSO, after the 5’ APS, or after the cell-tag...” is misplaced. Rep.23. 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.67).

With respect to (2), Petitioner mischaracterizes PO’s argument. Rep.24. PO’s REOS argument does not assume “bodily incorporat[ion].” POR.52-59. Rather, without further modification *to the Linnarsson base reference*, and a motivation for that modification and REOS, ligation fails. *Juniper*, IPR2021-01445, Pap.62, 26-28 (rejecting argument patentee “engag[ed] in an improper bodily *incorporation*” where patentee explained 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 Board’s determination teachings of references “could not be combined because...Binladen’s indexing (i.e., tagging) scheme could not be used with Dhallan’s restriction-digestible amplification primers.”); n.8.

Lastly, with respect to (3), Petitioner’s biotin modifications (*e.g.*, adding biotin after ligation, or including it with the ligated barcode) and cut site modifications (*e.g.*, modifying its location) were not in the Petition. Rep.24; *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) (discounting reply arguments, stating “[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 regarding proposed combination). Even 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.24; POR.59-60. Further, as PO explained (POR.46-52), POSITA would not have been motivated to make Linnarsson’s approach more complex merely to achieve “an equivalent method.” POR.46-50

(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). Petitioner’s inclusion of new Reply modifications (Rep.24) is also a concession that, without them, ligation would fail.

B. Petitioner Does Not Contest Ligation Adds Steps And Complexities To The Linnarsson-McCloskey Method

While Petitioner devotes pages to ligation’s “conventional[ity]” (Rep.18-20), this does not mean POSITA would have been motivated to ligate 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 in the art.” *Id.* at 886-88.!

Petitioner’s citation to *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) supports PO. Rep.24. 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.52-59; *infra*, §III.C. 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 ’981 does not say ligation

to a biotinylated nucleic acid as used in Linnarsson was routine and conventional.

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.52-59)). And in *Ball Aerosol & Specialty Container, Inc. v. Ltd. Brands, Inc.*, 555 F.3d 984, 992-93 (Fed. Cir. 2009) there was no dispute about REOS.

Substantively, Petitioner points to Cooper’s vague “flexibility” argument, but improperly flips the burden, arguing *PO* could have cross-examined Cooper for details. Rep.20; §316(e). And even after Cooper submitted a *second* declaration, his supposed “flexibility” benefit fails as unclear and conclusory. Rep.21; *Virtek*, 97 F.4th at 889 (reversing Board’s obviousness conclusion resting on “conclusory testimony” for motivation to combine). For example, Cooper argues that if one needs to tag a small number of molecules, then shorter barcodes could be used. EX1059, ¶102. But Petitioner doesn’t explain how such “**added** flexibility” is specifically achieved **by ligation** (as opposed to, *e.g.*, Petitioner’s Ground 1 theory). 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 entire purpose is to **determine that number of molecules in the**

sample. EX1059, ¶102; EX1001, Cl.1.

C. Petitioner’s New “Ligate To The Sample Sequence” Theory Is Late, And Fails

Petitioner’s original ligation theory was clear in one respect: the sequence is ligated “to the CDS or TSO.” Pet.67-68; Rep.23-24. But on Reply, instead of ligating the “second tag” to the CDS or TSO, Cooper now claims his theory was to ligate it to the sample sequence after extension. EX1059, ¶¶113, 115. This is new and improper—but, even if considered, Petitioner’s theory fails to explain how those modifications would work.

D. The Claims Are Not Practiced If Ligation Happens After Amplification

Petitioner’s arguments that the “claims have *no requirement* as to ligation timing” (Rep.17) ignores Petitioner’s burden to prove motivation and REOS. As the POR detailed, the claims are not practiced (and Petitioner’s motivation to eliminate amplification bias cannot be satisfied) if, *e.g.*, ligation occurs after amplification because, at that point, the second tag cannot distinguish between pre-amplification polynucleotides and amplified polynucleotides. EX1001, Cl.1; EX2020, 139:21-140:20 (conceding “it must occur prior to amplification”).

But contrary to his suggestion at deposition (*id.*), Cooper’s reply addresses timing for the first time, arguing “[t]here cannot be any confusion [as to timing] because I proposed to carry out ligation using linker sequences as set forth in prior

art such as the *Hug* reference....” EX1059, ¶113; EX2020, 137:11-141:4; EX2018, 54:8-21 (“I *did not explicitly say a timing element* there...”). But Cooper testifies “Hug is *not* a reference used as a basis for the grounds of my opinion,” and is only “one of four exemplary methods for ligation”¹⁰ (EX1059, ¶119 (emphasis orig.)), and thus cannot supply the missing timing details. (Cooper admits he did not provide analysis of how any other “exemplary method[]” would impact ligation timing. EX2020, 139:21-141:8.) Moreover, Cooper testified that “there would be options in terms [of] when exactly [ligation] occurred prior to amplification.” EX2020, 139:21-140:20. But there is no explanation as to whether or how ligation would be achieved at any of these “options,” or what further steps or other modifications might be required. *Id.*

III. Cooper’s Inconsistent Opinions Should Be Given Little To No Weight

Cooper repeatedly mischaracterized his prior report (EX1002) and contradicted his own testimony on the same references from related proceedings. For example, Cooper would not agree with *verbatim quotes* of his opinions in the

¹⁰ Cooper then offers modifications to Hug despite asserting it is not part of his combination. EX1059, ¶122; EX2020, 141:9-145:17. These modifications are new (EX2020, 141:20-143:22) and further confirm Petitioner’s failure to lay out its grounds with particularity. POR.43 n.15.

related '197 IPR (EX2022, ¶222) regarding POSITA's understanding of Linnarsson. EX2020, 28:18-36:14 (refusing to agree with quotes from prior declaration). Cooper similarly claimed he had "repeatedly" asserted in EX1002 that it would have been obvious to expand McCloskey's barcodes to different lengths, based on his citation to a page of McCloskey that "includes the 4n paragraph – which includes the 4n definition for the barcode"—but he *could not find even a single mention* of this "4n language" in EX1002. EX2020, 36:19-58:1, esp.39:18-41:13, 50:9-18. Because Cooper is simply not credible—*compare e.g.*, EX2018, 54:8-21 ("I *did not explicitly say a timing element* there...") *with* EX1059, ¶113 ("*As clearly discussed* in my original declaration, the second tag is ligated... *after the first reverse transcription step*...")—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").

IV. Grounds 1 and 2: Petitioner's Belated "McCloskey" Evidence Fails

Petitioner's attempt to cure its evidentiary failings regarding McCloskey *on reply* fail. Rep.3. The Petition asserts only that McCloskey was published online in October 2007, citing EX1028. Pet.29. But EX1028, Dr. Hall-Ellis's first declaration, *does not even mention McCloskey*, let alone establish prior art status. *See generally*, EX1028. PO timely objected to both McCloskey and EX1028, but

Petitioner *did nothing*. Pap.11, 1-2. Months after the POR, Petitioner belatedly included (without authorization) evidence to cure this failing, using a declaration pre-dating the Petition. Rep.3 n.2; EX1065. 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 to fix it. *Id.* Petitioner’s reliance on *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Pap.29, 15 (Dec. 20, 2019) (precedential) (Rep.3) fails: Petitioner’s new declaration is not “responsive” to PO’s assertion (and, as noted below, is also improperly incorporated by reference). POR.18; *Sirius XM*, IPR2018-00690, Pap.63, 13-15.

Petitioner’s Reply arguments that McCloskey was published online in October 2007 (Rep.3 (citing Pet.29)) 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 here should follow *Medivis*: a copyright date “is not sufficient [even] at... institution... to demonstrate public accessibility”—the same evidence is certainly deficient post-institution. *Medivis, Inc. v. Novarad Corp.*, IPR2023-00042, Pap.35, 27 (Mar. 6, 2024). As in *Medivis*,

the only other record argument is an unsubstantiated assertion the reference appeared online; this is insufficient, particularly without further evidence the reference was *accessible*. *Id.* at 28-30. Lastly, as in *Medivis*, the Reply’s citation ***without discussion*** to the improper Hall-Ellis declaration is improper incorporation by reference, and should not be considered. *Id.*

V. Grounds 1 and 2: Petitioner’s Improper New Analogous Art Arguments

Notwithstanding Cooper’s new claim he *already* provided a detailed explanation of how the asserted art was analogous to ’981 in his opening declaration—which fails the straight-face test (EX2020, 19:16-28:5)—Petitioner doesn’t dispute the Petition failed to analyze whether its art was analogous to ’981. Rep.24-25 (no Petition cites). Far from waiting for PO to raise the issue, and then respond, the Petition here affirmatively argued analogousness but failed to carry that burden (Pet.52)—and the POR noted that error without inviting a broadening reply. *Cf. Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1009 (Fed. Cir. 2023) (discussing prior decision that “petitioner is ***not required to anticipate and raise analogous art arguments in its petition***; instead a petitioner can use its reply’ to respond”), 1004-10 (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 (March 2, 2021), 25. The Board should not now permit Petitioner to rewrite its clearly-deficient Petition.

VI. Conclusion

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

Respectfully submitted: /J. Steven Baughman/ May 10, 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 5,590
words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

Dated: May 10, 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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