

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

Case No. IPR2023-00955
U.S. Patent No. 10,240,197

**PETITIONER'S REPLY
TO PATENT OWNER'S RESPONSE**

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I. INTRODUCTION

Patent Owner parrots the same meritless arguments from a parallel proceeding on another Brenner patent. *See* IPR2023-00876, Paper 13. Accordingly, this reply largely mirrors portions of Petitioner’s reply from that proceeding. *See* IPR2023-00876, Paper 22. That being said, there is meaningful new evidence in the form of Dr. Quackenbush’s District Court reports, where he repeatedly acknowledges that the allegedly inventive aspects of the ’197 patent are ***described in the prior art***. *See e.g.* EX1084. Dr. Quackenbush, for instance, affirms that ligation was a “conventional technique.” *Id.* ¶ 327. And, with regard to the allegedly inventive dual tagging method, Dr. Quackenbush affirmed that ***multiple*** prior art references “disclose the use of unique tags to identify the origins of a sample polynucleotide and to distinguish it from other polynucleotides from the same cell.” *Id.* ¶ 332.

Dr. Quackenbush’s assertions to this effect are unsurprising and are consistent with Patent Owners numerous previous assertions that tagging nucleic acids for tracking purposes was “as old as the scientific method” and “familiar to every student in any introductory science class.” EX1016.009; Petition at 12-14. Patent Owner even said this about the concept of ***dual-tagging***¹, *see* Petition at 13-14,

¹ Emphasis supplied unless otherwise noted.

which is supposedly the central feature of the '197 patent claims. Patent Owner still does not deny or explain away these prior assertions.

Far from it, when Patent Owner's expert, Dr. Quackenbush, was asked during deposition, what was inventive in the '197 patent, he said "I'm not really prepared to offer an opinion." EX1069 at 14:4-15, 13:1-10; *see also* EX1071² at 190:3-18, 203:21-204:5. If anyone should be "prepared" to say *something* about what might be inventive in the '197 patent, it is the Patent Owner's expert.³ Of course, the

² Dr. Quackenbush reaffirmed his testimony from the related '981 IPR as accurate and relevant to this proceeding. EX1069 at 8:3-9:6, 10:1-8.

³ The frequency with which Dr. Quackenbush purported to have no opinion on fundamental and basic issues is remarkable and underscores Patent Owner's weakness on the merits. *See, e.g.*, EX1069 at 10:9-11:1, 13:1-10, 13:16-14:3, 29:20-30:8, 31:9-17, 35:8-36:10, 38:9-39:25, 40:23-41:21, 45:14-18, 46:3-11, 58:13-61:11, 63:21-64:1, 64:12-18, 65:3-66:5, 68:5-69:10, 87:8-19, 100:4-14; *see also* EX1071 at 15:10-25, 16:8-17:3, 20:25-22:15, 23:1-8, 29:6-13, 59:21-60:6, 69:3-25, 73:6-74:8, 75:3-7, 75:8-22, 76:11-21, 77:17-79:11, 79:23-80:19, 92:6-12, 99:11-101:13, 128:5-25, 130:7-132:11, 132:21-133:10, 134:10-135:6, 141:9-18, 147:25-149:2, 149:10-151:2, 151:3-12, 151:18-152:2, 154:1-10, 164:15-165:9, 172:9-173:20, 173:22-174:6, 175:7-176:21, 177:10-179:16, 180:19-181:5, 189:21-190:18, 190:24-191:8, 198:14-199:19, 214:7-19.

reason Dr. Quackenbush ducked the question is not because he was not “prepared” to answer, but because there is nothing non-obvious in the ’197 patent.

As confirmed here, Petitioner has easily met its burden of showing that the claims of the ’197 patent are invalid.

II. REPLY REGARDING GROUND 1

A. McCloskey Is Prior Art

Patent Owner argues Petitioner failed to establish McCloskey is prior art. POR at 21. The Petition, however, states that McCloskey was published online in October 2007 and is hence prior art under § 102(a) and (b). Petition at 29. Patent Owner never disputes this publication date, which appears on the face of McCloskey. EX1004.001. Nonetheless, Dr. Sylvia Hall-Ellis in her non-hearsay testimony confirms McCloskey’s public availability and prior art status. *See* EX1085 ¶¶ 44-45, 50 (“...it is my opinion that the McCloskey article...was publically available on or shortly after January 3, 2008...”). Submitting a supporting declaration is allowed on reply. *See, e.g., Hulu v. Sound View Innovations*, IPR2018-01039, Paper 29 at 15 (P.T.A.B. Dec. 20, 2019) (precedential).

B. Sequencing “Entire” Tagged Polynucleotide Is Not Required, Nor Does Linnarsson Require Fragmentation

Patent Owner contends that Petitioner has somehow advanced a construction of claim [1G] that requires sequencing “the *entire tagged polynucleotide*” and that

the Petition is somehow premised on this. POR at 26-27. Petitioner, however, has never said any such thing, either here or in parallel district court proceedings. EX1072.

Petitioner cites ¶ 176 of Dr. Cooper's declaration to support its position about what is sequenced in Linnarsson. *See* Petition at 44. There, Dr. Cooper merely stated that a "POSA would have understood that the sequencing step of Linnarsson discloses determining the sample sequence, the first tag sequence, and the second tag sequence." Nothing about this statement suggests that either Petitioner or its expert believes the claims *require* sequencing the "entire" tagged polynucleotide, nor does it suggest that the Petition is fundamentally premised on sequencing the "entire" tagged polynucleotide. All it shows is that Dr. Cooper believes the prior art shows sequencing capable of capturing sequence information from the tags and sample, a point Dr. Cooper confirms in the declaration submitted herewith. *See* EX1070 ¶¶ 77-92. Petitioner's own expert, Dr. Quackenbush, cannot dispute this because he has admitted that sequencers in 2009 were capable of reading "around 300 nucleotides" in a single read, which is more than sufficient to generate sequence information from the tags and sample. EX1079 ¶ 97. This is all that the claims require.

Patent Owner, for its part, cites no intrinsic evidence to justify construing the claims to require sequencing the “entire” tagged polynucleotides. POR at 26-32. Indeed, the claims do not recite sequencing “entire” polynucleotide(s). As Dr. Cooper explains, a POSA would understand that “sequencing” a polynucleotide simply calls for generating sequence information from the polynucleotide, not sequencing the *entire* molecule. EX1070 ¶¶ 8-9, 75-106. While Patent Owner suggests in its response that the claims require sequencing the “entirety” of the tagged polynucleotide, it has since thoroughly disavowed any such suggestion. Indeed, Patent Owner’s own expert has explained in district court that the “claims *do not* require sequencing the entirety of the tagged polynucleotides.” See IPR2023-00876, Paper No. 36 & EX1067 ¶ 161. This turnabout is unsurprising because, in fact, the evidence that the claims do not require sequencing “entire” tagged polynucleotides is overwhelming. See EX1070 ¶¶ 23-32, 77-92; see also EX1069 at 12:12-19, 67:16-22, 68:16-17:2; EX1071 at 75:3-7, 78:15-24, 80:8-19, 171:24-172:19, 173:8-20.

Nevertheless, even if such a construction were adopted, Patent Owner’s contention that Linnarsson does not disclose sequencing “entire” polynucleotides should be rejected because it is based on the mistaken view that Linnarsson requires the fragmentation approach of Figure 11, which fragments the sample DNA and uses

biotin to capture the ends of the DNA fragments. POR at 27-29. A restriction enzyme is later used to release the captured DNA for sequencing. EX1003 at Fig. 11. The biotin and restriction enzyme are part-and-parcel for the fragmentation-based approach in Figure 11 of Linnarsson. EX1003.006-.007.

Patent Owner's heavy reliance on Figure of 11 as being Linnarsson's sole embodiment is a major error. Indeed, Linnarsson is clear that the steps of Figure 11 are optional, stating "Figure 11, panels A-F, show graphical representation of steps *optionally used* in the STRT method." EX1003 at 5:28-29. Dr. Cooper confirms Linnarsson does not require fragmentation. EX1070 ¶¶ 33-61, 93-106; EX2020 at 9:2-21:13; EX2018 at 23:4-14, 28:2-11, 30:3-31-11. Importantly, the CDS and TSO in Figures 3 and 4 of Linnarsson—which are cited throughout the Petition—include neither a biotin nor a restriction enzyme cut site.⁴ EX1070 ¶¶

⁴ Patent Owner in IPR2023-00876 has belatedly argued that Figures 3 and 4 include a sequence for a restriction enzyme known as BtsI. This, however, is irrelevant because Linnarsson does not use or ever mention this enzyme, but rather uses a *different* enzyme—BtsCI. EX1070 ¶¶ 57-58. The appearance of the BtsI sequence in Figures 3 and 4 is mere coincidence. Indeed, Petitioner's expert confirms there are "probably tens of thousands of restriction enzymes" that can be "easily found" on the internet. EX1069 at 22:6-24:6. Websites exist that identify restriction enzyme cut sites in arbitrary sequences. *See, e.g.,* <https://nc3.neb.com/NEBcutter/>. Analysis of the relevant sequence from Figure 3

44-50; 96-98; Petition at 18-19, 30-32, 48. As such, Linnarsson cannot possibly require fragmentation as in Figure 11, as Petitioner contends. EX1070 ¶¶ 44-61, 93-106.

This is excruciatingly clear from claims of Linnarsson, which recite “fragmenting,” only in *dependent* Claim 27. Notably, claim 27 depends from dependent claim 26 which recites “processing the cDNA library to obtain a library suitable for sequencing.” If Linnarsson required fragmenting, this would not be an optional feature of a *dependent* claim. *id.* ¶¶ 61, 106. Patent Owner and its expert ignore all of this. Dr. Quackenbush confirmed he did no analysis of Linnarsson’s claims. EX1069 at 40:1-18; EX1071 at 149:10-151:2, 164:15-165:9.

Moreover, as Dr. Cooper explains, even when it comes to fragmentation, it can be done in various ways such that the “full complement of fragments” shredded from the original tagged polynucleotide can be subjected to sequencing and reassembled to read the original tagged sequence. EX1070 ¶¶ 52-53, 78-83.

shows that it happens to include cut sequences for *numerous* different restriction enzymes. *See* EX1073. Thus, the mere coincidental existence of a restriction enzyme sequence in Figures 3 and 4 does not remotely evidence intent to use those sequences, particularly where, as here, Linnarsson calls out BtsCI, but *never* BtsI.

Patent Owner next asserts any theory that relies upon the CDS “fails” because Linnarsson does not sequence the “entire” tagged polynucleotide and omits sequencing of the CDS. POR at 31. This also mischaracterizes Linnarsson. True, in Figure 11 of Linnarsson, the CDS is not sequenced. But this is unsurprising because Figure 11’s CDS *does not* include a cell tag. There is no point sequencing Figure 11’s CDS because it supplies no information associating the fragment with a particular cell.

But, as Dr. Cooper explains, Linnarsson’s CDS *can* include a cell tag. EX1070 ¶¶ 44, 46, 100. A CDS with a cell tag is taught in Figure 4. EX1003 at Fig. 4. Linnarsson makes clear, where a cell-tag *is* included in the CDS, it is sequenced and used for identification. *Id.* at 19:4-11, 22:22-28. Dr. Quackenbush confirmed that this is precisely what the cell tag is used for. EX1071 at 137:14-19, 151:18-153:5. Thus, it would make no sense to include a cell tag in the CDS only to never determine its sequence and completely ignore it. EX1070 ¶¶ 44-46, 100-101.

C. A POSA Would Have Been Motivated To Combine Linnarsson and McCloskey

1. Petitioner’s Insufficient Number of Tags Argument Is Without Merit

Patent Owner’s primary response on motivation to combine is that “*McCloskey does not have enough barcodes to tag each mRNA molecule of*

Linnarsson.” POR at 34 (emphasis in original). Patent Owner states that it “would be impossible, using McCloskey’s 7-nucleotide barcode (amounting to only 16,348 unique barcodes), to distinguish the 50,000–300,000 mRNA molecules Petitioner admits POSITA would have expected to be present in a mammalian cell.” *Id.* at 35. This argument fails several times over.

First, Patent Owner’s “50,000-300,000” figure is solely for a *mammalian* cell. *Id.* But nothing in the claims of the ’197 patent or Linnarsson’s disclosures requires tagging all the mRNA molecules only in a *mammalian* cell. Linnarsson states that its method can be used with the simplest possible cells, explaining that “in general, cells from any population can be used in the methods, such as a population of prokaryotic or eukaryotic single celled organisms including bacteria or yeast.” EX1003 at 13:14-16. As Dr. Cooper explains, bacterium are known that contain only a little over 1,000 mRNA molecules (or even far less), such that the 16,384 tags used in McCloskey’s example is sufficient to tag all the mRNA molecules in such a sample.⁵ EX1070 ¶¶ 121-122.

⁵ In related IPR2023-00876, Patent Owner has argued for the first time on sur-reply that McCloskey’s barcode cannot tag mRNA molecules in bacteria because they cannot be polyadenylated. This is wrong. See EX1070 ¶ 123; EX1082;

Second, even assuming the claims required tagging mRNA from a mammalian cell, they do not require tagging *all* the mRNA molecules in such a cell, as the Patent Owner contends. They only require tagging the “sample polynucleotides,” which is a subset of molecules from the cell. EX1001 at claim 1. This is indeed Patent Owner’s own position. In District Court, for instance, Patent Owner asserted that the “‘sample polynucleotides’ are the polynucleotides in a cell that are being sampled (i.e., the polynucleotides of interest), not all polynucleotides of that cell.” EX1072 at 23. According to Patent Owner, to “argue that ‘sample polynucleotides’ means every polynucleotide of the cell would rewrite the claim and replace ‘sample’ with ‘all.’” *Id.* at 24. Patent Owner contention that Linnarsson requires tagging “substantially all mRNA molecules in a cell,” is incorrect. POR at 8. Dr. Cooper explains that Linnarsson’s design is capable of tagging all mRNA molecules but is not limited to such a method. EX1070 ¶ 127.

Third, while Petitioner argues that the use of “16,384 barcodes would not be enough to tag each mRNA molecule in Linnarsson,” POR at 35, McCloskey’s

EX1083.002 (“Polyadenylation is an important post-transcriptional modification of prokaryotic...RNA”).

disclosure is not limited to 16,384 barcodes. This is just an example in McCloskey. In fact, McCloskey includes a general formula for how long the barcodes must be to distinguish a specific number of molecules:

The number of distinguishable barcodes in a population of oligonucleotides used in a reaction is determined by the number of random bases, n . This enables one to distinguish among 4^n allele copies per reaction. We currently use seven nucleotides for the barcode, giving 16,384 possible barcodes for each encoding oligonucleotide.

EX1004.004. As Dr. Cooper explains, given this disclosure, a POSA would not interpret McCloskey as being narrowly limited to a specific approach based on the use of just 16,384 barcodes. EX1070 ¶¶ 62-70, 116-129. Dr. Quackenbush likewise confirmed that a POSA would know how to use “labels of different lengths depending on their purposes.” EX1069 at 61:20-22, *see also id.* at 58:13-62:15.

Finally, and related to the foregoing, Patent Owner’s reliance on ¶ 255 of Dr. Cooper’s declaration simply undermines their position. POR at 36 n.20. Dr. Cooper merely opines on what would “ensure” unique tagging of every molecule in a mammalian cell. EX1002 ¶ 255. But, the claims of the ’197 patent do not require that one “ensure” such tagging and, as noted above, are not limited to mammalian cells either.

But more importantly, Patent Owner neglects to inform the Board that Dr. Cooper's opined that even where one needs to tag many molecules as in a mammalian cell, it would have been obvious to increase the tag length to capture more molecules. *Id.* ¶¶ 254-55. Dr. Cooper opines that a POSA "would have easily designed tag sequences comprising 20-30 random nucleotide bases, which would allow the creation of 4^{20} - 4^{30} unique barcodes distinguishing among 1,099,511,627,776-1,152,921,504,606,846,976 polynucleotides." *Id.* ¶ 255.

2. Petitioner's Argument That McCloskey Does Not Describe Single Cell Analysis Is Without Merit

Patent Owner's argument that McCloskey "is not focused on single cell analysis" is irrelevant and meritless. Whether McCloskey "focuses" on a topic is irrelevant. What matters is whether McCloskey clearly teaches single cell analysis. It does. As McCloskey states, "[w]e recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs for forensic, clinical, *single cell*, and ancient DNA analyses." POR at 38; EX1004.004, .007; EX1002 ¶¶ 117, 160; EX1002 ¶¶ 130-133.

D. Patent Owner's Theory For The "First Tag Sequence" Is Clear, And McCloskey Discloses Such A Sequence

Patent Owner contends that Petitioner maps the "'first tag sequence' inconsistently" and McCloskey does not disclose the "first tag sequence." POR at

41-46. There is, however, no inconsistency, and Patent Owner's other arguments on McCloskey are incorrect and irrelevant.

Patent Owner's claims of confusion about Petitioner's theory for the "first tag sequence" are belied by the very first pages of the Petition. There, Petitioner states that its obviousness theory was based on Linnarsson disclosing the "first tag sequence" and McCloskey disclosing a "second tag." Petition 2-3 ("To the extent Linnarsson does not teach a second tag to distinguish among different molecules, this concept is undeniably taught in McCloskey...").

The Petition unambiguously states for element [1E] that "Linnarsson discloses that the tag polynucleotide comprises a *first tag sequence* with the single cell from which the sample polynucleotide is derived." *Id.* at 36. For element [1F], Petitioner does not "change its mapping" "mid-claim" and "abandon" Linnarsson in favor of McCloskey for the "first tag sequence." POR at 41, 43. Rather, Petitioner relies upon McCloskey for the "second tag sequence," stating "McCloskey teaches a second tag sequence (i.e., the barcode) distinguishing a sample polynucleotide (e.g., cDNA) from other sample polynucleotides derived from the same single cell." Petition at 38. Further, even the rationale underlying Petitioner's obviousness theory evidences that McCloskey's is relied on for the "second tag sequence." Petition at 40 (Linnarsson discloses the problem of

“potential amplification bias,” and “McCloskey’s method of including a *second tag sequence* on the oligonucleotide to distinguish sample polynucleotides derived from the same single cell solves this problem.”).

Patent Owner nonetheless goes on to argue that McCloskey’s “batch-stamp” is not a “cell tag” that can be used for “single cell analysis.” POR at 43-45. This is both incorrect and irrelevant for reasons aforementioned. *See supra* Part II.C.2. Nevertheless, McCloskey’s teaching of a “cell tag” is of limited relevance here because, as documented above, the Petition relies on Linnarsson for the claimed “first tag sequence.”

Petitioner next contends that a POSA would not modify Linnarsson’s cell-tag using McCloskey’s batch-stamp because Linnarsson’s cell tags include a particular benefit that McCloskey’s batch stamps allegedly do not offer, specifically, a design that prevents one barcode from being converted to another by a single amplification or transcription error. POR at 44-45. This makeweight argument is irrelevant and barely needs a response. Even if Petitioner were relying upon McCloskey’s batch stamp in the way Patent Owner contends, neither logic nor law suggests that a motivation to combine is lacking unless both Linnarsson and McCloskey offer the same particular benefits. EX1070 ¶¶ 112-115. As the Petition and Dr. Cooper explain, a POSA would be motivated to combine McCloskey with Linnarsson to

address PCR amplification bias, which was a well-understood problem with a well-understood solution. Petition at 40-42; EX1002 ¶¶ 89-93, 164-167. Patent Owner does not dispute that using barcodes to overcome amplification bias would have been one of the standard techniques in a POSA's toolkit. EX2013 ¶ 25; EX1071 at 33:8-13, 33:18-34:17, 63:8-64:16.

E. Petitioner's Response Regarding Claims 8 And 23-25 Are Without Merit

Patent Owner's arguments on Claim 8 are baseless. POR at 46. Patent Owner does not deny that Linnarsson's CDS hybridizes to the sample polynucleotide or contend that Linnarsson imposes any limitation that TSO cannot be hybridized to the sample polynucleotide and extended. *Id.* More importantly, Petitioner's expert recognizes that "hybridization using a label" is a conventional technique in the '197 patent. EX1069 at 31:9-32:3. Patent Owner's arguments on Claims 23-25 are likewise without merit for the reasons addressed in Part II.C.1.

III. REPLY REGARDING GROUND 2

A. The Rationale Of Ground 2 Is Straightforward And Clear

Patent Owner's contention that Ground 2 does not "clearly and consistently identify its actual combination" is just willful blindness to the clear disclosure of the Petition. POR at 47-48. Petition and Dr. Cooper sufficiently detail Ground 2's combination of Linnarsson and McCloskey, further in view of the knowledge of a

POSA. Petition at 55-65; EX1002 ¶¶ 223-250. Patent Owner raises meritless contentions on Claim 5 and cursorily quibbles on Claims 12 and 26. POR 47-68.

Patent Owner complains “Petitioner’s ligation theory is unclear⁶.” POR 49. As Petitioner explains, however, the proposed combination for claim 5 is based on using the existing cell tag from Linnarsson’s CDS and TSO and modifying either or both of the CDS and TSO by ligating the barcode from McCloskey so as to introduce a “second tag sequence.” Petition at 56-58; EX1002 ¶ 224, 227; EX2018 at 51:5-53:12, 56:5-59:10; EX2020 at 41:22-44:20 (Dr. Cooper’s explanation on ligation theory). Petitioner’s theory never contemplates “removal” of tags or use of “redundant tags,” as Patent Owner erroneously complains. POR at 46-47; EX1070 ¶¶ 144-147.

Patent Owner further contends that “Petitioner does not sufficiently explain *when* its argued ligation happens.” POR at 66 (emphasis in original). But the claims have *no requirement* as to ligation timing. EX1001 at claims 1, 5; EX2018 at 61:4-15. Regardless, Dr. Cooper clarifies that the tag sequence should be “added after extension.” EX1002 ¶ 230. Patent Owner’s complaints regarding failure to

⁶ Notably, Patent Owner’s expert could not identify any “specific examples” where Petitioner’s theory was “unclear.” EX1069 at 43:21-44:4.

account for the exact timing of ligation relative to PCR amplification and Linnarsson's second extension reaction, are without merit. POR at 67. Petitioner's theory is that McCloskey's barcode would be introduced *before* amplification to prevent bias that would otherwise result *from* amplification. EX2020 at 37:11-39:11; EX2018 at 18:19-21:1, 36:12-37:19, 53:4-12, 61:16-62:20; EX1002 ¶¶ 89-93, 113-117. Indeed, Dr. Cooper confirmed that ligation would happen after Linnarsson's first extension. EX2020 at 42:4-18 ("... ligate it on after you've made that *initial cDNA*...."); EX2018 at 53:4-12; 58:7-8); EX1070 ¶ 153-158. Nevertheless, it is irrelevant whether ligation happens before or after Linnarsson's second extension because the result is the same either way. EX1070 ¶¶ 153-158.

Next, Patent Owner's assertion that there was a "failure to explain" the relevance of Hug is baseless. POR at 62. Hug is one of four references cited in the Petition and by Dr. Cooper as teaching the standard prior art technique of ligation using linker sequences. EX1002 ¶¶ 227-29. This is the exact method in the '197 patent. EX1001 at 19:15-23; EX1070 ¶¶ 159-164. The Petition is clear that Hug—and the three other cited references—are illustrative of background knowledge on *how* a POSA would perform ligation. Petition at 57-58.

Patent Owner's contentions on Claims 12 and 26 are also unfounded. POR 68-69. On Claim 12, Patent Owner ignores the articulated motivation that "a POSA would have readily understood that increasing the amount of oligonucleotide tags relative to the number of sample molecules would drive the tagging reaction to completion so that every sample polynucleotide is associated with the same first tag sequence." Petition at 60-61; EX1002 ¶ 235. Likewise, for Claim 26, Patent Owner does not explain how Petitioner's analysis is directed to an "entirely different concept," when the petition unequivocally explains that targeting a subset of polynucleotides having the same sequence would have been an obvious design choice. Petition 63-65.

Compared to claim 1, dependent claim 5 merely adds the requirement that one of the tag sequences, such as the second tag sequence, be introduced via ligation. When asked if this could be considered inventive, Patent Owner's expert ducked the question, repeating his refrain that he was "not in a position today to render an opinion." EX1071 at 190:24-191:8. Yet, as Patent Owner's expert on non-obviousness, Dr. Quackenbush was plainly "in a position" to answer. That was his job. The reason he tried to avoid the topic was because ligation is, in fact, a trivial and obvious modification, a point he ultimately could not deny.

B. Ligation Was An Obvious Modification That A POSA Would Be Motivated To Pursue

Patent Owner contends that there would be “no motivation” to use ligation to introduce a second tag into Linnarsson’s method. POR at 49-51. Patent Owner, however, ignores the overwhelming evidence showing otherwise.

To begin, Patent Owner does not deny its admissions in federal court that ligation to introduce tags for DNA sequencing was routine and conventional. Petition at 57; EX1002 ¶ 225; EX1017.011-.012; EX1016.020, .025. Indeed Patent Owner’s expert has *repeatedly* confirmed that ligation was conventional, including for the claimed purpose of introducing tags. EX1069 at 31:9-32:3 (’197 patent includes “... ligation ... to be [a] conventional technique[.]”), 53:19-54:6; 111:19-112:7; EX1071 at 33:14-34:17, 57:12-58:1, 59:13-60:18, 185:9-15, 186:6-9, 189:12-19; EX1084 ¶ 327 (admits in parallel district court proceedings that ligation is a “conventional technique”). This is a powerful indicator of obviousness that precludes Patent Owner from now relying upon ligation to “evade invalidity.” *See, e.g., I/P Engine, Inc. v. AOL Inc.*, 576 Fed.Appx. 982, 987 (Fed. Cir. 2014) (“Given that its own patents acknowledge that using the original search query for filtering was a ‘conventional’ technique, I/P Engine cannot now evade invalidity by arguing that integrating the query into the filtering process was a non-obvious departure from the prior art.”); *see McCoy v. Heal Sys., LLC*, 850 Fed.Appx. 785, 789 (Fed. Cir.

2021) (“The Board did not err by accepting the specification’s own assertions of what is well known in the art.”).

What is most critical, though, is that the undisputedly routine, standard, and conventional nature of ligation shows motivation to combine. As documented in the Petition—and as undisputed by Patent Owner—a POSA would be motivated to use McCloskey’s barcode with Linnarsson to avoid bias. Petition at 44. To introduce this tag, a POSA would be naturally motivated to use the conventional techniques in his or her toolkit. As the Supreme Court has held, a person of ordinary skill “has *good reason* to pursue the known options within his or her technical grasp,” such that § 103 bars the patentability of obvious variations. *KSR Intl. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

Federal Circuit cases are in accord with this basic principle. *See, e.g., I/P Engine*, 576 Fed.Appx. at 987 (reversing verdict of non-obviousness, explaining that the “fundamental flaw in I/P Engine’s argument is that using an individual user’s search query for filtering was a technique widely applied in the prior art”); *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 274 (Fed. Cir. 2022) (rejecting contention that Board erroneously found motivation to combine where two prior art components could be “interchangeably used” and substitution was “routine and predictable” because agents were “known for use”); *Ball Aerosol & Specialty*

Container, Inc. v. Ltd. Brands, Inc., 555 F.3d 984, 992-93 (Fed. Cir. 2009) (reversing district court finding of non-obviousness based on alleged “conclusory statements in lieu of an explanation of a motivation to combine” where district court failed to take account of “routine steps” an inventor would employ).

Beyond this, Dr. Cooper explained that a POSA would be motivated to use ligation because it would offer added flexibility in tag choice. EX1002 ¶¶ 230-231; EX1070 ¶ 142. Patent Owner never challenged Dr. Cooper on this during cross-examination but now complains that this motivation is “conclusory.” But the motivation is clear. There are only two reasonable ways to introduce a second tag: one can include it from the outset when synthesizing the combined tag, or one can prepare the first and second tags separately and then connect the two by conventional ligation. EX1070 ¶¶ 139-142. As Dr. Cooper explains, the latter choice allows one the flexibility to choose the second tags during the experiment depending upon the needs of the experiment, while at the same time achieving a result equivalent to the alternative approach. *Id.* ¶¶ 136-142; EX2020 at 44:5-20. Selecting an approach would be nothing more than an obvious and routine design choice. EX1002 ¶¶ 230-31.

In sum, the facts here are precisely those that prove obviousness. Ligation is not challenging, but rather a routine and conventional way to introduce a tag that

is interchangeable with the alternative approach and that would offer a specific benefit. *See, e.g., Cardiovalve, Ltd. v. Edwards Lifesciences Corp.*, No. 2022-2230, 2024 WL 1208638, at *3-4 (Fed. Cir. Mar. 21, 2024) (“The device-attachment option would have been obvious, as the Board found, whether or not there were a small number of other options that were also obvious.”); *Uber Techs., Inc. v. X One, Inc.*, 957 F.3d 1334, 1340 (Fed. Cir. 2020) (“[B]ecause Okubo’s terminal-side plotting and Konishi’s server-side plotting were both well known in the art, and were the only two identified, predictable solutions...it would have been obvious to substitute server-side plotting for terminal-side plotting in a combination of Okubo and Konishi.”); *Nike, Inc. v. Adidas AG*, No. 2021-1903, 2022 WL 4002668, at *8 (Fed. Cir. Sept. 1, 2022) (citing *Sandt Technology*, explaining that “clear motivation” to modify exists where modification was “slight variation that produced convenience” and “was common”); *ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016) (explaining that where an “ordinary artisan would...be left with two design choices ...[e]ach of these two design choices is an obvious combination”); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1241 (Fed. Cir. 2010) (holding that a motivation to combine and a reasonable expectation of success exist when “it is simply a matter of common sense” to combine known elements of the prior art to solve a known problem).

Notably, the '197 patent never suggests that ligation is inventive, nor does Patent Owner point to indicia of non-obviousness. EX1069 at 15:9-21. If anything, it would be error to conclude that a POSA would be unmotivated to pursue ligation. *See, e.g., Uber*, 957 F.3d at 1339 (reversing Board finding of no motivation where *inter alia* “the alleged novelty of the '593 patent is not related to the differences between server-side or terminal-side plotting”); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1363 (Fed. Cir. 2013) (reversing Board finding of no motivation where *inter alia* claimed element was a familiar component and “neither FG nor the Board points to any objective indicia of non-obviousness”).

C. Ligation Could Be Easily Used Successfully In Combination With Linnarsson

Patent Owner argues that ligation is incompatible with Linnarsson’s Figure 11, contending that biotin would block ligation and that the restriction enzyme cut sites are either absent or in the wrong spot to accommodate ligation. POR at 52-68.

These arguments, however, are all irrelevant for the simple reason that Linnarsson’s disclosure is not limited to Figure 11. Linnarsson discloses embodiments—most notably in Figures 3 and 4—that do not use fragmentation and capture. Hence there is no biotin that would block ligation, nor are there any

complications from the use of restriction enzymes because such enzymes are simply not used. *See supra* Part II.AB; EX1070 ¶¶ 39-61, 96-100.

Patent Owner argues that the biotin and other components of Figure 11 are mandatory. POR at 56. But Linnarsson says just the opposite, explaining that “Figure 11...show[s] ...steps *optionally used* in the STRT method.” EX1003 at 5:28-29; EX1070 ¶¶ 39-61, 96-100.

What’s more, while Patent Owner complains of alleged barriers to adding other sequence to Linnarsson’s TSO and/or CDS, Linnarsson teaches just this, stating, for instance, that “[a]rbitrary sequence can be inserted at the 5' end of the TSO, after the 5' APS, or after the cell-tag, but not at the 3' end.” EX1003 at 25:1-2; EX1070 ¶¶ 149-152. If Linnarsson taught solely a narrow technique based on biotin and restriction enzymes that was incompatible with additional tag sequences, it would never state that one can introduce “arbitrary” sequences.

Even if Figure 11 were Linnarsson’s sole embodiment, Patent Owner’s arguments that ligation might clash with Linnarsson still fail 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*, 550 U.S. at 421.

As Dr. Cooper explains, a POSA would be intelligent enough to know that if one wanted to ligate a sequence to the CDS or TSO and still use biotin for fragmentation and capture, the biotin could not be at the end of the CDS or TSO but would instead need to be added after ligation or included with the barcode. EX1070 ¶¶ 149-152. Likewise, a POSA would understand that if one wished to use fragmentation and capture through the use of a restriction enzyme, one would need to include the restriction enzyme cut site upstream (not downstream) of the molecular barcodes site so that the barcode is released from the capture bead for sequencing. EX1070 ¶¶ 153-158.

IV. REPLY REGARDING GROUND 3

Patent Owner's contention that there is no motivation to "further modify" Ground 1 for the purposes of Ground 3 is baseless. POR at 69. Patent Owner ignores Petitioner's articulated motivation, that a "POSA would have understood that increasing the number of polynucleotides tagged with a unique second tag sequence increases the accuracy of counting, and would have thus been motivated to ensure that each polynucleotides is tagged with a unique second tag sequence." Petition at 65-67; EX1002 ¶ 251-256. Thus, "a POSA would have been motivated to ensure that each sample polynucleotide is tagged" and would have looked to the

methods of McCloskey II to “design molecular tags to have a sufficient number of randomly selected nucleotides.” *Id.*; EX1002 ¶¶ 165-166.

V. LINNARSSON, MCCLOSKEY AND MCCLOSKEY II ARE ANALOGOUS ART

Patent Owner alleges that Petitioner fails to establish that Linnarsson, McCloskey and McCloskey II are analogous to the '197 patent. Yet, a “petitioner is not required to anticipate and raise analogous art arguments in its petition; instead a petitioner can use its reply” to address such arguments. *Sanofi-Aventis Deutschland GmbH v. Mylan Pharms.*, 66 F.4th 1373, 1379 (Fed. Cir. 2023).

Linnarsson and the '197 patent meet the analogous art standard as both references deal with “analysis of gene expression in single cells or in a plurality of single cells” based on nucleic acid tagging and sequencing. *Compare, e.g.*, EX1003 at Abstract, 1:6-9, 3:25-4:2, 9:23-10:2, 10:15-30, Fig. 11, claims 1, 23-24 with EX1001 at Title, Abstract, 6:33-7:22, claim 1; EX1070 ¶ 169.

McCloskey, McCloskey II and the '197 patent also meet the analogous art standard as both references deal with tagging polynucleotides for amplification,⁷ with McCloskey even teaching a two-part tag that identifies the “DNA source such as the patient or sample identification” and also “distinguishes among sequences

⁷ Hug is analogous for similar reasons. EX1070 ¶ 164.

arising from different cell or allele copies.” *Compare, e.g.*, EX1004.002, Fig. 1
with EX1001 at Title, Abstract, 6:33-7:22, claim 1; EX1070 ¶ 170.

VI. CONCLUSION

The '197 patent should be cancelled.

Dated: August 2, 2024

Respectfully submitted,

/Derek C. Walter/

Lead Counsel for Petitioner

Reg. No. 74,656

Weil, Gotshal & Manges LLP

201 Redwood Shores Parkway

Redwood Shores, CA 94065

Tel: (650) 802-3934

derek.walter@weil.com

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 5,600 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: August 2, 2024

By: /Derek C. Walter/
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656

CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing **PETITIONER'S
REPLY TO PATENT OWNER'S RESPONSE** are being served on August 2,
2024, via electronic mail pursuant to 37 C.F.R. § 42.6(e) to the counsel for Patent

Owner at the addresses below:

J. Steven Baughman (Reg. No. 47,414)
Megan Raymond (Reg. No. 72,997)
GROOMBRIDGE, WU, BAUGHMAN
& STONE LLP
801 17th Street, NW, Suite 1050
Washington, DC 20006
P: (202) 505-5832
steve.baughman@groombridgewu.com
megan.raymond@groombridgewu.com

10X-Parse-IPR@groombridgewu.com

Counsel for Patent Owner

Dated: August 2, 2024

By: /Derek C. Walter/
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656