

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

IPR2023-00958
Patent 10,697,013 B1

Before MICHAEL J. FITZPATRICK, SHERIDAN K. SNEDDEN, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

FITZPATRICK, *Administrative Patent Judge*.

DECISION

Granting Petitioner's Request on Rehearing of
Decision Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.71(d); 35 U.S.C. § 314

I. INTRODUCTION

Petitioner, Parse Biosciences, Inc., filed a Petition to institute an *inter partes* review of all claims, namely claims 1–28, of U.S. Patent No. 10,697,013 B1 (“the ’013 patent”) pursuant to 35 U.S.C. § 311(a). Paper 1 (“Pet.”). Patent Owner, 10X Genomics, Inc., filed a Preliminary Response pursuant to 37 C.F.R. § 42.107(b). Paper 6 (“Prelim. Resp.”). On December 13, 2023, we issued a Decision denying the Petition. Paper 7 (“Dec.”). Petitioner has filed a Request for Rehearing of that Decision. Paper 8 (“Reh’g Req.”).

For the reasons explained below, we grant the Request along with the Petition, thus instituting an *inter partes* review.

II. REHEARING STANDARD

“A party dissatisfied with a decision may file a single request for rehearing without prior authorization from the Board.” 37 C.F.R. § 42.71(d). The burden of showing a decision should be modified lies with the party making the request and said party “must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply.” *Id.*

III. WHETHER REHEARING IS WARRANTED

Petitioner argues that we misconstrued the claims “as requiring one to add tags in a way that can provide a distinction based on a ‘polynucleotide *sequence*.’” Req. 6 (quoting Dec. 14 (Petitioner’s emphasis)). Petitioner is correct. More specifically, we implicitly construed the claim language

reciting “a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell,” as requiring said “distinguishing” to be based on the sequences of the sample polynucleotides. *See, e.g.*, Dec. 14 (“[E]ach strand of cDNA that is tagged in Linnarsson is tagged regardless of the polynucleotide sequence of the cDNA or its corresponding mRNA. Thus, Linnarsson’s tags do not distinguish between ‘sample polynucleotides,’ whether cDNA or mRNA, of different sequences.”). Based on that misunderstanding, we erroneously determined that the proposed modification could not achieve the claim language, stating the following:

Petitioner’s proposal appears to defeat satisfaction of another portion of claim 1, namely a “second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell.” Ex. 1001, 30:62–64. For if the second tag is “added to the CDS or TSO after extension,” as opposed to the sample polynucleotide, as Petitioner argues (Pet. 39 (emphasis added)), it would appear that the second tag would be incapable of distinguishing any sample polynucleotide from other sample polynucleotides. Rather, the second tag would be ligated to each and every extension product bearing a CDS or TSO without regard to the sequence of any sample polynucleotide.

Dec. 16. We now reconsider whether to institute.

IV. REHEARING WHETHER TO INSTITUTE

A. The ’013 Patent

The ’013 patent is titled “Methods For Analyzing Nucleic Acids From Single Cells.” Ex. 1001, code (54). The focus of the ’013 patent Specification, other than the claims, however, is directed to the “reflex

method.” For example, the “Summary of the Invention” states in its entirety the following:

Aspects of the present invention are drawn to processes for moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide, also referred to as a “reflex method” (or reflex process, reflex sequence process, reflex reaction, and the like). In certain embodiments, the reflex method results in moving a region of interest into functional proximity to specific domain elements present in the polynucleotide (e.g., primer sites and/or MID). Compositions, kits and systems that find use in carrying out the reflex processes described herein are also provided.

Ex. 1001, 1:63–2:6.

The ’013 patent’s filing date is March 12, 2020. *Id.*, code (22). However, it claims priority through numerous continuation applications and ultimately to a provisional application filed August 20, 2009. Ex. 1001, codes (63), (60), 1:7–34. The Petition does not challenge the asserted priority date of August 20, 2009. *See* Pet. 6 (“[T]he earliest priority date of the ’013 Patent is August 20, 2009.”).

B. The Challenged Claims

Review is sought for all of the claims of the ’013 patent, namely claims 1–28. Claim 1 is the sole independent claim and reproduced below:

1. A method for multiplexed analysis of nucleic acids from single cells, the method comprising:

(a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides;

(b) performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags,

wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:

(A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and

(B) ligating a second oligonucleotide tag to said extension product, and

wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises:

(i) a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides;

(ii) a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells; and

(iii) a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell;

(c) amplifying said tagged polynucleotide, thereby generating a plurality of amplified polynucleotides corresponding to the tagged polynucleotide; and

(d) sequencing said plurality of amplified polynucleotides to determine sequences of the amplified polynucleotides corresponding to the sample sequence, the first tag sequence, and the second tag sequence of the tagged polynucleotide; and

(e) using the sequences determined in step (d) to count sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells.

Ex. 1001, 30:38–31:10.

C. The Asserted Prior Art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §¹	Basis
1–12, 19–28	103(a)	Linnarsson, ² McCloskey, ³ and “further in view of the knowledge of a [person of ordinary skill in the art]”
13–18	103(a)	Linnarsson, McCloskey, McCloskey II ⁴ and “further in view of the knowledge of a [person of ordinary skill in the art]”

Pet. 5.

1. Linnarsson

Linnarsson is titled “Gene Expression Analysis In Single Cells.” Ex. 1003, code (54). Linnarsson discloses “a method of preparing [complimentary DNA or] cDNA libraries which can be used to analyze gene

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, which was enacted September 16, 2011, made amendments to 35 U.S.C. §§ 102 and 103. AIA § 3(b)–(c). Those amendments became effective eighteen months later on March 16, 2013. *Id.* at § 3(n). Because the application from which the ’013 patent issued claims priority to an application filed before March 16, 2013, any citations herein to 35 U.S.C. §§ 102 and 103 are to their pre-AIA versions. *Id.* at § 3(n)(1).

² WO 2010/117620 A2, published Oct. 14, 2010 (“Linnarsson,” Ex. 1003).

³ Megan L. McCloskey et al., *Encoding PCR Products with Batch-Stamps and Barcodes*, 45 BIOCHEM. GENET., 761–767 (2007) (“McCloskey,” Ex. 1004).

⁴ US 2007/0020640 A1, published Jan. 25, 2007 (“McCloskey II,” Ex. 1055).

expression in a plurality of single cells.” *Id.* at 3:22–23. Linnarsson discloses the following “overview” of such a method:

(A) the tissue of interest is dissected; (B) a plurality of single cells are selected; (C) single cells are placed in separate wells of a 96-well plate and lysed; tagged reverse transcription is performed on each sample to produce cDNA; (D) cDNA samples are pooled and amplified; (E) sequencing is performed to obtain 100 million reads; and (F) identification of expressed genes and identification of cells from which they originated.

Id. at 4:8–13. Linnarsson discloses that the tag may be incorporated during cDNA synthesis via a tagged cDNA synthesis primer (“CDS”) and/or a tagged template switching oligonucleotide (“TSO”). *Id.* at 18:31–32 (“In some aspects of the invention, a tag can be incorporated into the cDNA during its synthesis. For example, the CDS and/or the TSO can include a tag.”).

Linnarsson claims priority to U.S. Provisional Patent Application No. 61/164,759 (“Linnarsson Provisional,” (Ex. 1015)), filed on March 30, 2009. Ex. 1003, code (30). Petitioner argues that the Linnarsson Provisional supports at least one claim of Linnarsson, and, thus, Linnarsson is prior art as of the March 30, 2009, filing date of the Linnarsson Provisional. Pet. 15–17. As such, Petitioner asserts that Linnarsson is prior art to the challenged claims under 35 U.S.C. § 102(e). *See id.* at 16 (“Linnarsson is prior art to the challenged claims even if the Challenged Claims are entitled to their earliest priority date of August 20, 2009.”). Patent Owner does not dispute that Linnarsson is prior art to the challenged claims. *See generally* Prelim. Resp.

2. *McCloskey*

McCloskey is titled “Encoding PCR Products with Batch-stamps and Barcodes.” Ex. 1004, 1. McCloskey explains that when employing the polymerase chain reaction (“PCR”), there is “always uncertainty concerning the source of the template DNA that gave rise to a particular PCR product.”

Id. McCloskey reports that it solved this problem by using:

an encoding oligonucleotide with five distinct informational regions (Fig. 1): (1) the batch-stamp, unique to each experiment, specifies the DNA source such as the patient or sample identification, and the date of reaction; (2) the random barcode distinguishes among sequences arising from different cell or allele copies; (3) the primer-binding site facilitates specific PCR amplification; (4) the genomic target-binding site targets the locus to be encoded prior to amplification; and (5) the extra 5' bases serve as an internal sentinel of recoding. This encoding oligonucleotide is annealed to denatured DNA and extended by Sequenase (USB) (Fig. 1). Sequenase-extension products are column-filtered to remove any unincorporated, encoding oligonucleotides and amplified using standard PCR protocols (Fig. 1).

Ex. 1004, 2. Such an encoding oligonucleotide with two tag sequences is the heart of what Petitioner relies upon with respect to McCloskey. *See, e.g.,* Pet. 22–23 (“McCloskey discloses a method of DNA analysis for single-cell samples that utilizes an ‘encoding oligonucleotide’ having ‘five distinct information regions,’ two of which are tag sequences that distinguish, respectively, polynucleotides and samples.”).

McCloskey was published in 2007 (*see* Ex. 1004, 1), which is more than one year before the earliest possible effective filing date of the challenged claims (i.e., August 20, 2009). As such, Petitioner asserts that McCloskey is prior art to the challenged claims under 35 U.S.C. § 102(a)

and (b). *See* Pet. 22. Patent Owner does not dispute that McCloskey is prior art to the challenged claims. *See generally* Prelim. Resp.

3. *McCloskey II*

McCloskey II is titled “Molecular Encoding Of Nucleic Acid Templates For PCR And Other Forms Of Sequence Analysis.” Ex. 1055, code (54). Petitioner asserts that the disclosure of McCloskey II is “similar” to that of McCloskey, with the main difference being that “McCloskey II discloses that its barcode sequence may comprise up to 30 nucleotides.” Pet. 26 (citing Ex. 1055 ¶21).

McCloskey II was published in 2007 (*see* Ex. 1055, code (43)), which is more than one year before the earliest possible effective filing date of the challenged claims (i.e., August 20, 2009). As such, Petitioner asserts that McCloskey II is prior art to the challenged claims under 35 U.S.C. § 102(a) and (b). *See* Pet. 22. Patent Owner does not dispute that McCloskey II is prior art to the challenged claims. *See generally* Prelim. Resp.

D. *Discretion Under 35 U.S.C. § 325(d)*

Section 325(d) provides, in pertinent part here, that “[i]n determining whether to institute [an inter partes review among other proceedings], the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). Patent Owner argues the Board should exercise its discretion under 35 U.S.C. § 325(d) and deny institution under *Advanced Bionics*. Prelim. Resp. 23.

In assessing whether to exercise the Board’s authority to deny institution under § 325(d), the Board considers a two-part analysis.

Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH, No. IPR2019-01469, Paper 6 at 8–9 (Feb. 13, 2020) (precedential). First, the Board considers whether “the same or substantially the same” art or arguments were previously presented to the Office. *Id.* at 8. If so, the Board then considers whether the petition demonstrates that the Office “erred in a manner material to the patentability of the challenged claims.” *Id.* In applying the two-part framework, the Board considers several nonexclusive factors set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, No. IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

I. Advanced Bionics Part One

Patent Owner argues that the same or substantially the same art was previously presented to the Office. Prelim Resp. 21.

With respect to Linnarsson, Patent Owner argues “it was the basis of explicit rejections—both in the application that issued as the ’981 Patent (which the Challenged Claims are terminally disclaimed against) and in its parent ’094 application—which Applicant ultimately overcame.” Prelim. Resp. 25 (citing Ex. 2001, 193–96; Ex. 2004, 1085–87). This is true. In fact, Linnarsson was cited as an anticipatory reference twice during the examination of the ’957 application from which the ’981 patent issued. *See* Ex. 2001, 154 (Dec. 27, 2017, Final Action: “Claim(s) 1–6 are rejected under pre-AIA 35 U.S.C. 102(A)(1)/(A)(2) as being anticipated by Linnarsson.”), 193 (July 10, 2018, Final Action stating the same). Thus, the Examiner clearly was aware of Linnarsson and its relevance to the claimed subject matter.

With respect to McCloskey, Patent Owner argues that, although it was not before the Office during examination, McCloskey II was before the Office. Prelim. Resp. 26 (citing Ex. 1001, code (56) (listing McCloskey II under “References Cited”)). Patent Owner further argues that Petitioner admits that McCloskey II includes the same teaching by McCloskey that is relied upon in the Petition. *See* Prelim. Resp. 27 (quoting Pet. 26: “[S]imilar to McCloskey, McCloskey II also discloses a method for tagging polynucleotides with ‘a molecular barcode and batch-stamp.’”). We agree with both Patent Owner arguments.

The Petition reproduces McCloskey Figure 1 and argues that, as shown, “McCloskey’s encoding oligonucleotide comprises *inter alia* two tag sequences: (1) a ‘batch-stamp’ sequence . . . to identify the experimental batch or genomic source (e.g., a single cell) and (2) a ‘barcode’ . . . to distinguish polynucleotide sequences ‘arising from different cell or allele copies.’” Pet. 34–35 (quoting Ex. 1004, 1–3). McCloskey Figure 1 is strikingly similar to Figure 1 of McCloskey II. *Compare* Ex. 1004, Fig. 1, *with* Ex. 1055, Fig. 1; *see also* Ex. 1055 ¶13 (“FIG. 1 shows an exemplary bar-coded oligonucleotide of the invention containing a sequence complementary to the target nucleic acid molecules (1), a batch-stamp sequence (2), random barcode (3), a leftward primer binding site (4), and a 5' tethering sequence (5).”).

We also agree that McCloskey '640 was of record during examination of the '013 patent. *See* Ex. 1005, 5 (IDS by Applicant filed in prosecution of the '013 patent and listing numerous references, including McCloskey '640); *see also* Ex. 1001, code (56) (listing McCloskey '640 under “References

Cited”). Because we find that the same or substantially the same art was previously presented to the Office, we proceed to part two of the analysis.

2. Advanced Bionics Part Two

Patent Owner argues that the Petition “fails to show any error in the Examiner’s application during prosecution of the prior art teachings Petitioner now purports to invoke from . . . McCloskey.” Prelim Resp. 23; *see also id.* at 24–25 (“Revisiting the same art and arguments already overcome during prosecution is a waste of the Board’s limited resources and would unfairly burden PO.”). However, Petitioner argued that “the Examiner committed major error in Examination by erroneously stating that the prior art fails to teach a dual tagging approach when, in fact, this approach is plainly taught in both McCloskey and McCloskey II.” Pet. 67. The record supports Petitioner’s position, and we agree that the error was material to patentability. *See* Ex. 1005, 131 (Notice of Allowance).

Accordingly, and having considered all of the *Becton, Dickinson* factors, we do not exercise discretionary denial.

E. Merits of the Petition

Petitioner argues that claims 1–12 and 19–28 would have been obvious over Linnarsson, McCloskey, and the knowledge of a person of ordinary skill in the art. Pet. 5. As discussed below, there is a reasonable likelihood that Petitioner would prevail in proving that claim 1 is unpatentable on this ground.

Claim 1 is directed to “[a] method for multiplexed analysis of nucleic acids from [a plurality of] single cells.” Ex. 1001, 30:38–39. The method contemplates that each “single cell of the plurality of cells comprises a

plurality of sample polynucleotides” and recites the step of “performing combinatorial tagging” in which “a first tag sequence distinguish[es] said sample polynucleotide from sample polynucleotides from other cells” and “a second tag sequence distinguish[es] said sample polynucleotide from other sample polynucleotides from said cell.” *Id.* at 30:40–64.

In mapping the prior art to claim 1, the Petition breaks the claim into eleven portions, labeled [1A] through [1K], and organizes its arguments accordingly. *See* Pet. 27–46.

For limitations [1A], [1B], [1D], [1F], [1G], [1I], and [1J], Petitioner relies on Linnarsson alone, which discloses incorporating tags into “cDNA during its synthesis,” wherein each tag has a “barcode” unique to the particular single cell whose mRNA generated the cDNA sample “such that once the tagged cDNA samples [are subsequently] pooled, the tag can be used to identify which single cell from each cDNA sample originated.” Ex. 1003, 18:31–19:11; *see* Pet. 27–28 (regarding [1A]), 28–29 (regarding [1B]), 31–34 (regarding [1D]), 39–42 (regarding [1F]), 42–43 (regarding [1G]), 44 (regarding [1I] and [1J]). In its Preliminary Response, Patent Owner does not dispute that Linnarsson teaches these limitations (i.e., limitations [1A], [1B], [1D], [1F], [1G], [1I], and [1J]). *See* Prelim. Resp. 45–65.

However, the remaining limitations, i.e., [1C], [1E], [1H], and [1K], relate to “combinatorial tagging” by “ligating a second oligonucleotide tag” and thereafter using the tags ultimately to “count sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells.” Ex. 1001, 30:43–31:10. For these limitations, Petitioner relies on modifying Linnarsson in view of McCloskey’s second tag and the knowledge of a person of ordinary skill in the art that such a

second tag could be attached by ligation, although McCloskey uses a different mechanism. Pet. 29–30, 34–39, 43, 45–46. In Petitioner’s words: “it would have been obvious to utilize Linnarsson’s cDNA library preparation to introduce a cell tag and then further introduce a second tag to distinguish polynucleotides (as taught by McCloskey) using ligation techniques that were well-known in the art.” Pet. 35.

It is unclear from this statement alone how the prior art teachings purportedly would have been combined, at least because the statement fails to identify the structure to which the second tag would be ligated.

Ultimately, however, Petitioner identifies said structure as Linnarsson’s CDS or TSO. *See* Pet. 38 (“[A person of ordinary skill in the art] would have had a reasonable expectation of success in ligating a second sequence to Linnarsson’s CDS or TSO.”). Petitioner further states that it would have been obvious to ligate the second tag to Linnarsson’s CDS or TSO “after extension.” *See id.* at 39 (In the proposed combination, “the second tag sequence is added to the CDS or TSO after extension.”); *see also* Ex. 1002 ¶149 (“The only difference is in the timing: with the combination of Linnarsson and McCloskey discussed above, Section XII.A.1, the tag sequence is part of the CDS or TSO prior to extension whereas by using ligation, the tag sequence is added after extension.”).

Petitioner’s proposal that the second tag would be “added to the CDS or TSO after extension,” appears to satisfy the portion of claim 1 specifying that the second tag must be ligated to an “extension product.” *See* Ex. 1001, 30:43–51 (claim 1 language reciting: “(A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and (B) ligating a

second oligonucleotide tag to said extension product.”). In addition, Petitioner’s proposal appears to satisfy another portion of claim 1, namely a “second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell.” Ex. 1001, 30:62–64. This is so because, as Patent Owner argues, McCloskey teaches “a ‘barcode’ that uniquely identifies and distinguishes polynucleotides.” Pet. 9 (citing Ex. 1004, 2, 4; *see* Ex. 1004, 2 (“Each encoding oligonucleotide is unique because of distinct batch-stamp and random barcode regions.”)).

Patent Owner presents myriad arguments against institution. *See* Prelim Resp. 46 (arguing the Petition fails to establish the asserted references constitute analogous art), 47–48 (arguing the Petition fails to clearly identify the art being relied upon), 48–57 (arguing the Petition fails to articulate how the references allegedly would have been combined), 58–60 (arguing that Linnarsson and McCloskey are incompatible), 60–62 (arguing a lack of motivation to add a second tag *via ligation*), 62–63 (arguing a lack of motivation for adding a second tag), 63–65 (arguing lack of reasonable expectation of success). For the reasons that follow, none of these arguments is persuasive, and we determine there is a reasonable likelihood Petitioner would prevail in its challenge to claim 1.

3. *Analogous Art*

Patent Owner argues that the Petition fails to assert or prove any of the three references is analogous art to the ’013 patent as opposed to each other. Prelim. Resp. 46 (citing Pet. 35; *Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373, 1374 (Fed. Cir. 2023)). As *Sanofi-Aventis* holds, a petitioner bears the burden of persuasion to establish that an

asserted prior art reference is analogous art to the claimed invention. *See Sanofi-Aventis*, 66 F.4th at 1377 (“We agree with [the patent owner] that [the petitioner] did not carry its burden to argue that de Gennes is analogous to the [challenged] patent.”); *id.* (“In evaluating whether a reference is analogous, we have consistently held that a patent challenger must compare the reference to the challenged patent.”); *id.* at 1378–79 (“We have routinely held that the petitioner has the burden of proving unpatentability.”).

However, the Petition should not be denied for failing to state explicitly that the cited prior art references are analogous art *to the '013 patent*. Rather, as *Sanofi-Aventis* further held: “A petitioner is not required to anticipate and raise analogous art arguments in its petition; instead a petitioner can use its reply to ‘respond to arguments raised in the corresponding opposition, patent owner preliminary response, patent owner response, or decision on institution.’” *Sanofi-Aventis*, 66 F.4th at 1379 (quoting 37 C.F.R. § 42.23). Accordingly, we need not address this issue for purposes of deciding whether to institute trial.

4. Identity of the Asserted Art

Patent Owner argues that “[i]t is unclear what Petitioner’s various grounds actually are.” Prelim. Resp. 47. According to Patent Owner, it is unclear because Petitioner relies on the knowledge of a person of ordinary skill in the art “in arguing obviousness of the ‘ligation reaction’” but then “*also* cites, e.g., Hug, Okayama, Shibata, and Hayazhizaki.” *Id.* (citing Pet. 5, 37–39).

We are not persuaded by this argument. Petitioner’s argument is clear. It is that “ligation techniques . . . were well-known in the art.”

Pet. 35. Petitioner cites Hug (Ex. 1007), Okayama (Ex. 1024), Shibata (Ex. 1039), and Hayazhizaki (Ex. 1040) as evidence to support its argument. Pet. 39.

5. How the References Allegedly Would Have Been Combined

Patent Owner asserts that the Petition fails to explain how the prior art features allegedly would have been combined. Prelim. Resp. 48.

In that regard, Patent Owner first argues that it is unclear “whether Petitioner proposes *adding* a ‘tag’ to Linnarsson or *replacing* a Linnarsson ‘tag’ with a McCloskey ‘tag.’” Prelim. Resp. 50 (citing Pet. 33–35). This argument is not persuasive, as the Petition explains that it is the former—adding, not replacing—that is being proposed. *See* Pet. 39 (In the proposed combination, “the second tag sequence is added to the CDS or TSO after extension.”), 38 (“[A person of ordinary skill in the art] would have had a reasonable expectation of success in ligating a second sequence to Linnarsson’s CDS or TSO.”).

Patent Owner next argues that “the Petition is also unclear about *where* the second tag is added or *when* it is added in Linnarsson’s reverse transcription process.” Prelim. Resp. 51. Patent Owner explains, “[f]or example, it is not clear whether Petitioner’s theory involves ligating the ‘second tag’ to Linnarsson’s TSO/CDS or to some part of a(nother) polynucleotide.” *Id.* However, the Petition explains that the second tag sequence is added to the CDS/TSO after extension. *See* Pet. 39 (In the proposed combination, “instead of having the tag sequence be part of the CDS or TSO prior to extension, the second tag sequence is added to the CDS or TSO after extension.”). In short, Petitioner’s arguments about where and

when the second tag would be added in the proposed modification are sufficient for institution purposes.

Patent Owner also argues that it is unclear whether Petitioner proposes adding “all or part of McCloskey’s ‘encoding oligonucleotide’” to Linnarsson’s CDS or TSO. Prelim. Resp. 57; *see* Ex. 1004, 2 (McCloskey’s “encoding oligonucleotide” has “five distinct informational regions”). This is because, at times, Petitioner refers to the added feature as “McCloskey’s molecule tag” despite that the phrase does not appear in McCloskey; nor is that phrase explicitly defined in the Petition. *Id.*; *see, e.g.*, Pet. 35–36 (“[A person of ordinary skill in the art] would have been motivated to combine Linnarsson’s use of a cell tag with *McCloskey’s molecule tag* to distinguish individual molecules within a sample because this approach addresses the amplification bias issue set forth in Linnarsson.” (emphasis added)). However, it is sufficiently clear that “McCloskey’s molecule tag” refers to the “barcode” portion of McCloskey’s encoding oligonucleotide. For example, the Petition notes that McCloskey teaches “counting sequences with nonredundant barcodes” and then immediately refers to the barcodes as “unique molecular tags.” Pet. 36 (quoting Ex. 1004, 6). Further, in the discussion of dependent claim 10, which specifies that “said second tag sequences . . . are random sequences,” the Petition notes that the second tag in the proposed modification is McCloskey’s “randomly generated barcode.” Pet. 48 (quoting claim 10 and Ex. 1004, 3).

6. Petitioner’s Proposed Combination and Reasons Therefor

The Petition relies on McCloskey for teaching “combinatorial tagging” and for “a second oligonucleotide tag.” *See* Pet. 11 (“McCloskey

discloses using a first tag to distinguish polynucleotides from different cells and a second tag to distinguish one polynucleotide from other polynucleotides from the same single cell.”), 22–23 (“McCloskey discloses a method of DNA analysis for single-cell samples that utilizes an ‘encoding oligonucleotide’ having ‘five distinct information regions,’ two of which are tag sequences that distinguish, respectively, polynucleotides and samples.”). As noted by Petitioner, in McCloskey, “the batch-stamp, unique to each experiment, specifies the DNA source such as the patient or sample identification, and the date of reaction” and “the random barcode distinguishes among sequences arising from different cell or allele copies.” Pet. 10 (quoting Ex. 1004, 2). The Petition additionally relies on McCloskey for teaching “that the ‘batch-stamps and barcodes [should] be used when amplifying irreplaceable DNAs and cDNAs for forensic, clinical, *single cell*, and ancient DNA analyses.’” Pet. 26 (quoting Ex. 1004, 5).”

Ultimately, Petitioner argues that “[i]t would have been obvious to utilize Linnarsson’s cDNA library preparation to introduce a cell tag and then further introduce a second tag to distinguish polynucleotides (as taught by McCloskey) using ligation techniques that were well-known in the art.” Pet. 35. Petitioner offers two general reasons in support. First, Petitioner argues that “[b]oth references describe methods of genetic analysis of single cells whereby polynucleotides are annealed to oligonucleotides comprising tag sequences.” *Id.* Second, Petitioner argues a skilled artisan would have made the combination because Linnarsson discloses a problem, PCR-induced amplification bias, for which McCloskey teaches a solution. *Id.* at 35–36 (citing *inter alia* Ex. 1002 ¶¶171–174; Ex. 1003, 2:3–15; Ex. 1004, 1, 5).

Patent Owner argues that the references are incompatible, thereby undermining any reason to combine their teachings. Prelim. Resp. 58–60. In particular, Patent Owner argues that “Linnarsson is focused on gene *expression* (based on mRNA transcribed from the genes to be expressed),” whereas “McCloskey is about tagging copies of the DNA of a *particular gene*.” *Id.* at 58. Patent Owner explains that “McCloskey’s tag is not designed to anneal to Linnarsson’s mRNA sample polynucleotides or a reverse-transcribed cDNA, which Petitioner does not establish are present in McCloskey.” *Id.* at 59–60. However, Petitioner’s proposed combination does not call for annealing McCloskey’s tag to the polynucleotides of Linnarsson. Rather, Petitioner proposes ligating a second tag to Linnarsson’s CDS or TSO. *See* Pet. 38 (“Given the undisputedly well-known and routine nature of ligation to attach label tags to polynucleotides, a POSA would have had a reasonable expectation of success in ligating a second sequence to Linnarsson’s CDS or TSO.”).

Petitioner has presented, sufficient for institution, an adequate reason why a person of ordinary skill in the art would have combined the teachings of Linnarsson and McCloskey with the person of ordinary skill in the art’s knowledge of ligation technology to obtain the claimed subject matter.

7. Reasonable Expectation of Success

Patent Owner argues that the Petition fails to establish a reasonable expectation of success “because it expressly depends on Petitioner’s expert’s unexplained and unsupported assumption that McCloskey has a tag that ‘that uniquely identifies each sample polynucleotide.’” Prelim. Resp. 64 (quoting Ex. 1002 ¶173). This argument is not persuasive because Dr. Cooper’s

declaration testimony is supported by citation to McCloskey. For example, within paragraph 173 of his Declaration, Dr. Cooper quotes McCloskey as disclosing that a “benefit” of its tagging method “is that counting sequences with *nonredundant* barcodes provides a quantitative measure of template diversity.” Ex. 1004, 6 (emphasis added); *see also* Ex. 1002 ¶166 (quoting Ex. 1004, 2 as teaching that “the random barcode distinguishes among sequences arising from different cell or allele copies”), ¶167 (“Therefore, because McCloskey’s random barcode distinguishes among ‘allele copies,’ it distinguishes sample polynucleotides (i.e., DNA) derived from within the same single cell.”).

We are persuaded there is a reasonable likelihood that Petitioner would prevail in demonstrating that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Linnarsson and McCloskey with the knowledge of a person of ordinary skill in the art to obtain the claimed subject matter.

8. Conclusion as to Claim 1

There is a reasonable likelihood that Petitioner would prevail in proving that claim 1 is unpatentable.

9. Claims 2–12, 19–28 (Ground I) and 13–18 (Ground II)

In *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), the Supreme Court held the following:

Section 314(a) [of Title 35] does not require the Director to evaluate every claim individually. Instead, it simply requires him to decide whether the petitioner is likely to succeed on “at least 1” claim. Once that single claim threshold is satisfied, it doesn’t matter whether the petitioner is likely to prevail on any

additional claims; the Director need not even consider any other claim before instituting review. Rather than contemplate claim-by-claim institution, then, the language anticipates a regime where a reasonable prospect of success on a single claim justifies review of all.

SAS, 138 S. Ct. at 1356. Thus, because we have decided to grant review of claim 1, we do the same for all challenged claims on all challenged grounds. *Id.*; *see also* 37 C.F.R. § 42.108(a) (“When instituting *inter partes* review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.”).

V. CONCLUSION

For the reasons discussed above, we are persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing in establishing that at least one of claims 1–28 of the ’013 patent is unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is granted and *inter partes* review is hereby instituted as to claims 1–28 of the ’013 patent on the grounds presented; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial on the grounds of unpatentability authorized above; the trial commences on the entry date of this decision.

IPR2023-00958
Patent 10,697,013 B1

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