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Paper 7
Date: October 13, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

IPR2023-00876
Patent 10,155,981 B2

Before MICHAEL J. FITZPATRICK, KRISTI L. R. SAWERT, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

FITZPATRICK, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
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 1–6, of U.S. Patent No. 10,155,981 B2 ("the '981 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.").

Institution of an *inter partes* review requires that "the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Determining whether to institute has been delegated to the Board. *See* 37 C.F.R. § 42.4(a) ("The Board institutes the trial on behalf of the Director.").

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that there is a reasonable likelihood that Petitioner would prevail with respect to at least one claim. Accordingly, we grant the Petition.

A. Related Matters

The parties identify the following related matter involving the '329 patent: *10x Genomics v. Parse Biosciences, Inc.*, 22-cv-01117 (D. Del.). Pet. 4; Paper 4, at 1.

B. Real Parties In Interest

Each party identifies itself as the sole real party in interest. Pet. 4; Paper 4, at 1.

C. The '981 Patent

The '981 patent is titled "Methods For Analyzing Nucleic Acids From Single Cells." Ex. 1001, code (54). The focus of the '981 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, 1:49–61.

The '981 patent's filing date is August 15, 2017. *Id.*, code (22). However, it claims priority as the sixth in a string of continuation applications and ultimately to a provisional application filed August 20, 2009. Ex. 1001, code (63), 1:7–22. The Petition does not challenge the asserted priority date of August 20, 2009. *See* Pet. 15 ("[T]he priority date of the '981 Patent is no earlier than August 20, 2009.").

D. The Challenged Claims

Review is sought for all of the claims of the '981 patent, namely claims 1–6. Claim 1 is the sole independent claim and reproduced below:

> 1. A method of analyzing nucleic acids from a plurality of single cells, the method comprising:

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

(b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides, wherein each tagged polynucleotide comprises:

(i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and

(ii) a multiplex identifier (MID) sequence comprising:

I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and

II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;

(c) sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences;

(d) using the first tag sequence to correlate the identified polynucleotide sequence with the single cell from which the identified polynucleotide sequence is derived; and

(e) using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.

Ex. 1001, 30:18–48.

C. The Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §[1]	Basis
1–6	103(a)	Linnarson, McCloskey
5	103(a)	Linnarson, McCloskey, "further in view of the knowledge of a [person of ordinary skill in the art]"

Pet. 5.

II. ANALYSIS

A. Claim Construction

The challenged claims should be read in light of the specification, as it would be interpreted by one of ordinary skill in the art. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Thus, we generally give claim terms their ordinary and customary meaning. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("The ordinary and customary meaning is the meaning that the term would have to a person of ordinary skill in the art in question." (internal quotation marks omitted)); *see also* 37 C.F.R. § 42.100(b) (stating that claims are construed in IPRs according to the same standard as used in federal court).

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[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 '981 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).

The Petition states that "Petitioner does not believe that any terms require explicit construction in view of the prior art being presented." Pet. 36. Despite this stated position, Petitioner proposes constructions for "multiplex-identifier (MID)" and "providing a sample." *Id.* Patent Owner, for its part, states that it "agrees that at this time, solely for purposes of an institution decision on the Petition, no terms require explicit construction." Prelim. Resp. 45.

On the record before us, and for purposes of institution, we find there is no need to provide an express construction of any claim term.

B. Obviousness Generally

A claim is unpatentable "if the differences between the subject matter should to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2004). "Obviousness is a question of law based on underlying facts." *MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1167 (Fed. Cir. 2015). The underlying facts include (i) the scope and content of the prior art, (ii) any differences between the prior art and the claimed invention, (iii) the level of ordinary skill in the field of the invention, and (iv) any relevant objective considerations of nonobviousness. *Id.* (citing *Graham v. John Deere of Kan. City*, 383 U.S. 1, 17–18 (1966)). An additional underlying fact is whether there was a reason to combine prior art teachings when so asserted. *Id.*

C. Level Of Ordinary Skill In The Art

In determining whether an invention would have been obvious at the time it was made, we consider the level of ordinary skill in the pertinent art at the time of the invention. *Graham*, 383 U.S. at 17. "The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991). The "person having ordinary skill in the art" is a hypothetical construct, from whose vantage point obviousness is assessed. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

According to Petitioner:

> A person of ordinary skill in the art ("POSA") relating to the '981 Patent would have had (1) a Masters degree and/or Ph.D. in molecular biology, genetics, chemistry, engineering, or a related discipline and at least two years of post-Masters, postdoctoral, or industry experience or (2) a Bachelor of Science in such disciplines and at least five years of academic or industry experience (including any experimental work toward a graduate degree), relating to DNA sequencing technologies, amplification methods, and gene expression analysis. Further, a POSA would have been familiar with associated tools, methods, and techniques including: (1) polynucleotide tagging; (2) amplification; (3) use of tags to overcome amplification bias; (4) single cell analysis; (5) ligation and primer extension; and (6) sequencing.

Pet. 21–22 (citations omitted). At this stage of the proceeding, Patent Owner does not dispute the level of skill proposed by Petitioner.

Because Petitioner's formulation of the level of ordinary skill in the art appears consistent with the disclosure of the '981 patent and the asserted

prior art, and because there is no argument to the contrary at this stage of the proceeding, we apply Petitioner's formulation in our analysis below.

D. The Prior Art

"A petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent . . . only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). Petitioner here asserts the following two printed publications as prior art: (1) WO 2010/117620 A2, published Oct. 14, 2010 ("Linnarsson," Ex. 1003) and (2) McCloskey, Megan L., et al., "Encoding PCR Products with Batch-stamps and Barcodes," 45 BIOCHEM GENET 761–67 (2007), published Oct. 23, 2007 ("McCloskey," Ex. 1004).

1. Linnarsson

Linnarsson is titled "Gene Expression Analysis In Single Cells." Ex. 1003, code (54). Linnarsson discloses a "method for preparing a [complimentary DNA or] cDNA library from a plurality of single cells." *Id.* at 3:25. In one embodiment

> the method includes the steps of releasing [messenger RNA or] mRNA from each single cell to provide a plurality of individual mRNA samples, synthesizing a first strand of cDNA from the mRNA in each individual mRNA sample and incorporating a tag into the cDNA to provide a plurality of tagged cDNA samples, pooling the tagged cDNA samples and amplifying the 30 pooled cDNA samples to generate a cDNA library having double-stranded cDNA.

Id. at 3:26–30. 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. 22–24. As such, Petitioner asserts that Linnarsson is prior art to the challenged claims under 35 U.S.C. § 102(e). *See* Pet. 22–23 ("Linnarsson is prior art to the challenged claims even if the Challenged Claims of the '981 Patent 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 50 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. 30 ("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. 28–29. Patent Owner does not dispute that McCloskey is prior art to the challenged claims. *See generally* Prelim. Resp.

E. 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). As stated above, the decision whether to institute has been delegated to the Board. 37 C.F.R. § 42.4(a). Patent Owner argues the Board should exercise its discretion

under 35 U.S.C. § 325(d) and deny institution under *Advanced Bionics*. Prelim. Resp. 21.

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).

1. 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 and in its parent '094 application—which Applicant ultimately overcame." Prelim. Resp. 23 (citing Ex. 1005, 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. 1005, 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, "the far-more-detailed McCloskey '640" (i.e., US 2007/0020640 A1, published Jan. 25, 2007 (Ex. 2001)) was. Prelim. Resp. 24 (citing Ex. 2001). Regardless of whether McCloskey '640 is "far-more-detailed" than McCloskey, the teachings of McCloskey on which the Petition now relies are also taught by McCloskey '640. Specifically, the Petition reproduces McCloskey Figure 1 and argues that, as shown, "McCloskey's encoding oligonucleotide comprises 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. 50–51. McCloskey Figure 1 is strikingly similar to Figure 1 of McCloskey '640. *Compare* Ex. 1004, Fig. 1*, with* Ex. 2001, Fig. 1; *see also* Ex. 2001 ¶13 ("FIG. 1 shows an exemplary bar-coded oligonucleotide of the invention containing a sequence complementary to the target nuclei[c] 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 '981 patent. *See* Ex. 1005, 124 (IDS by Applicant filed in prosecution of the '957 application and listing numerous references, including McCloskey '640); 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. 21; *see also id.* at 22 ("Revisiting the same art and arguments already overcome during prosecution is a waste of the Board's limited resources and would unfairly burden PO."). In that regard, Patent Owner asserts that McCloskey '640's "substantive teachings that Petitioner" now relies upon were "raised *by the Office*, argued, and overcome . . . in prosecuting the related '450 application in the '981's priority chain." *Id.* at 24 (citing Pet. 70; Ex. 1001, 1; Ex. 1005, 1124; Ex. 2002, 335–36, 372–73, 383).

To the contrary, Petitioner preemptively argued that "***no arguments*** were made during examination with respect to McCloskey or any similar reference disclosing an oligonucleotide with two tags." Pet. 70.

The record supports Petitioner's position.

As discussed below, none of Patent Owner's citations to the prosecution history reveals any issue raised, argued, or overcome regarding the specific McCloskey teachings relied upon in the Petition.

The first citation is to "EX1005, 1124." Prelim. Resp. 24. According to Petitioner, Exhibit 1005 is the file history of the '957 application, from which the '981 patent issued. Pet. vii. Exhibit 1005 contains 348 pages. We understand the page reference of "1124" to be a typographical error, with page 124 having been intended. Page 124 is an Information Disclosure

Statement, or IDS, filed by Applicant during prosecution of the '957 application and listing numerous references, including McCloskey '640. Ex. 1005, 124. In other words, Patent Owner's cited evidence shows that McCloskey '640 was of record in the prosecution of the '981 patent.

The second citation is to pages 335 and 336 of Exhibit 2002, which, according to Patent Owner is the file history of the '450 application. Prelim. Resp. 24. The '450 application is a great-, great-grandparent application to that of the '981 patent. Ex. 1001, code (63). Prelim. Resp. i, 24. The cited pages 335 and 336 are portions of a July 27, 2013, dated document that Applicant "filed in follow-up to telephonic interviews with [the Examiner] held on July 24, 2013, and July 26, 2013." Ex. 2002, 331, 335–36. In the document, Patent Owner states that McCloskey '640 "does not provide *segments* of a region, where each of the segments has the same MID sequence; also doesn't provide composition in which all of the segments have a multiplex identifier that uniquely identifies the individual molecule of said contiguous region from which said segments originate." Ex. 2002, 335. This statement by Patent Owner during prosecution of the '450 application does not, on its face, implicate the specific teaching of McCloskey on which the Petition relies. Nor does Patent Owner explain how it might.

The third citation is to pages 372 and 373 of Exhibit 2002. Prelim. Resp. 24. Pages 372 and 373 are portions of an August 23, 2013, dated Notice of Allowability entered in the same great-, great-grandparent '450 application. Ex. 2002, 368, 370, 372–73. In an "Interview Summary" portion of the document, the Examiner states the following:

> August 7, 2013: Discussed the amended claims of July 30, 2013. The specific claim languages were discussed to overcome

> the potential rejection of said amended claims over Laird (PNAS, 2004, cited in the IDS of 4/9/13) in view of McKloskey ['640] (cited in the previous interview). Also, the Examiner suggested the need for further clarification for the "wherein" clause of claims 21 and 31. The representative agreed to further amend said claims and send them electronically for further review and discussion. The amended claims were sent to the Examiner electronically on the same day.

Id. at 372–73. Again, this does not, on its face, implicate the specific teaching of McCloskey on which the Petition relies. Nor does Patent Owner explain how it might.

The fourth citation is to page 383 of Exhibit 2002. Prelim. Resp. 24. Page 383 is a portion of an "Examiner-Initiated Interview Summary" regarding a July 30, 2013, interview in the same great-, great-grandparent '450 application. Ex. 2002, 382–383. In it, the Examiner wrote, in relevant part, the following:

> August 7, 2013: Discussed the amended claims of July 30, 2013. The specific claim languages were discussed to overcome the potential rejection of said amended claims over Laird (PNAS, 2004, cited in the IDS of 4/9/13) in view of McKloskey ['640] (cited in the previous interview). Also, the Examiner suggested the need for further clarification for the "wherein" clause of claims 21 and 31. The representative agreed to further amend said claims and send them electronically for further review and discussion. The amended claims were sent to the Examiner electronically on the same day. The representative also discussed that a plurality of "different" segments of the nucleic acid molecule encompasses overlapping or non-overlapping segments of the nucleic acid molecule. The Examiner concurred with the interpretation of a plurality of "different" segments of the nucleic acid molecule can be overlapping or non-overlapping.

Id. at 383. Again, this statement by Patent Owner during the prosecution of the '450 application does not, on its face, implicate the specific teaching of McCloskey on which the Petition relies. Nor does Patent Owner explain how it might.

In sum, on the record presented, it appears that Petitioner is correct in stating that "***no arguments*** were made during examination with respect to McCloskey or any similar reference disclosing an oligonucleotide with two tags." Pet. 70 (underlining added).

Instead, the asserted art includes Linnarsson and McCloskey. Linnarsson was evaluated and served as the basis of an anticipation rejection. Ex. 1005, 154, 193. However, Patent Owner successfully distinguished Linnarsson from the claimed subject matter by arguing that "Linnarsson does not describe the 'second tag sequence' element." Ex. 1005, 215. The prosecution history does not reveal any evaluation of McCloskey '640's teaching of an encoding oligonucleotide with two tag sequences, in combination with Linnarsson or otherwise, during the prosecution of the '981 patent, let alone during prosecution of an ancestor application involving claims directed to different subject matter.

As discussed above, Petitioner has pointed out sufficiently how the Examiner erred, namely by failing to consider the teaching by McCloskey '640 of an encoding oligonucleotide with two tag sequences, that distinguish, respectively, polynucleotides and samples. Likewise, Petitioner has shown a reasonable likelihood that McCloskey, like McCloskey '640, teaches such a feature.

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

F. Analysis of Challenge to Claim 1

Petitioner argues that claim 1 would have been obvious over Linnarsson and McCloskey. Pet. 37–59. As discussed below, there is a reasonable likelihood that Petitioner would prevail in proving that claim 1 is unpatentable on this ground.

In mapping the prior art to claim 1, the Petition breaks the claim into nine portions and organizes its arguments accordingly. *See* Pet. 37–59 (addressing limitations labeled by Petitioner as [1A] through [1I]).

For limitations [1A]–[1E], [1G], and [1H], Petitioner relies on Linnarsson alone. *See* Pet. 37 (stating with respect to [1A]: "Linnarsson discloses this claim element."), 38 (same statement regarding [1B]), 39 (same statement regarding [1C]), 44 (same statement regarding [1D]), 47 (same statement regarding [1E]), 56 (same statement regarding [1G]), 57 (same statement regarding [1H])).

Based on the citations to Linnarsson provided in the Petition, there is a reasonable likelihood that Linnarsson teaches these limitations. Pet. 37–49, 56–58 (citing Ex. 1003 extensively). Patent Owner does not dispute that Linnarsson teaches these limitations (i.e., limitations [1A]–[1E], [1G], and [1H]). *See* Prelim. Resp. 45–54. Further, as noted by Petitioner (*see* Pet. 50), Patent Owner successfully distinguished Linnarsson during prosecution exclusively on the basis that it "does not describe the 'second tag sequence' element," which is recited in limitations 1F and 1I. Ex. 1005, 215. The Examiner essentially agreed with that argument, stating in an August 28, 2018, Notice of Allowability, the following:

> The closest prior art, Linnarsson (WO 2010/117620), does not teach or suggest generating a plurality of tagged

> polynucleotides comprising an identifier sequence of instant claim 1(ii). The claimed identifier sequence comprises a first tag sequence, which distinguishes each single cell in a sample of a plurality of cells, and a second tag sequence, which distinguishes a sample polynucleotide from other sample polynucleotides derived from a single cell, which is not taught by Linnarsson.

Id. at 238.

Patent Owner's arguments on the merits of the Petition are limited to whether Linnarsson and McCloskey are analogous art, whether a person of ordinary skill in the art would have combined them, and whether a person of ordinary skill in the art would have had a reasonable expectation of success in doing so. Prelim. Resp. 45–54. We address these arguments below.

1. Linnarsson and McCloskey as Analogous Art

Patent Owner argues that the Petition "entirely fails to assert or analyze whether [Linnarsson and McCloskey] are analogous art to the '981 Patent (instead discussing only whether they are analogous to one another)" and consequently must be denied in view of *Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373 (Fed. Cir. 2023). Prelim. Resp. 2.

We agree with Patent Owner that *Sanofi-Aventis* holds that a petitioner bears the burden of persuasion to establish that an asserted prior art reference is analogous art. *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, we disagree with Patent Owner that the Petition must be denied for failing to state that the cited prior art references are analogous art "to the '981 patent." Rather, as *Sanofi-Aventis* further stated: "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.

2. Petitioner's Proposed Combination and Reasons Therefor

Limitations [1F] and [1I] relate to the concept of using a "second tag sequence" in addition to the recited "first tag sequence." Specifically, limitation [1F] recites that the "multiplex identifier (MID) sequence" comprises "a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell," and limitation [1I] recites the step of "using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived." Pet. 50, 58 (quoting portions of claim 1).

The Petition relies on McCloskey for teaching a MID with two tag sequences. *See* Pet. 51 (As shown [in Ex. 1004, Fig. 1], McCloskey's encoding oligonucleotide comprises 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."). 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. 51 (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 . . . single cell . . . analyses,' and that its method of tagging applies 'to single-stranded [DNA or] cDNA templates.'" *Id.* (quoting Ex. 1004, 1–2).[2] Based on these teachings and declaration testimony of Gregor Cooper, Ph.D., Petitioner argues that a person of ordinary skill in the art would "would have understood that McCloskey's reference to 'different cell or allele copies' encompasses cDNA (i.e., sample polynucleotides) from single cell experiments." Pet. 51 (citing Ex. 1002 ¶¶65, 184; Ex. 1004, 1–2).

Ultimately, Petitioner argues that "[i]t would have been obvious to combine Linnarsson's methods of cDNA library preparation and analyzing tagged nucleic acids with McCloskey's teachings to use a MID (i.e., encoding oligonucleotide) comprising a second tag sequence that distinguishes sample polynucleotides derived from the same single cell." Pet. 52. Petitioner offers two general reasons in support. First, Petitioner argues that substituting [McCloskey's] MID in lieu of Linnarsson's CDS

[2] The Petition cites to pages 1 and 5 of Exhibit 1004 for these quotes. Pet. 51. However, we located the quotes on pages 1 and 2.

and TSO is an obvious design choice, as both references disclose methods of genetic analysis of single cells whereby polynucleotides are annealed to oligonucleotides comprising one or more tag sequences. Pet. 52. Second, Petitioner argues a skilled artisan would have made the combination because Linnarsson discloses a problem, PCR-induced amplification, for which McCloskey teaches a solution. *Id.* at 53 (citing Ex. 1002 ¶¶188–191; Ex. 1003, 2:3–15, 11:6–10; Ex. 1004, Abstract).

Patent Owner argues that the references are incompatible, thereby undermining any reason to combine their teachings. Prelim. Resp. 48–52. 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 48. Patent Owner explains that "McCloskey's tag is not designed to anneal to Linnarsson's mRNA sample polynucleotides or a series of cytosine nucleotides at the end of a newly-synthesized and reverse transcribed strand, which Petitioner does not establish are present in McCloskey." However, Petitioner's proposed combination does not call for annealing McCloskey's tag to the polynucleotides of Linnarsson. Rather, Petitioner proposes, with declaration testimony in support, that "Linnarsson's tagged oligonucleotides—CDS or TSO—could be modified through routine methods to incorporate a second tag to uniquely identify each sample polynucleotide." Prelim. Resp. 55 (citing Ex. 1002 ¶¶192–193). In particular, Petitioner's declarant, Dr. Cooper, testifies that a person of ordinary skill "could conceptually divide each of Linnarsson's cell-tag sequence into two portions, wherein the first portion performs the function of McCloskey's 'batch-stamp,', used to track individual cells, and the

second portion performs the function of McCloskey's 'barcode', used to differentiate polynucleotides within a cell." Ex. 1002 ¶192.

We are persuaded there is a reasonable likelihood that Petitioner will prevail in demonstrating an adequate reason for a person of ordinary skill in the art to have combined Linnarsson and McCloskey.

3. Reasonable Expectation of Success

Patent Owner argues that the Petition fails to establish a reasonable expectation of success because it does not explain how the proposed combination could achieve the recited "correlat[ions]." Prelim. Resp. 53; *see also* Ex. 1001, 30:41–48 (claim 1 steps (d) and (e)). This is so, Patent Owner argues, because "Linnarsson's CDS tags anneal to a sequence present in *all mRNA* molecules and Linnarsson's TSO tags anneal to a generic repeat sequence ("a series of cytosine nucleotides") present in *recently synthesized cDNA created from cellular mRNA* (and therefore cannot target a particular sequence)." However, as stated above, Petitioner offers declaration testimony that a person of ordinary skill "could conceptually divide each of Linnarsson's cell-tag sequence into two portions, wherein the first portion performs the function of McCloskey's 'batch-stamp,', used to track individual cells, and the second portion performs the function of McCloskey's 'barcode', used to differentiate polynucleotides within a cell." Ex. 1002 ¶192.

We are persuaded there is a reasonable likelihood that Petitioner will 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 to obtain the claimed subject matter.

4. Conclusion as to Claim 1

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

5. Claims 2–6

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 claims 2–6. *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.").

III. 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 1–6 of the '981 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 1–6 of the '981 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.

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