

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*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

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.”). After initially denying the Petition, we granted it on rehearing and instituted an *inter partes* review. Paper 9 (“Dec. on Reh’g”).

During the review, Patent Owner filed a Patent Owner Response to the Petition (Paper 21 (“PO Resp.”)), Petitioner filed a Reply (Paper 27 (“Pet. Reply”)), and Patent Owner filed a Sur-reply (Paper 33 (“PO Sur-reply”). Additionally, each party filed a motion to exclude. Paper 39 (“Pet. Mot. To Exclude”); Paper 38 (“PO Mot. To Exclude”).¹

An oral hearing was held November 6, 2024. A transcript of the hearing is of record in this case. Paper 47 (“Tr.”).

We have jurisdiction under 35 U.S.C. § 6, and this Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during the trial. For the reasons discussed below, we determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–28 of the ’013 patent are unpatentable.

¹ Petitioner’s Motion to Exclude does not identify any exhibit it seeks to exclude and instead exclusively targets arguments. *See* Pet. Mot. To Exclude 1 (“Pursuant to FRE 401, 402, and 403, Petitioner moves to exclude all arguments in Patent Owner’s Sur-Reply (Paper 33) (‘POSR’) that pertain to a restriction enzyme known as BtsI.”). Petitioner’s Motion is improper and denied. *See* 37 C.F.R. § 42.64(c) (providing for a “motion to exclude evidence” (emphasis added)).

A. Real Parties In Interest

Each party identifies itself as the sole real party in interest. Pet. 3; Paper 5, at 1.

B. Related Matters

The parties identify *10x Genomics v. Parse Biosciences, Inc.*, 22-cv-01117 (D. Del.) as involving the '013 patent. Pet. 3; Paper 5, at 1. Additionally, the parties identify IPR2023-00876 and IPR2023-00955. Pet. 4; Paper 5, at 1. In IPR2023-00876, the Board issued a final written decision that all claims of related U.S. Patent No. 10,155,981 B2 (“the '981 patent”) are unpatentable, and Patent Owner has filed a Notice of Appeal. IPR2023-00876, Papers 47 and 48. In IPR2023-00955, the Board issued a final written decision that all claims of related U.S. Patent No. 10,240,197 B1 (“the '197 patent”) are unpatentable. IPR2023-00955, Paper 46.

C. 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

MID²). 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.”).

D. The Challenged Claims

Petitioner challenged 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

² The acronym “MID” is short for “multiplex identifier” and “refers to a tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag DNA sequence) can be used to differentiate polynucleotides in a sample.” Ex. 1001, 6:33–36.

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 Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. § ³	Basis
1–12, 19–28	103(a)	Linnarsson, ⁴ McCloskey, ⁵ and “further in view of the knowledge of a [person of ordinary skill in the art]”
13–18	103(a)	Linnarsson, McCloskey, McCloskey II ⁶ and “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*

³ 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).

⁴ WO 2010/117620 A2, published Oct. 14, 2010 (“Linnarsson,” Ex. 1003).

⁵ Megan L. McCloskey et al., *Encoding PCR Products with Batch-Stamps and Barcodes*, 45 BIOCHEM. GENET., 761–767 (2007) (“McCloskey,” Ex. 1004).

⁶ US 2007/0020640 A1, published Jan. 25, 2007 (“McCloskey II,” Ex. 1055).

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).

The Petition states that “Petitioner does not believe that any terms require explicit construction in view of the prior art being presented.” Pet. 27. Despite this stated position, Petitioner argues that the ’013 patent provides a definition for the claim term “sample,” namely, “a quantity of material from a biological, environmental, medical, or patient source in which detection, measurement, or labeling of target nucleic acids is sought.” *Id.* (quoting Ex. 1001, 12:15–18). Patent Owner, in its Preliminary Response, stated 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. In instituting the IPR, we found no need to provide an express construction of any claim term. *See generally* Dec. on Reh’g; *see also* Paper 7, at 7 (“Inst. Dec.”).

In the Patent Owner Response, Patent Owner repeats that it “does not believe any term needs construction,” but nonetheless “applies the Petition’s definition for ‘sample.’” PO Resp. 22. We apply this same definition in our analysis.

B. Obviousness Generally

A claim is unpatentable “if the differences between the subject matter sought 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). “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)). Further, if all the elements of an invention are found in a combination of prior art references, then:

a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1164 (Fed. Cir. 2006).

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 ’013 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. EX1002 ¶ 51. 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. EX1002 ¶¶ 52, 74–95.

Pet. 14–15.⁷

Patent Owner does not directly dispute Petitioner’s proposal but does offer its own proposal. PO Resp. 21. Patent Owner proposes that the skilled artisan “would have had a Ph.D. in molecular biology, molecular genetics, biochemistry, physics, mechanical engineering, or a related discipline, with

⁷ Exhibit 1002 is a declaration by Petitioner’s witness, Gregory Cooper, Ph.D.

two years of academic, research, or industry experience in the field of genomic or transcriptome sequencing.” *Id.* (citing Ex. 2013 ¶¶25–26⁸).

Both of the parties’ proposals as to the level of ordinary skill in the art are consistent with the disclosure of the ’013 patent and the asserted prior art. The distinction between the parties’ proposals would not change the outcome of this Decision. Thus, we adopt and apply Patent Owner’s proposal.

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 a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications.” 35 U.S.C. § 311(b). Petitioner here asserts three printed publications: Linnarsson (Ex. 1003), McCloskey (Ex. 1004), and McCloskey II (Ex. 1055).

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 expression in a plurality of single cells.” *Id.* at 3:22–23. 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

⁸ Exhibit 2013 is a declaration by Patent Owner’s witness, John Quackenbush, Ph.D.

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 pooled cDNA samples to generate a cDNA library having double-stranded cDNA.

Id. at 3:26–30. 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. Indeed, in its Preliminary Response, Patent Owner pointed out that Linnarsson “was the basis of multiple rejections by the Office in Application No. 15/677,957” (“the ’957 application”), which is an ancestor to the ’013 patent. Prelim. Resp. 7 (citing Ex. 2001, 153–156). This is true. In fact, Linnarsson was cited as an anticipatory reference twice during the examination of the ’957 application. *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).

Patent Owner, however, does dispute that Linnarsson is analogous art. PO Resp. 51–53. We address that issue below.

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.”).

According to the face of McCloskey, it was published in 2007, which is more than one year before the earliest possible effective filing date of the challenged claims (i.e., August 20, 2009). Ex. 1004, 1. As such, Petitioner asserts that McCloskey is prior art to the challenged claims under 35 U.S.C. § 102(a) and (b). Pet. 22.

Patent Owner disputes that McCloskey is prior art, which we address below. PO Resp. 20–21. Patent Owner also disputes that McCloskey is analogous art, which we also address below. *Id.* at 51–53.

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). Pet. 26.

Patent Owner does not dispute that McCloskey II is prior art to the challenged claims. Indeed, in its Preliminary Response, Patent Owner pointed out that McCloskey II was considered as prior art during prosecution of an ancestor application. Prelim. Resp. 12–13 (citing Ex. 2002, 335–336). Patent Owner, however, does dispute that McCloskey II is analogous art, which we address next. PO Resp. 51–53.

4. Linnarsson, McCloskey, and McCloskey II are Analogous Art

“Although § 103 does not, by its terms, define the ‘art to which [the] subject matter [sought to be patented] pertains,’ this determination is frequently couched in terms of whether the art is analogous or not, i.e., whether the art is ‘too remote to be treated as prior art.’” *In re Clay*, 966 F.2d 656, 658 (Fed. Cir. 1992) (quoting *In re Sovish*, 769 F.2d 738, 741 (Fed. Cir. 1985)). “Whether a reference in the prior art is ‘analogous’ is a fact question.” *Clay*, 966 F.2d at 658. “Two criteria have evolved for determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of the inventor’s endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.” *Id.* at 658–59.

Patent Owner argues that “[n]owhere does Petitioner assert—let alone attempt to show—that any of the three references named in its grounds (primary reference Linnarsson and secondary references McCloskey and McCloskey II) is analogous art *to* ’013.” PO Resp. 51 (citing Pet. 35–36, 60–62). As Patent Owner explains it, the Petition asserts that the references are analogous *to each other* but does not assert that they are analogous *to the challenged claims*. *Id.* at 51–52 (citing *Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373, 1380 (Fed. Cir. 2023)).

Patent Owner is correct that, under *Sanofi-Aventis*, 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, as we noted when instituting this proceeding, “*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.”’” Dec. on Reh’g 16 (quoting *Sanofi-Aventis*, 66 F.4th at 1379 (quoting 37 C.F.R. § 42.23)).

In its Reply, Petitioner argues that Linnarsson is analogous art because, like the specification and claims of the ’013 patent, it “deal[s] with ‘analysis of gene expression in single cells or in a plurality of single cells’

based on nucleic acid tagging and sequencing.” Pet. Reply 27 (citing Ex. 1003, Abstr., 1:6–9, 3:25–4:2, 9:23–10:2, 10:15–30, Fig. 11, claims 1, 26–27; Ex. 1001, code (54), Abstr., 6:41–7:30, claim 1; Ex. 1070 ¶¶147–149). In its Reply, Petitioner also argues that McCloskey and McCloskey II are analogous art because, like the specification and claims of the ’013 patent, they “deal with tagging polynucleotides for amplification,[] 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 arising from different cell or allele copies.’” Pet. Reply 27–28 (citing Ex. 1004, 2, Fig. 1; Ex. 1055, 5–6; Ex. 1001, code (54), Abstr., 6:33–7:22, claim 1; Ex. 1070 ¶¶150–152).

We find that all three references are analogous art to the ’013 patent, as there is ample supporting evidence in the record, including that to which the Reply cites (citations identified in the immediately preceding paragraph). Indeed, Patent Owner does not dispute the merits of Petitioner’s Reply arguments. PO Sur-reply 29–30. Rather, Patent Owner, argues that we “should not now permit Petitioner to rewrite its clearly-deficient Petition.” *Id.* at 30.

Petitioner’s Reply does not re-write its Petition. What Petitioner’s Reply does, in response to Patent Owner’s arguments, is precisely what *Sanofi-Aventis* contemplates as being proper in a reply brief. Indeed, in ruling against the petitioner in *Sanofi-Aventis*, the Federal Circuit specifically noted that the petitioner could have used its reply brief “to explain how [the prior art reference] is analogous to the [challenged] patent” *but did not do so*. 66 F.4th at 1379–1380. Here, in contrast, Petitioner uses

its Reply to explain how the references are analogous to the '013 patent. Petitioner's explanation in its Reply is both proper and persuasive.

5. McCloskey is a Prior Art Printed Publication; Patent Owner's Motion to Exclude is Granted-in-Part and Denied-in-Part

McCloskey is an article titled "Encoding PCR Products with Batch-stamps and Barcodes," and authored by Megan L. McCloskey, Reinhard Stoger, R. Scott Hansen, and Charles D. Laird. Ex. 1004, 1. Petitioner argues that McCloskey is a prior art printed publication because it was published in BIOCHEMICAL GENETICS in 2007, as indicated on the cover of McCloskey. Pet. 22 (citing Ex. 1004, 1; Ex. 1028). Exhibit 1028 is not relevant to the prior art status of McCloskey and appears to have been prepared for another matter. See Ex. 1028 ¶¶43, 50, 57 (discussing three references, none of which is McCloskey, McCloskey II, or Linnarsson).

Patent Owner argues that "Petitioner failed to establish McCloskey is, in fact, prior art to '013." PO Resp. 20 (citing *Standard Innovation Corp. v. Lelo, Inc.*, No. IPR2014-00148, Paper 41 at 18–28 (Apr. 23, 2015); *Dropbox, Inc. v. Synchronoss Techs.*, No. IPR2016-00850, Paper 41 at 18–23 (Oct. 5, 2016); *Liquidia Techs. v. United Therapeutics Corp.*, No. IPR2020-00770, Paper 45, at 56–57 (Oct. 8, 2021)). Patent Owner does not explain how Petitioner allegedly failed to prove McCloskey is prior art. Instead, Patent Owner implies, via its description of *Standard Innovation's* holding, that Petitioner failed to prove that McCloskey is what it has been represented to be and/or that it was actually published in 2007. PO Resp. 20–21.

With its Reply, Petitioner submitted a second declaration from the same witness who executed the irrelevant Exhibit 1028, i.e., Sylvia Hall-Ellis, Ph.D. Ex. 1085. In that second declaration, Dr. Hall-Ellis includes an Exhibit A, which she testifies includes a copy of McCloskey that she obtained from Linda Hall Library of Science, Engineering & Technology. *Id.* ¶¶43–50, “Exhibit A.” Dr. Hall-Ellis testifies that McCloskey is the article it appears to be, was published in BIOCHEMICAL GENETICS in 2007, and was received, catalogued, and indexed, and made publicly available by Linda Hall Library on or shortly after January 3, 2008. *Id.* ¶¶43–50.

Patent Owner filed a Motion to Exclude the second Hall-Ellis declaration (Ex. 1085) and McCloskey (Ex. 1004). PO Mot. To Exclude.

With respect to the second Hall-Ellis declaration, Patent Owner objected to its admissibility on the basis that, among other things, it “should have been served, but was not, as supplemental evidence within ten business days of [Patent Owner] 10x’s timely objection under 37 C.F.R. § 42.64(b)(2)” to McCloskey. Paper 27, 4. More specifically, Patent Owner had previously objected -- on February 15, 2024 -- to McCloskey as allegedly unauthenticated, undated (absent hearsay), and thus irrelevant as not a prior art printed publication as to the challenged claims. Paper 12, 1–3.

Clearly, the second Hall-Ellis declaration is offered to prove that McCloskey is a prior art printed publication. *See, e.g.*, Ex. 1085 ¶50 (“In view of the foregoing, it is my opinion that [McCloskey] was publicly available no later than [January 3, 2008].”). Thus, the second Hall-Ellis declaration should have been served within ten business days of Patent Owner’s February 15, 2024, objection to the admissibility of McCloskey. *See* 37 C.F.R. § 42.64(b)(2) (“The party relying on evidence to which an

objection is timely served may respond to the objection by serving supplemental evidence within ten business days of service of the objection.”).

In its Opposition to the Motion to Exclude, Petitioner argues that, under *Hulu LLC v. Sound View Innovations, LLC*, No. IPR2018-01039, Paper 29 (Dec. 20, 2019) (precedential), it was allowed to wait until its Reply to file the second Hall-Ellis declaration. Paper 37, 2. The Board in *Hulu* does state that, “if the patent owner challenges a reference’s status as a printed publication, a petitioner may submit a supporting declaration with its reply to further support its argument that a reference qualifies as a printed publication.” *Hulu*, at 15 (37 C.F.R. § 42.23). However, the Board’s statement was referring to the scope of permissible reply arguments under 37 C.F.R. § 42.23(b). *See Hulu* at 14 (quoting 37 C.F.R. § 42.23(b)’s requirement that “[a] reply may only respond to arguments raised in the corresponding opposition, patent owner preliminary response, or patent owner response”). The Board in *Hulu* does not purport to interpret 37 C.F.R. § 42.64 or even discuss supplemental evidence. Petitioner clearly missed the deadline imposed by 37 C.F.R. § 42.64(b)(2), which was triggered by Patent Owner’s February 15, 2024, objection to McCloskey (i.e., Ex. 1004). Patent Owner’s Motion to Exclude is granted with respect to the second Hall-Ellis declaration (i.e., Ex. 1085).

Despite the exclusion of the second Hall-Ellis declaration, there is ample evidence in the record demonstrating that McCloskey is a prior art printed publication. McCloskey itself states: “Received: 31 January 2007 / Accepted: 29 May 2007 / Published online: 23 October 2007.” Ex. 1004, 1. McCloskey additionally states that it was published in a 2007 print issue of

“Biochem Genet,” with Petitioner adding that the full name of the journal is BIOCHEMICAL GENETICS and that McCloskey was published in a December 2007 volume of the journal. *Id.*; Pet. 22. McCloskey also includes a copyright notice by “Springer Science+Business Media, LLC” with a date of 2007. Ex. 1004, 1. Patent Owner argues that this is unreliable hearsay that should be excluded. PO Mot. To Exclude 4 (citing *Neste Oil Oyj v. REG Synthetic Fuels, LLC*, No. IPR2013-00578, Paper 53 at 5–7 (Mar. 12, 2015); *Standard Innovation Corp. v. Lelo, Inc.*, No. IPR2014-00148, Paper 42⁹ at 13–18, 21–22 (Apr. 23, 2015)). We are not persuaded by Patent Owner’s argument or its reliance on these cases. The facts before us are different.

In *Neste Oil*, the Board “note[d] that the alleged ‘stamps’ of Exhibits 1125 and 1132 are actually handwritten dates, added to the documents by an unknown person at an unknown time.” *Neste Oil*, Paper 53 at 6. In contrast, the dates relied upon by Petitioner are printed, appear to have been included at the time of printing, and appear to have been printed by, or at the direction of, the journal and/or copyright holder, both of which are identified by McCloskey. Ex. 1004, 1.

In *Standard Innovation*, the alleged prior art exhibits were “printouts of ... webpages” bearing a copyright indication of “© 2003-2013,” which the petitioner argued was proof of subset of the webpages being disseminated publicly in 2003. *Standard Innovation*, Paper 42 at 13. This is a far cry from McCloskey, which is a journal article and which includes

⁹ Patent Owner actually cited to “Pap.41” of *Standard Innovation*. PO Mot. To Exclude 4. There is no Paper 41 in the record of that case. We presume Patent Owner intended to cite Paper 42, which is the final written decision in that case.

specific date information, not only of publishing, but also of when the journal received and accepted the article for publication and when it was copyrighted. Ex. 1004, 1.

That McCloskey is what it purports to be (a journal article) and that it was published in 2007 are corroborated by multiple pieces of evidence.

McCloskey names four authors, all of whom are named inventors of McCloskey II. Ex. 1004, 1; Ex. 1055, code (76). Patent Owner concedes that McCloskey and McCloskey II involve the same subject matter, having argued that the consideration of McCloskey II supported discretionary denial of the Petition based on McCloskey. *See, e.g.*, Prelim. Resp. 26 (“McCloskey is cumulative of McCloskey II.”). Notably, McCloskey II was published on January 25, 2007. Ex. 2001, code (43). That is just days before McCloskey was received by BIOCHEMICAL GENETICS on January 31, 2007. *See* Ex. 1004, 1 (“Received: 31 January 2007 / Accepted: 29 May 2007 / Published online: 23 October 2007”). In other words, it appears that the authors sought to have their research published in a scientific journal promptly after the subject matter of their research had been published by the Office.

Further, the existence of McCloskey and its publication year of 2007 is confirmed by other references in the record. *See* Ex. 1029, code (56) (United States Patent identifying as a cited reference: “McCloskey, et al. Encoding Pcr products with batch-stamps and barcodes. Biochem Genet. Dec. 2007;45(11-12):761-7. Epub Oct. 23, 2007.”); Ex. 1053, code (56) (same); Ex. 1060, 13 (article’s bibliography citing “McCloskey ML, Stöger R, Hansen RS, Laird CD. Encoding PCR products with batch-stamps and barcodes. Biochem. Genet 2007;45:761–767. [PubMed: 17955361]”).

Patent Owner points out that *one* of the three just-cited references of record, i.e., Exhibit 1053, “***issued in 2017 and thus post-dates the priority date by eight years***, and therefore does not constitute evidence that McCloskey was publicly accessible as of the ***2009 priority date***.” PO Mot. To Exclude 6 (citing Ex. 1053). Although Exhibit 1053, published in 2017, is not *contemporaneous* evidence of the 2007 publication of McCloskey, it nonetheless is evidence helping to corroborate that McCloskey was, in fact, published in 2007. More importantly, additional corroborative evidence exists in the record. In particular, another of the three references cited above, i.e., Ex. 1060, was published relatively shortly after McCloskey, in December 2008, and references McCloskey as being published in the same page range (pages 761–767) of the same volume (45) of the same periodical (Biochemical Genetics) as appears on McCloskey itself. *Compare* Ex. 1060, 13 (“Biochem. Genet 2007;45:761–767”), *with* Ex. 1004, 1 (“Biochem Genet (2007) 45:761–767”). This evidence is the figurative nail in the coffin for Patent Owner’s argument that McCloskey is not a prior art printed publication.¹⁰

¹⁰ During the hearing, counsel for Patent Owner stressed the applicability of *Medivis, Inc. v. Novarad Corp.*, No. IPR2023-00042 to the present set of facts. Tr. 82:21–83:2. Patent Owner cites a first decision from *Medivis* as stating that “any reference can state it was published without actually being published.” PO Mot. To Exclude 5 (quoting *Medivis* Paper 35 at 28 (Mar. 6, 2024)). Patent Owner quotes a second decision from *Medivis* as stating that “the Petition [in *Medivis*] . . . cites no evidence for public accessibility, except the references . . . themselves. This is insufficient and tantamount to submitting no proof of public accessibility.” *Id.* at 5–6 (quoting *Medivis* Paper 37 at 4 (Apr. 23, 2024)). We find *Medivis* inapposite to the facts

Patent Owner's Motion to Exclude is denied with respect to McCloskey (i.e., Ex. 1004). In sum, Petitioner has shown that McCloskey is a printed publication as of 2007 and, thus, prior art to the challenged claims of the '013 patent.

E. Ground I: Claim 1

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.

Claim 1 is directed to “[a] method for multiplexed analysis of nucleic acids from single cells.” Ex. 1001, 30:39–40. The method involves “performing combinatorial tagging to generate a plurality of tagged polynucleotides” in which “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.” *Id.* at 30:43–53. Said tagged polynucleotide “comprises: (i) a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides; (ii) a

before us. McCloskey need not stand on its own statement of publication. Instead, we have three other references in the record corroborating that McCloskey was published in 2007. Ex. 1029; Ex. 1053; Ex. 1060. We also have McCloskey II indisputably being published by the Office on January 25, 2007, just days before McCloskey, which Patent Owner characterizes as “cumulative of McCloskey II” (Prelim. Resp. 25), states that it was “[r]eceived” by BIOCHEMICAL GENETICS on January 31, 2007. Ex. 1055, code (43); Ex. 1004, 1.

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,” which tag sequences ultimately facilitate the “count[ing of] sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells.”

Id. at 30:54–31:9

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. We preserve Petitioner’s labeling in our discussion.

For limitations [1A], [1B], [1D], [1F], [1G], [1I], and [1J], Petitioner essentially 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]).

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, 30:43–31:9. 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.¹¹ 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.” *Id.* at 35.

As explained below, we find that Petitioner has shown that the asserted prior art satisfies each limitation of the claim and that the subject matter as a whole would have been obvious at the time of the claimed invention – August 20, 2009.

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

A claim’s preamble is not necessarily limiting. *See, e.g., Pitney Bowes Inc. v. Hewlett Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). The Petition all but presumes that the preamble of claim 1 is limiting and directs us to prior art disclosures of the subject matter. *See* Pet. 27 (“To the extent the preamble is limiting, Linnarsson discloses this limitation.”). For example, Petitioner directs us to Linnarsson’s statement that its “invention

¹¹ Petitioner suggests, without any explanation, that Linnarsson alone *might* teach ligating a second tag. *See* Pet. 34 (“To the extent Linnarsson does not teach ligating a second oligonucleotide tag to the claimed ‘extension product,’ this would have been obvious in view of McCloskey and the knowledge of a POSA.”). We discern no evidence to support that Linnarsson teaches tagging a polynucleotide with a second tag, whether by ligation or otherwise.

provides methods and compositions for the analysis of gene expression in single cells or in a plurality of single cells.” *Id.* at 27–28 (quoting Ex. 1003, 9:23–24; *see also* Ex. 1003, 4:8–13, Fig. 1 (cited at Pet. 28)).

Patent Owner does not dispute that the prior art teaches the preamble of claim 1. *See generally* PO Resp. We are persuaded that it does.

2. [1B] “(a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides”

Petitioner argues that Linnarsson discloses this limitation. Pet. 28. Petitioner cites multiple disclosures from Linnarsson in support, including that “[s]ingle cells useful in the methods described herein can be obtained from a tissue of interest, or from a biopsy, blood sample, or cell culture.” Ex. 1003, 13:11–12 (cited at Pet. 28). As for the recitation that “a single cell of the plurality of cells comprises a plurality of sample polynucleotides,” Petitioner cites disclosure from Linnarsson that “single cells are placed in separate wells of a 96-well plate and lysed [and] tagged reverse transcription is performed on each sample to produce cDNA” and, “[i]n some aspects of the invention, mRNA can be released from the cells by lysing the cells.” Ex. 1003, 4:10–11, 13:28 (cited at Pet. 28).

Patent Owner does not dispute that the prior art teaches limitation [1B]. *See generally* PO Resp. We are persuaded that it does.

3. [1C] “(b) performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags”

Petitioner argues that Linnarsson discloses all of the subject matter of this limitation except the “combinatorial” aspect of the tagging. Pet. 29–30. Petitioner cites multiple disclosures from Linnarsson in support, including the following two excerpts:

The invention provides method for preparing a cDNA library from a plurality of single cells. In one aspect, the method includes the steps of releasing 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 pooled cDNA samples to generate a cDNA library having double-stranded cDNA.

* * *

As the tag is present in the CDS and/or the TSO it will be incorporated into the cDNA during its synthesis and can therefore act as a “barcode” to identify the cDNA.

Ex. 1003, 3:25–30, 19:4–5 (both excerpts cited at Pet. 30).

Patent Owner does not dispute that Linnarsson teaches tagging, albeit not *combinatorial* tagging.

With respect to the “combinatorial” aspect of the “tagging,” Petitioner argues that it would have been obvious over Linnarsson in view of McCloskey, which teaches using two tags. Pet. 29–30. In support, Petitioner directs us to its analysis for limitations [1G] and [1H], which delineate the scope of the “combinatorial tagging.” Collectively, they recite that “said tagged polynucleotide . . . comprises: . . . (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.” Ex. 1001, 30:54–64. We address those limitations below in Sections II.E.(5), (7), and (8).

4. [1D] “*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*”

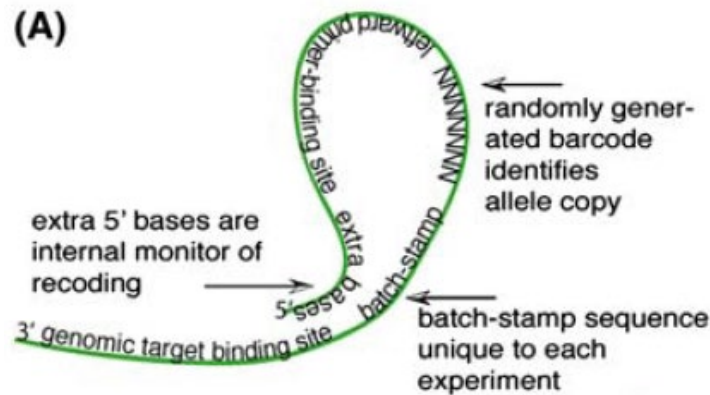
Petitioner argues that Linnarsson discloses this limitation. Pet. 31–34. As with limitation [1C], Petitioner again points to column 3, lines 25 through 30, and column 19, lines 4 to 5. *Id.* at 31 (citing Ex. 1003, 3:25–30, 19:4–5). In addition, Petitioner directs us to Figures 3 and 4 of Linnarsson, which illustrate primer extension that results in tagged polynucleotides. *See id.* at 31–33 (reproducing Ex. 1003, Figs. 3–4).

Patent Owner does not dispute that the prior art teaches limitation [1D]. *See generally* PO Resp. We are persuaded that it does.

5. [1E] “*(B) ligating a second oligonucleotide tag to said extension product*”

Petitioner argues that this limitation would have been an obvious modification of Linnarsson in view of McCloskey and the knowledge of the skilled artisan. Pet. 34.

First, Petitioner directs us to McCloskey’s disclosure of an “encoding oligonucleotide” that comprises two tag sequences. Pet. 34 (citing Ex. 1004, 1–3, Fig. 1.). Figure 1(A) of McCloskey is reproduced below.



Ex. 1004, Fig. 1(A). Figure 1(A) of McCloskey above shows encoding oligonucleotide having “five distinct regions,” namely “a genomic target-binding site, a batch-stamp, a barcode, a primer-binding site for PCR, and extra bases that serve as internal sentinels of recoding as well as tethering the oligonucleotide to itself.” Ex. 1004, 3. Patent Owner argues that “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. 35 (quoting Ex. 1004, 2).

Petitioner argues that “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. Although McCloskey introduces both of its tags through a primer extension reaction, Petitioner argues that “it would have been nothing more than an obvious and routine design choice to instead introduce the molecule tag via ligation.” *Id.* at 37 (citing Ex. 1002 ¶144).

Patent Owner does not dispute that McCloskey teaches the use of two tags in combination to track individual polynucleotides. *See, e.g.*, PO Resp. 18 (acknowledging McCloskey’s teachings). Nor does Patent Owner dispute that ligation was well known in the art. *See generally* PO Resp. (not arguing to the contrary); PO Sur-Reply 3 (acknowledging “[t]hat ‘ligation’ is conventional”). Instead, Patent Owner disputes that the skilled artisan would have had a reason to make the proposed modification or, even if she did, whether she would have had a reasonable expectation of success in achieving the claimed subject matter. *See* PO Resp. 22 (“**Ground 1: Petitioner’s Obviousness Analysis Fails To Establish A Motivation To Combine With REOS**”).

We are persuaded that Petitioner’s proposed modification of Linnarsson in view of McCloskey and the knowledge of the skilled artisan would have resulted in the claimed subject matter, including “ligating a second oligonucleotide tag to said extension product.” Ex. 1003, 3:25–30, 19:4–5; Ex. 1004, 1–3, Fig. 1(A); Ex. 1002 ¶144. Further, and as discussed below in Sections II.E.(12) and (13), we are persuaded that a person of ordinary skill in the art would have had a sufficient reason to make the modification and a reasonable expectation of success in doing so.

6. *[IF] “wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises: a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides”*

Petitioner argues that Linnarsson discloses this limitation. Pet. 39–42. Petitioner, with supporting testimony from Dr. Cooper, explains that by virtue of the way a CDS and a TSO work, the sequence of a polynucleotide

(whether it is mRNA in the case of a CDS or cDNA in the case of a TSO) is preserved as the amplification occurs. *See, e.g.*, Ex. 1002 ¶154 (Dr. Cooper testifying that “a cDNA synthesized from a sample mRNA comprises the same sample sequence.”); Pet. 40 (citing Ex. 1002 ¶154).

Patent Owner does not dispute that the prior art teaches limitation [1F]. *See generally* PO Resp. We are persuaded that it does.

7. [1G] “*wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises: ...a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells*”

Petitioner argues that Linnarsson discloses this limitation. Pet. 42–43. Petitioner cites multiple disclosures from Linnarsson in support, including that “tagged reverse transcriptase is performed on each sample to produce cDNA” and this allows for “identification of expressed genes and identification of cells from which they originated.” Ex. 1003, 4:8–13 (cited at Pet. 43); *see also* Ex. 1003, 19:5–11 (disclosing that the use of its tagged CDS and TSO results in tagged cDNA).

Patent Owner does not dispute that the prior art teaches limitation [1G]. *See generally* PO Resp. We are persuaded that it does.

8. [1H] “*wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises: ...a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell.*”

Limitation [1H] recites “a second tag sequence,” which is in addition to the “first tag sequence” recited in limitation [1G]. Petitioner relies on a modification of Linnarsson in view of McCloskey and the level of skill in the art to reach this dual-tag feature. *See, e.g.*, Pet. 43 (“The combination of

Linnarsson and McCloskey in view of the knowledge of the skilled artisan teaches this claim element.”). For reasons discussed above in Section 2.E.(5), we are persuaded that the proposed modification would include this limitation.

9. [1I] “(c) amplifying said tagged polynucleotide, thereby generating a plurality of amplified polynucleotides corresponding to the tagged polynucleotide”

Petitioner argues that Linnarsson discloses this limitation. Pet. 44. Petitioner cites multiple disclosures from Linnarsson in support, including that the tagged “cDNA samples are pooled and amplified.” Ex. 1003, 4:11–12 (cited at Pet. 44); *see also* Ex. 1003, 10:20–22 (“[T]he cDNA in each tagged cDNA sample is complementary to mRNA from a single cell pooling the tagged cDNA samples and amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA.” (cited at Pet. 44)).

Patent Owner does not dispute that the prior art teaches limitation [1I]. *See generally* PO Resp. We are persuaded that it does.

10. [1J] “(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”

Petitioner argues that Linnarsson teaches this limitation. Pet. 44. Petitioner cites multiple disclosures from Linnarsson in support, including that, “after generating the tagged polynucleotides, ‘sequencing is performed’ thereon.” Pet. 44 (quoting Ex. 1003, 4:12); *see also* Ex. 1002, 21:24–25

(“This cDNA library can be sequenced to provide an analysis of gene expression in single cells or in a plurality of single cells.” (cited at Pet. 44)).

Patent Owner disputes that Linnarsson teaches sequencing an entire tagged polynucleotide and instead teaches sequencing only portions or fragments of tagged polynucleotides. PO Resp. 42–48. One might reasonably assume, based on those arguments, that Patent Owner construes the limitation to require sequencing the entire tagged polynucleotide. But Patent Owner does not. Patent Owner’s position, which we explain in more detail below, is a curious one. It is not persuasive.

In the Patent Owner Response, Patent Owner cites numerous references by Linnarsson to *fragmenting* the tagged polynucleotides (cDNA) such as its statement that “the cDNA library can be processed by fragmenting the cDNA library (e.g. with DNase) to obtain a short fragment 5' -end library.” Ex. 1002, 21:18–25 (quoted at PO Resp. 44). Thus, according to Patent Owner, Petitioner “fail[s] to show Linnarsson discloses sequencing the entirety of the ‘tagged polynucleotide’.” PO Resp. 43.

In its Reply, Petitioner maintains that Linnarsson, in fact, teaches sequencing the entirety of tagged polynucleotides. *See, e.g.*, Pet. Reply 16 (“Patent Owner’s contention that Linnarsson does not disclose sequencing “entire” polynucleotides . . . is based on the mistaken view that Linnarsson requires the fragmentation approach of Figure 11,” which it does not.). We need not find whether it does, however, because Petitioner persuasively argues that the “sequencing” limitation does not require sequencing of an entire tagged polynucleotide. *Id.* at 14 (citing Ex. 1070 ¶¶8–9, 23–30, 96–127).

Indeed, Patent Owner does not argue that the “sequencing” limitation requires sequencing of an entire tagged polynucleotide. *See* PO Sur-reply 17–18 (referring to such a claim construction as one that Patent Owner “never argued”); Tr. 27:22–23 (Counsel for Petitioner confirming “we’ve never argued” that the limitation requires sequencing the entire tagged polynucleotide). Rather, Patent Owner argues that “***Petitioner’s sole argument for disclosure of the sequencing limitation***” is that Linnarsson discloses sequencing the entire polynucleotide. PO Sur-reply 18. In Patent Owner’s view, any reliance by Petitioner on sequencing less than an entire and unfragmented tagged polynucleotides constitutes a new and improper argument. *See id.* (“Petitioner is foreclosed from starting over now with improper ***new*** arguments for mapping this limitation.”). We disagree with Patent Owner’s characterization of Petitioner’s argument.

It cannot be disputed that Linnarsson explicitly teaches “sequencing is performed” on tagged polynucleotides after they are amplified, as set forth in the following disclosure:

Figure 1, panels A–F, show an overview of a method of analyzing gene expression in a plurality of single cells. (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.

Ex. 1003, 4:8–13 (emphasis added). Nor can it be disputed that Petitioner cited this very disclosure as teaching limitation [1J]. *See* Pet. 44 (“Linnarsson teaches that after generating the tagged polynucleotides, ‘sequencing is performed’ thereon. *See* EX1003 at 4:8–13.”). This alone

adequately supports Petitioner's challenge, and it is not a new or improper argument.

We are persuaded that the prior art teaches limitation [1J].

11. [1K] “(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”

Petitioner relies on a modification of Linnarsson in view of McCloskey to satisfy this limitation. *See, e.g.*, Pet. 45 (“The combination of Linnarsson and McCloskey discloses this claim element.”). In support, Petitioner first recalls that “the combination of Linnarsson and McCloskey discloses and renders obvious using a first tag to identify the single-cell origin of tagged polynucleotides, and using a second tag to uniquely identify each [of the] tagged polynucleotides.” *Id.* We are persuaded of this, as discussed above in Sections 2.E.(3)–(5). Petitioner next directs us to McCloskey's disclosure that “counting sequences with nonredundant barcodes provides a quantitative measure of template diversity.” Ex. 1004, 6 (quoted at Pet. 45). Thus, according to Petitioner and Dr. Cooper, “McCloskey's method provides that counting unique molecular tags would provide a count of sample polynucleotides.” Pet. 45 (citing Ex. 1002 ¶¶240–242). In addition, Petitioner cites evidence, including the '013 patent, that the use of molecular tags for counting sample polynucleotides was well-known and routine. *Id.* at 45–46 (citing Ex. 1002 ¶72; Ex. 1001, 22:47–49). Indeed, the '013 patent states that “[t]he reflex process described herein can be used to perform powerful linkage analysis by combining it with nucleic acid counting methods” of the prior art. Ex. 1001, 22:45–47; *see also id.* at

22:47–54 (stating that “[a]ny convenient method for tagging and/or counting individual nucleic acid molecules with unique tags may be employed” and identifying prior art patents/applications disclosing the same).

Patent Owner does not dispute that the prior art teaches limitation [1K]. *See generally* PO Resp. We are persuaded that it does.

12.Reason To Combine

“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). “[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *Id.*; *see also In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”).

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 supports its assertion with several reasons, primarily the following four. First, Petitioner points out that Linnarsson and McCloskey “focus on significantly the same subject matter” as both “describe methods of genetic analysis of single cells whereby polynucleotides are annealed to oligonucleotides comprising tag sequences.” *Id.* Second, Petitioner points

out that Linnarsson teaches that “there is potential amplification bias” with its method and asserts that “McCloskey provides the exact solution to this problem, which is to tag the polynucleotides *before amplification* with a tag that distinguishes different molecules within a sample from one another.” Pet. 36 (citing Ex. 1003, 2:3–13; Ex. 1004, 1). Third, Petitioner argues that, “while McCloskey introduces both the cell tag and the molecule tag through a primer extension reaction, it would have been nothing more than an obvious and routine design choice to instead introduce the molecule tag via ligation.” *Id.* at 37 (citing Ex. 1002 ¶144; Ex. 1001, 6:31–40, 13:40–47). Fourth, Petitioner argues that doing so via ligation “would allow for added flexibility in selecting tag sequences during an experiment.” *Id.* at 39 (citing Ex. 1002 ¶149).

The Supreme Court has “set forth an expansive and flexible approach” to “the question of obviousness” under 35 U.S.C. § 103. *KSR*, 550 U.S. at 415. In *KSR*, the Supreme Court held the following:

When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. [The relevant question is] whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR, 550 U.S. at 417; *see also Uber Techs., Inc. v. X One, Inc.*, 957 F.3d 1334, 1338 (Fed. Cir. 2020) (quoting the same excerpt from *KSR* and referring to it as a “discussion of design choices and predictable variations”).

Here, Petitioner argues that, “while McCloskey introduces both the cell tag and the molecule tag through a primer extension reaction, it would have been nothing more than an obvious and routine design choice to instead introduce the molecule tag via ligation.” Pet. 37 (citing Ex. 1002 ¶144; Ex. 1001, 6:31–40, 13:40–47). This is so, according to the Petition, because “it was well-known and routine in the art to attach tag sequences to other sequences by ligation.” *Id.* (citing Ex. 1002 ¶144). In addition to citing Dr. Cooper’s testimony on that point, the Petition points to admissions in the ’013 patent. *Id.* For example, the ’013 patent states:

The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. *Such conventional techniques include* polymer array synthesis, hybridization, *ligation*, and detection of hybridization using a label.

Ex. 1001, 13:40–47 (emphasis added). The ’013 patent lists nine references that describe ligation reactions and incorporate them by reference. *See id.* at 6:31–40 (“A variety of template-driven ligation reactions are described in the following references, which are incorporated by reference.”). The Petition also directs us to positions Patent Owner took in patent litigation involving other patents. *See* Pet. 38 (“Patent Owner stated with respect to the Fodor Patents, for instance, that ‘the specification admits that “in one embodiment” of the invention “the label-tag is attached by ligation” and that “methods of ligation will be known to those of skill in the art.”’” (quoting Ex. 1007, 11–12)); *see also* PO Sur-Reply 3 (acknowledging “[t]hat ‘ligation’ is conventional”).

Petitioner further argues that 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” and that “it would have been obvious to do this by using a linker molecule” in view of Hug.¹² Pet. 38 (citing Ex. 1007, 8; Ex. 1002 ¶¶228–229).

Patent Owner argues that “Petitioner has failed to show why POSITA would have added such a [ligation] step.” PO Resp. 25. However, Petitioner did provide reasons, arguing:

As Dr. Cooper explains, this approach would be entirely equivalent to the method already disclosed . . . except that 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. A [skilled artisan] would have been motivated to utilize this design choice because it would allow for added flexibility in selecting tag sequences during an experiment.

Pet. 39 (citing Ex. 1002 ¶149); *see also* Ex. 2020, 42:9–15 (Dr. Cooper: “And so then the question becomes how does one add the second tag effectively to a Linnarsson process. And there’s really only a couple of options. Right? There is to build it into the primers they used to make the cDNA or to ligate it on after you’ve made that initial cDNA.”).

Patent Owner argues that, because the ligation approach would have been “*entirely equivalent* to the method [already] disclosed by the combination of Linnarsson and McCloskey,” that fact “negates” any reason to implement the ligation. PO Resp. 25–26 (quoting Ex. 1002 ¶149). Patent Owner cites a non-precedential opinion, *South-Tek Sys., LLC v. Engineered*

¹² Hubert Hug et al., *Measurement of Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation*, 221 J. THEOR. BIO., 615-624 (2003) (Ex. 1007, “Hug”).

Corrosion Sols., LLC, No. IPR2016-00136, Paper 52, 20–23 (May 10, 2017), as supporting its argument, but it does not. Patent Owner does not quote from *South-Tek* but characterizes it as “finding no motivation to combine where the modification rendered a feature in the primary reference redundant.” PO Resp. 26.

Patent Owner’s reliance on *South-Tek* is misplaced. In *South-Tek*, the Board wrote:

The proposed combination, as asserted in the Petition, adds a new component to Viking. Petitioners did not assert in the Petition that Wood’s automatic condensate drain would replace the manual condensate drain, or drum drip 24, in Viking, or any other drain in Viking. Thus, Petitioners’ proposed modification results in two condensate drains in Viking, one a manual drain (drum drip 24) and one an automatic drain, without a persuasive explanation as to why a person of ordinary skill would make this change.

South-Tek, Paper 52, at 20. Here, Patent Owner has not identified any feature that would be redundant in Petitioner’s proposed modification. Certainly, the second tag sequence is not redundant of the first tag sequence, as they serve different tracking purposes.

Next, Patent Owner erroneously characterizes the Petition, stating that “Petitioner’s *sole* purported justification for th[e] proposed modification is the conclusory assertion that ‘it would allow for added flexibility in selecting tag sequences during an experiment.’” PO Resp. 26 (quoting Pet. 39; emphasis added). In fact, the Petition also relied on “design choice,” as discussed above. Pet. 37.

Patent Owner does not show that the proposed modification would have been beyond the level of skill in the art. Nor does Patent Owner show that the modification would have resulted in anything beyond what would

have been predicted based on these prior art teachings. In fact, the Patent Owner Response does not even address Petitioner's design choice rationale. PO Resp. 26 (erroneously asserting that the Petition relies solely on providing "added flexibility in selecting tag sequences during an experiment"). We find Petitioner's un rebutted rationale of obvious design choice persuasive.

Although we find Petitioner's "design choice" rationale adequate, we also address Petitioner's additional rationale that a skilled artisan would have made the modification because "it would allow for added flexibility in selecting tag sequences during an experiment." Pet. 39 (citing Ex. 1002 ¶149). Patent Owner argues that this stated benefit is a "conclusory assertion" that is "parroted verbatim with no further explanation or evidence by its expert." PO Resp. 26 (citing Pet. 39; Ex. 1002 ¶149). However, Dr. Cooper does provide some explanation, testifying:

A POSA would have understood that such an approach, using ligation to add the tag sequences to the CDS and/or TSO, would have been entirely equivalent to the method disclosed by the combination of Linnarsson and McCloskey. 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. Using ligation to add the tag after extension would allow for increased flexibility in selecting tag sequences during an experiment. Thus, a POSA would have understood that using ligation was a routine choice and would have been motivated to use ligation because of the increased flexibility in tag choice.

Ex. 1002 ¶149. Thus, Dr. Cooper suggests that the increased flexibility stems from the different (delayed) timing of selecting tag sequences.

As Petitioner points out, Patent Owner could have cross-examined Dr. Cooper about this testimony but chose not to do so. Pet. Reply 8. Patent Owner responds that it was under no obligation to “ask deposition questions to enable Petitioner’s expert to volunteer new opinions.” PO Sur-reply 2; *see also id.* at 7 (characterizing Petitioner’s failure to cross-examine argument as “improperly flip[ping] the burden” onto Patent Owner). We agree that Patent Owner was not obligated to ask any particular questions of Dr. Cooper during his deposition. However, Patent Owner’s decision to not inquire as to the meaning or further details of the “increased flexibility” identified by Dr. Cooper undermines its argument that it has been deprived of the same.

In sum, although the Petition does not elaborate as to the details of the added flexibility, the Petition clearly identified it as a benefit, citing Dr. Cooper’s testimony as its evidentiary support. Patent Owner has not rebutted that such flexibility would have been viewed by a skilled artisan as a benefit.

Patent Owner also argues that the proposed modification would not have been obvious because it “would add more steps and complexity to achieve only an ‘equivalent’ method.” PO Resp. 26. This argument is not well developed and is unpersuasive in view of the fact Petitioner identified a benefit to the modification, i.e., the increased flexibility. Furthermore, that a combination might be inferior does not mean that it is non-obvious. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (“[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.”).

We find Petitioner's reasons sufficient to support the proposed modification.

13. Reasonable Expectation of Success

"[A]n obviousness determination requires not only the existence of a motivation to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination." *Medichem*, 437 F.3d at 1165. "While the definition of 'reasonable expectation' is somewhat vague, [Federal Circuit] case law makes clear that it does not require a certainty of success." *Id.*

Petitioner argues that a person of ordinary skill in the art would have had a reasonable expectation of success "[g]iven the undisputedly well-known and routine nature of ligation to attach label tags to polynucleotides." Pet. 38. Petitioner cites multiple pieces of evidence, already discussed above, which show this to be true. Pet. 37–38 (citing Ex. 1002 ¶149; Ex. 1001, 6:31–40, 13:40–47. Further, both Patent Owner and its witness, Dr. Quackenbush, concede that ligation was well known in the prior art. *See, e.g.*, PO Sur-Reply 3 (acknowledging "[t]hat 'ligation' is conventional"); Ex. 1071, 187:23–25 ("I'm not contesting that ligation was a well-known method of attaching oligonucleotides."), 188:17–8 ("I told you earlier ligation was a conventional technique."), 186:6–9 ("Ligation is a method that was known in the art just like PCR was known in the art.").¹³

¹³ More broadly, during his cross-examination, Dr. Quackenbush could not describe *anything* he thought was "inventive" about the claims of the '013

Although Patent Owner concedes that ligation was well known and conventional in the art, it disputes that a skilled artisan could have implemented ligation as proposed to achieve the claimed invention. PO Resp. 28–42.

In that regard, Patent Owner argues that “the biotin on [Linnarsson’s] CDS’s 5’ end would block ligation of a tag to the CDS” and any “tag added [to Linnarsson’s TSO] via ligation would not be extended, and would therefore not be included in the cDNA that is subsequently amplified during PCR. . . and would not be part of the ‘tagged polynucleotide’ that is sequenced.” *Id.* at 29, 34.

In its Reply, Petitioner rebuts both arguments.

As for Patent Owner’s argument regarding a TSO-based approach, it is not persuasive because it is erroneously premised on the skilled artisan ligating the second tag after completion of the PCR amplification. Dr. Cooper testified that the second tag sequence would be ligated onto the TSO

patent, stating during his deposition: “I’m not prepared to offer an opinion about the inventive concepts in the patent today.” Ex. 1069, 14:1–3. Yet, in his declaration, Dr. Quackenbush implies a familiarity with the “invention” of the ’013 patent, including a section titled “The ’013 Patent’s Invention.” Ex. 2013 ¶¶27–32. In that section, he testifies: “*Until inventions such as the ’013 Patent*, most nucleotide sequencing was performed using polynucleotides (e.g., DNA or RNA) from a population of cells in a process called bulk analysis.” *Id.* ¶29 (emphasis added). Near the end of his declaration, Dr. Quackenbush “conclude[s] that each of the Challenged Claims is not invalid as obvious under 35 U.S.C. § 103.” *Id.* ¶97. The inventiveness (or not) of the claims of the ’013 patent was squarely within the scope of Dr. Quackenbush’s direct testimony. His refusal or inability, on cross-examination, to identify anything inventive about the claims reinforces our ultimate conclusion that they are unpatentable under 35 U.S.C. § 103.

(or CDS) “after extension,” *not* after amplification. *See* Ex. 1002 ¶149 (Dr. Cooper testifying that “with the combination of Linnarsson and McCloskey [asserted against claim 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”); Ex. 2020, 42:9–15 (Dr. Cooper: “And so then the question becomes how does one add the second tag effectively to a Linnarsson process. And there’s really only a couple of options. Right? There is to build it into the primers they used to make the cDNA or to ligate it on *after you’ve made that initial cDNA.*” (emphasis added)).

As for Patent Owner’s argument regarding a CDS-based approach, Petitioner replies that the argument is erroneously premised on Linnarsson requiring the use of biotin. Pet. Reply 11–12 (“Linnarsson discloses embodiments—most notably in Figures 3 and 4—that do not use fragmentation and capture and hence do not use biotin or any restriction enzymes.” (citing Ex. 1070 ¶¶31–59, 114–127)); *see also* Pet. Reply 13–20. Petitioner also argues that, even if a person of ordinary skill in the art wanted to use biotin, she would know “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.” *Id.* at 13 (citing Ex. 1070 ¶¶81–84); *see also* Ex. 1071, 175:2–6 (Dr. Quackenbush: “So if there’s already a biotin attached, you wouldn’t be able to create that bond, hence, ligation wouldn’t occur. And a person in 2009 would have understood this.”).

Patent Owner argues that Petitioner’s argument that Linnarsson does not require biotin is a new and improper argument on reply. PO Sur-Reply 1, 5. We disagree. Petitioner’s argument is directly responsive to Patent Owner’s argument. *See* 37 C.F.R. § 42.23(b) (“A reply may only respond to

arguments raised in the corresponding opposition, patent owner preliminary response, patent owner response, or decision on institution.”). Petitioner’s argument is not only proper, but also persuasive; Linnarsson does not require biotin. *See* Ex. 1003, 3:25–4:2 (“Summary of the Invention” not mentioning biotin), 5:28–29 (“Figure 11 [which does include biotin], panels A-F, show graphical representation of steps *optionally used* in the STRT method.” (emphasis added)), Figs. 3–4 (not including biotin).

Patent Owner additionally argues that Petitioner has not “explained how Linnarsson’s method would work without biotin or fragmentation.” PO Sur-Reply 4. However, Petitioner bears no burden in that regard. *See Apple Inc. v. Corephotonics, Ltd.*, 861 F. App’x 443, 450 (Fed. Cir. 2021) (holding that in the context of AIA trial proceedings, “regardless of the forum, prior art patents and publications enjoy a presumption of enablement, and the patentee/applicant has the burden to prove nonenablement for such prior art” and that “[i]t was error for the Board to suggest otherwise”).

Further, we are persuaded by Petitioner’s argument that a person of ordinary skill in the art would have known how to use biotin in a manner that did not interfere with the proposed modification. Pet. Reply 13 (citing Ex. 1070 ¶¶81–84); *see also KSR*, 550 U.S. at 421 (“A person of ordinary skill is also a person of ordinary creativity, not an automaton.”); Ex. 1071, 175:2–6 (Dr. Quackenbush: “So if there’s already a biotin attached, you wouldn’t be able to create that bond, hence, ligation wouldn’t occur. And a person in 2009 would have understood this.”).

Patent Owner argues that Petitioner’s modification is “unclear [as to] *how* the ligation and subsequent steps” would be implemented and improperly relies on Hug, which is “*not* part of its stated Ground.” PO Resp.

38–39. We do not find these arguments persuasive. As already discussed above, it is clear from numerous evidentiary sources, including Hug, that ligation was well known and conventional in the art. Ex. 1002 ¶144; Ex. 1007, 7. Also, as already discussed above, those evidentiary sources include the '013 patent itself and Patent Owner's own declarant. Ex. 1001, 6:31–40, 13:40–47; Ex. 1071, 187:23–25, 188:17–8, 186:6–9. Further, a “person of ordinary skill is also a person of ordinary creativity, not an automaton.” *KSR*, 550 U.S. at 421. Patent Owner's argument that the skilled artisan could not have ligated a second tag sequence as proposed by Petitioner is not credible in view of this evidence.

In sum, Petitioner has demonstrated by a preponderance of the evidence 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 as proposed and resulting in the subject matter of claim 1.

14. Conclusion as to Claim 1

We conclude that claim 1 would have been obvious over Linnarsson, McCloskey, and the knowledge of a person of ordinary skill in the art as asserted by Petitioner based on the evidence presented.¹⁴

¹⁴ “[E]vidence rising out of the so-called ‘secondary considerations’ must always when present be considered en route to a determination of obviousness.” *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). The record before us, however, lacks any secondary considerations evidence.

F. Ground 1: Dependent Claims

Each of claims 2–12 and 19–28 ultimately depends from claim 1. Ex. 1001, 31:10–44, 32:8–59. Petitioner argues the proposed modification of Linnarsson, McCloskey, and the knowledge of a person of ordinary skill in the art, as already discussed above in relation to claim 1, includes each of the additional limitations recited in these dependent claims. Pet. 46–60. Patent Owner does not present any arguments specifically directed to any of these dependent claims, relying exclusively on their dependence from claim 1. PO Resp. 22–49.

In view of our analysis of claim 1 and our review of Petitioner’s mapping of the prior art to the additional limitations recited in claims 2–12 and 19–28, which is unrebutted by Patent Owner, we conclude that they would have been obvious over Linnarsson, McCloskey, and the knowledge of a person of ordinary skill in the art as asserted by Petitioner based on the evidence presented.

G. Ground II

In Ground II, Petitioner argues that claims 13–18 would have been obvious over Linnarsson, McCloskey, McCloskey II, and the knowledge of a person of ordinary skill in the art. Pet. 5. Each of claims 13–18 ultimately depends from claim 1. Ex. 1001, 31:46–32:7.

Claims 13 and 14 depend from claim 1 and add a limitation regarding how much of “said plurality of tagged polynucleotides have a second tag sequence that is different from second tag sequences of the other tagged polynucleotides.” Ex. 1001, 31:46–53. Claim 13 recites “at least 90 percent,” and claim 14 recites “substantially” all. *Id.*

Each of claims 15–18 ultimately depends from claim 1 and adds a limitation regarding “the number of different second tag sequences.” Ex. 1001, 31:54–32:7. Claim 15 specifies that the number “is larger than the number of sample polynucleotides.” *Id.* at 31:54–57. Claim 16 specifies that the number “is at least ten times the number of sample polynucleotides.” *Id.* at 31:58–61. Claim 17 specifies that the number “is at least one hundred times the number of sample polynucleotides.” *Id.* at 32:1–4. Claim 18 specifies that the number “at least 200,000.” *Id.* at 32:5–8.

For these limitations, Petitioner argues that a person of ordinary skill in the art “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 [sic] is tagged with a unique second tag sequence.” Pet. 60 (citing Ex. 1002 ¶252). According to Petitioner, the skilled artisan would have used “at least 100 times more” unique second tag sequences than polynucleotides to achieve that objective. *Id.* at 61. Petitioner further argues that the skilled artisan would have had a reasonable expectation of success in doing so. *Id.* at 60–61. Petitioner points out that McCloskey teaches the skilled artisan that “using second tag sequences each containing n number of random base pairs ‘enables one to distinguish among 4^n allele copies per reaction.’” *Id.* (quoting Ex. 1004, 4). Petitioner also points to paragraph 21 of McCloskey II, which teaches that “[t]he length of the second sequence is sufficient to provide, with high probability, a unique identity to each target nucleic acid molecule in the sample prior to amplification.” Ex. 1055 ¶21 (cited at Pet. 62). For example, the length of the second sequence can be up 25, 29, or 30 nucleotides. *Id.*

Patent Owner argues against Ground 2 on the basis that it employs the same motivation as Ground 1. *See* PO Resp. 51 (“Petitioner *repeats [its Ground 1] motivation as its motivation in Ground 2.*”). According to Patent Owner, “there can be no motivation to *further* modify the Ground 1 combination in accordance with Ground 2 if, as Petitioner argues, Ground 1 itself *already* uniquely tags each molecule, as its supposed motivation for this additional Ground 2 modification would have *already been accomplished.*” *Id.* This argument is not persuasive.

The proposed modification in Ground 1 is the essentially the same as the proposed modification in Ground 2. As Patent Owner previously argued, McCloskey II is “a more detailed version of McCloskey.” Prelim. Resp. 13; *see also id.* at 24 (“McCloskey is cumulative of McCloskey II.”).

Petitioner’s reliance on McCloskey II reflects this fact. In Ground 2, after the Petition cites to McCloskey’s “second tag” teachings (which are discussed above in relation to Ground 1), the Petition additionally cites to McCloskey II’s more detailed teachings regarding the second tag sequence, including that it could be up to 30 nucleotides long. Pet. 61–62 (citing Ex. 1055 ¶21). As the Ground 2 modification is essentially the same, it is logical that the Ground 2 motivation is essentially the same.

Furthermore, Patent Owner’s argument that Petitioner’s Ground 2 is deficient is premised explicitly on the condition that “Ground 1 itself *already* uniquely tags each molecule.” PO Resp. 51. In other words, Patent Owner argues the motivation for the Ground 2 combination fails because the Ground 1 combination (without McCloskey II) already achieves the subject matter of claims 13 through 18. If that were the case, then claims 13 and 18 are unpatentable regardless.

III. CONCLUSION

We conclude, based on a preponderance of the evidence, that claims 1–28 are unpatentable. In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–12, 19–28	103(a)	Linnarsson, McCloskey, and “further in view of the knowledge of a [person of ordinary skill in the art]”	1–12, 19–28	
13–18	103(a)	Linnarsson, McCloskey, McCloskey II and “further in view of the knowledge of a [person of ordinary skill in the art]”	13–18	
Overall Outcome			1–28	

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–28 of U.S. Patent No. 10,697,013 B1 are proven unpatentable;

FURTHER ORDERED that Patent Owner’s Motion To Exclude is granted-in-part and denied-in-part (Patent Owner’s Motion to Exclude is granted with respect to the second Hall-Ellis declaration (i.e., Ex. 1085) and denied with respect to McCloskey (i.e., Ex. 1004));

FURTHER ORDER that Petitioner's Motion To Exclude is denied;
and

FURTHER ORDERED that, because this Decision is final, a party to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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Patent 10,697,013 B1

PETITIONER:

Derek Walter
Adrian Percer
William Ansley
WEIL, GOTSHAL & MANGES LLP
derek.walter@weil.com
adrian.percer@weil.com
sutton.ansley@weil.com

PATENT OWNER:

Jon Baughman
Megan Raymond
GROOMBRIDGE, WU, BAUGHMAN & STONE LLP
steve.baughman@groombridgewu.com
megan.raymond@groombridgewu.com