

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

IPR2023-01030
Patent 10,619,207 B2

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

SNEDDEN, *Administrative Patent Judge*.

DECISION

Denying Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

A. *Background and Summary*

Parse Biosciences, Inc., (“Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–29 of U.S. Patent No. 10,619,207 B2 (“the ’207 patent,” Ex. 1001). Paper 1 (“Pet.”). 10X Genomics, Inc. (“Patent Owner”) filed a Preliminary Response to the Petitioner. Paper 6 (“Prelim. Resp.”).

To institute an *inter partes* review, we must determine that the information presented in the Petition shows “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) (2018). The Supreme Court has held that a decision to institute under 35 U.S.C. § 314 may not institute on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018).

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that the information presented does not show a reasonable likelihood that Petitioner would prevail with respect to any claim. *See* 35 U.S.C. § 314(a). Accordingly, we deny the Petition.

B. *Real Parties in Interest*

Each party identifies itself as the sole real party in interest. Pet. 4; Paper 5, 1 (explaining that Patent Owner is the exclusive licensee of the ’207 patent).

C. *Related Matters*

The parties indicate that the ’207 patent is involved in *10x Genomics v. Parse Biosciences, Inc.*, Case No. 1:22-cv-01117-JHS, (D. Del), filed Aug. 8, 2022. Pet. 5; Paper 5, 1.

Petitioner has also filed petitions for *inter partes* review in IPR2023-00878 against U.S. Patent No. 10,150,995 and IPR2023-01033 against U.S. Patent No. 10,738,357. Pet. 6; Paper 5, 1.

D. The '207 patent (Ex. 1001)

The '207 patent is titled “Transposition of Native Chromatin for Personal Epigenomics.” Ex. 1001, code (54). According to the '207 patent, chromatin (1) “refers to a complex of molecules including proteins and polynucleotides (e.g. DNA, RNA), as found in a nucleus of a eukaryotic cell” and (2) “is composed in part of histone proteins that form nucleosomes, genomic DNA, and other DNA binding proteins (e.g., transcription factors) that are generally bound to the genomic DNA.” *Id.* at 12:58–64.

The '207 patent explains that “[e]ukaryotic genomes are hierarchically packaged into chromatin, and the nature of this packaging plays a central role in gene regulation.” *Id.* at 1:27–29. The '207 patent states that “[m]ajor insights into the epigenetic information encoded within the nucleoprotein structure of chromatin have come from high-throughput, genome-wide methods for separately assaying the chromatin accessibility (‘open chromatin’), nucleosome positioning, and transcription factor (TF) occupancy.” *Id.* at 1:29–34. However, according to the '207 patent, those prior art methods have “limitations [that] are problematic.” *Id.* at 1:35–39.

The '207 patent discloses “a method for analyzing polynucleotides such as genomic DNA.” *Id.* at 1:57–58.

In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with a transposase and molecular tags to produce tagged fragments of polynucleotides; (b) sequencing a portion of the tagged fragments to produce a plurality of sequence reads; and (c) making an epigenetic map of a region of the genome of the cells

by mapping information obtained from the sequence reads to the region.

Id. at 1:58–65.

The '207 patent's filing date is May 21, 2019. *Id.*, code (22). However, it claims priority, through a parent continuation application No. 16/160,719 (now U.S. Patent 10,337,062 B2); a parent continuation application No. 16/043,784 (now U.S. Patent 10,150,995 B2); a parent continuation application No. 14/784,250 (now U.S. Patent 10,059,989 B2); and to a provisional application filed May 23, 2013. Ex. 1001, codes (60), (63), 1:7–115. The Petition does not challenge the asserted priority date of May 23, 2013. *See* Pet. 11 (“[T]he priority date of the '207 patent is no earlier than the date of . . . May 23, 2013.”).

E. Relevant Prosecution History

The Applicant submitted an Information Disclosure Statement identifying cited art, Grunenwald and Song. Ex. 1007, 11, 14.

During the prosecution of the patent, the Examiner rejected the claims as indefinite and for double patenting in a non-final rejection. *See* Ex. 1007, 151–157. Citing the prior art of Boles and Fernandez, the Examiner acknowledged that “the art teaches various aspect of the instant invention,” but found that “the prior art does not teach contacting the cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tag fragments in combination with the additional steps.” Ex. 1007, 155.

In the List of References cited by the Applicant and considered by Examiner, the Examiner indicated that the cited art of Grunenwald and Song was acknowledged and considered. Ex. 1007, 182, 185.

In response to the Examiner's rejections, the Applicant amended the claims so that the double patenting rejection and "the rejections under 35 USC 112 can be withdrawn" by the Examiner. Ex. 1007, 196, 197.

Following the Applicant's amendment, the Examiner issued a notice of allowance. Ex. 1007, 209. The Notice of Allowance did not state any reasons for the allowance. *See* EX1007, 209–221.

F. The Challenged Claims

Petitioner challenges claims 1–29. Representative independent claim 1 is reproduced below with Petitioner's annotations in brackets.

1. [Preamble] A method for generating a sequencing library from a plurality of cells, comprising:

- a) [1A] lysing a plurality of cells to provide a plurality of cell nuclei, wherein the plurality of cell nuclei comprises chromatin;
- b) [1B] contacting a cell nucleus of the plurality of cell nuclei with a transposase complex such that *polynucleotides of the cell nucleus are tagmented at regions of open chromatin* to produce a plurality of tagged fragments; and
- c) [1C] performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

23. [Preamble] A method for generating a sequencing library from a plurality of cells, comprising:

- a) [23A] lysing a plurality of cells to isolate a plurality of cell nuclei, wherein the plurality of cell nuclei comprise chromatin;
- b) [23B] contacting a cell nucleus of the plurality of cell nuclei with a Tn5 transposase complex such that *polynucleotides of the cell nucleus are tagmented at regions of open chromatin* to produce a plurality of tagged fragments,

wherein the Tn5 transposase complex comprises a first sequencing adapter sequence and a second sequencing adapter sequence,

wherein the Tn5 transposase complex does not comprise an antibody specific to a protein that is part of chromatin,

wherein a tagged fragment of the plurality of tagged fragment comprises

i. a nucleotide sequence corresponding to a region of open chromatin,

ii. the first sequencing adapter sequence, and

iii. the second sequencing adapter sequence; and

c) [23C] performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

Ex. 1001, 43:57–67, 44:56–67. Claims 2–22 depend from claim 1 and claims 24–29 depend from claim 23.

G. Evidence

Petitioner relies upon information that includes the following.

Ex. 1003, Grunenwald et al., US 2010/0120098 A1, published May 13, 2010 (“Grunenwald”).

Ex. 1004, Lingyun Song et al., *DNase-seq: A High-Resolution Technique for Mapping Active Gene Regulatory Elements across the Genome from Mammalian Cells*, COLD SPRING HARBOR PROTOCOLS, 1–11 (2010) (“Song”).

Ex. 1005, Henriette O’Geen et al., *Using ChIP-Seq Technology to Generate High-Resolution Profiles of Histone Modifications*, 791 METHODS IN MOLECULAR BIOLOGY, 265–286 (2011) (“O’Geen”).

Ex. 1009, Andrew Adey et al., *Rapid, Low-input, Low-bias Construction of Shotgun Fragment Libraries by High-density in vitro Transposition*, GENOME BIOLOGY 1–17 (2010) (“Adey”).

Petitioner also relies on the Declaration of Gregory Cooper, Ph.D., (Ex. 1002) to support its contentions.

H. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–29 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–16, 22–24	103	Grunenwald, Song
2	17–21, 25–29	103	O’Geen, Grunenwald, Song
3	13–16	103	Grunenwald, Song, Adey

I. 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).

Petitioner proposes constructions of four limitations: “insertional enzyme complex,” “nucleic acid insert element,” “adapter sequence,” “barcode sequence,” and “tagged fragments.” Pet. 20–23. Patent Owner, for its part, states that “[n]o terms require construction for considering institution.” Prelim. Resp. 15.

We determine that none of the four limitations identified by Petitioner requires an express construction for purposes of this Decision. It bears

mentioning, however, that the '207 patent states that “[t]he insertional enzyme can be a transposase.” Ex. 1001, 3:44–45. There is no dispute that Grunenwald discloses the use of a transposase and, thus, an insertional enzyme complex. *See* Pet. 17 (citing Ex. 1003 ¶¶ 17, 93–94, 162); Prelim. Resp. 13 (“Grunenwald further defines ‘transposase’ to mean ‘an enzyme that is capable of forming a functional complex . . . and catalyzing insertion or transposition of the transposon end-containing composition into the double-stranded target DNA with which it is incubated in an *in vitro* transposition reaction.” (citing Ex. 1003 ¶ 93)).

Although neither party has proposed that we do so, we provide an express construction of the term “chromatin.” The '207 patent itself provides a definition, stating:

The term “chromatin,” as used herein, refers to a complex of molecules including proteins and polynucleotides (e.g. DNA, RNA), as found in a nucleus of a eukaryotic cell. Chromatin is composed in part of histone proteins that form nucleosomes, genomic DNA, and other DNA binding proteins (e.g., transcription factors) that are generally bound to the genomic DNA.

Ex. 1001, 12:58–64. This is the meaning that we apply in this Decision.

J. Level of Ordinary Skill in the Art

The level of ordinary skill in the art usually is evidenced by the prior art references themselves. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

Petitioner proposes that a person of ordinary skill in the art (“POSA” or “POSITA”) at the time of the invention

would have had (1) a Masters 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 sample preparation techniques (including electroporation and permeabilization), tagmentation, amplification methods, and DNA sequencing technologies (including next generation sequencing).

Pet. 15–16. Patent Owner does not dispute Petitioner’s proposal about the POSA’s qualifications. *See generally*, Prelim. Resp.

For this Decision, we adopt and apply Petitioner’s proposal for the level of skill in the art, which does not appear to be inconsistent with the level of skill reflected in the asserted prior art.

II. ANALYSIS

A. Legal Standards

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). Moreover, a petitioner should not “place the burden on [the Board] to sift through information presented by the Petitioners, determine where each element [of the challenged claims] is found in [the cited references], and identify any differences between the claimed subject matter and the teachings of [the cited references.]” *Google Inc. v. EveryMD.com LLC*, IPR2014-00347, Paper 9, 25 (PTAB May 22, 2014).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish a reasonable likelihood of success at trial.

Petitioner relies on obviousness in its challenges.

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). “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.*

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan

would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

B. Summary of the Cited Prior Art

1. Grunenwald (Ex. 1003)

Grunenwald is titled “TRANSPOSON END COMPOSITIONS AND METHODS FOR MODIFYING NUCLEIC ACIDS.” Ex. 1001, code (54). Grunenwald “relates to methods, compositions and kits for using transposase and [] transposon end compositions for generating a library of tagged DNA fragments from target DNA.” *Id.* ¶ 2.

Figure 2 of Grunenwald, reproduced below, illustrates a schematic diagram showing fragmentation and tagging of target DNA by insertion of transposon ends in a transposition reaction. *Id.* ¶ 60.

FIG. 2 Fragmenting by In Vitro Transposition

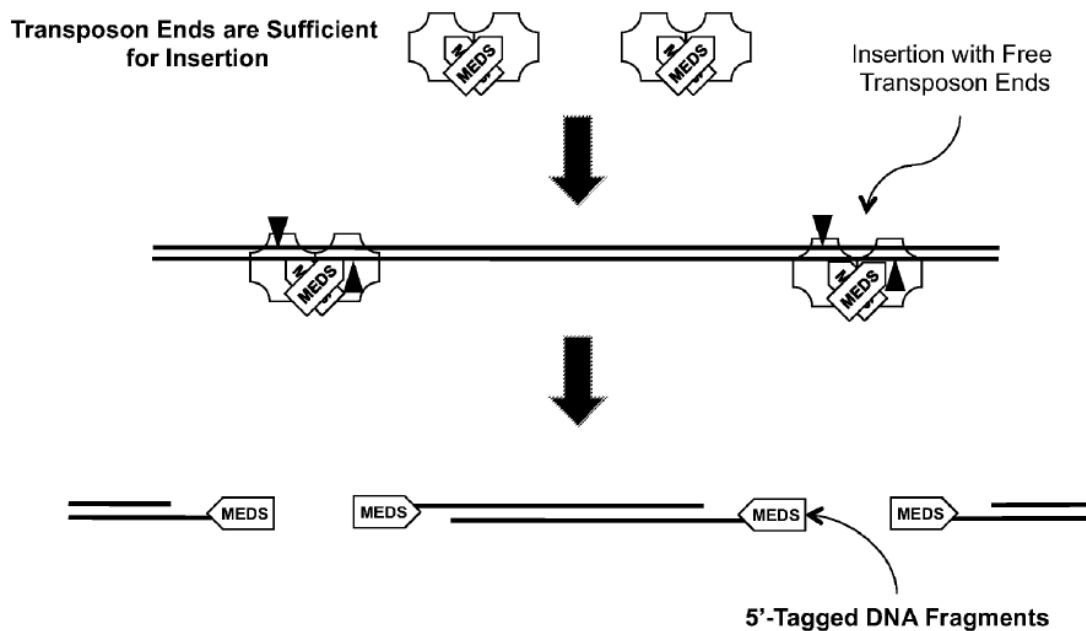


Figure 2 (above) depicts fragmentation and tagging of target DNA by insertion of transposon ends in a transposition reaction. *Id.*

Grunenwald explains that a “transposon end composition” comprises tags, which may further comprise a “tag domain,” such as a “restriction site tag domain, a capture tag domain, a sequencing tag domain, an amplification tag domain, a detection tag domain, an address tag domain, and a transcription promoter domain.” *Id.* ¶ 103. According to Grunenwald, the transposase enzyme can fragment the DNA while simultaneously inserting tags into the DNA fragment. *Id.* ¶ 93.

Grunenwald discloses contacting “chromosomal DNA (e.g., from an isolated chromosome or a portion of a chromosome, e.g., from one or more genes or loci from a chromosome)” with transposase. *Id.* ¶146. Grunenwald discloses, *inter alia*, that,

[i]n some embodiments, the insertion of a transposon end into target DNA according to the present invention can also be carried out in vivo. If transposition is carried out in vivo, transposition

into the target DNA is preferably achieved by electroporating a synaptic complex of a transposase and a suitable transposon end composition into the host cell as described in U.S. Pat. No. 6,159,736 (herein incorporated by reference).

Ex. 1003 ¶ 157. U.S. Patent No. 6,159,736 (“the ’736 patent”) reports demonstrated success only with “nonnucleated target systems, such as bacterial cells.” Ex. 3001, 7:39–40; *see also* IPR2023-00878, Paper 9, 13 (making the same finding).

2. *Song (Ex. 1004)*

Song teaches a technique for digesting regions of DNA in a cell that are not “tightly wrapped in nucleosome and higher-order structures” so that they can be subject to DNA sequencing. Ex. 1004, 1. According to Song, the disclosed technique facilitates the identification of the “most active regulator regions from potentially any cell type.” *Id.* Song teaches isolating cell nuclei by applying a lysis buffer containing an IGEPAL detergent to cells followed by centrifugation. *Id.* at 3.

3. *O’Geen (Ex. 1005)*

O’Geen teaches a prior art method of fragmenting and tagging DNA in preparation for sequencing and subsequently using sequence information to determine epigenetic features of the DNA, known as chromatin immunoprecipitation and sequencing (ChIP-Seq). Ex. 1005, 5. O’Geen discloses that its protocol is “based on sonication,” which is the use of ultrasound to fragment DNA, and that such sonication may shear chromatin. *Id.* at 21.

4. *Adey (Ex. 1009)*

Adey describes a prior art method of tagmentation using Epicentre’s Nextera™ Technology in which a transposase is used to insert distinct adapter sequences. Ex. 1009, 2.

C. Ground 1: Obviousness of Claims 1–16 and 22–24 by Grunenwald and Song

1. Summary of Parties’ Contentions Related to Claim 1

a) [Preamble] A method for generating a sequencing library from a plurality of cells

Petitioner contends that Grunenwald teaches generating a sequencing library of tagged DNA fragments from a plurality of cells. Pet. 24 (citing Ex. 1003 ¶¶ 2, 18, 71, 121, 146; Fig. 13). Patent Owner does not challenge Petitioner’s contention that Grunenwald discloses the preamble of claim 1 of the ’207 patent. Prelim. Resp. 16.

b) [1A] Lysing a plurality of cells to provide a plurality of cell nuclei, wherein the plurality of cell nuclei comprises chromatin

Petitioner contends that it would have been obvious to incorporate Song’s method of lysing cells to provide a plurality of cell nuclei into Grunenwald’s tagmentation method for three reasons. Pet. 26.

First, Petitioner contends that “Song teaches a routine method for nuclei isolation based on cell lysis using the IGEPAL detergent and that includes subsequent centrifugation.” *Id.* (citing Ex. 1004, 3; Ex. 1001, 25:4–15; Ex. 1002 ¶ 139).

Second, Petitioner contends that one of ordinary skill in the art would have been motivated to combine Song and Grunenwald because both references are in the same field and cover modification and sequencing of DNA. Pet. 26 (citing Ex. 1002, ¶¶ 143–144; Ex. 1003 Abstract; Ex. 1004, 1). In particular, Petitioner argues that Grunenwald teaches that the tagmentation method can be applied to chromosomal DNA *in vivo*, which is packaged in nuclei in the form of chromatin and, thus, “Grunenwald necessarily and inherently discloses performing its method on a plurality of

cell nuclei wherein the cell nuclei comprises chromatin.” Pet. 28 (citing Ex. 1003 ¶¶ 146, 157; Ex. 1002 ¶¶ 52–59, 134–135). Petitioner further argues that instead of “using the permeabilization method set forth in Grunenwald, it would have been a simple design choice to instead simply isolate the nuclei from the cells” using Song’s cell lysis method. Pet. 29.

Third, Petitioner contends that one of ordinary skill in the art would have had a reasonable expectation of success in combining Song and Grunenwald because “the references provide compatible methods of accomplishing analogous goals.” Pet. 30 (citing Ex. 1002 ¶ 148).

Patent Owner contends that “Petitioner identifies no disadvantage of” Grunenwald’s “electroporation, no benefit of isolating the nuclei, or any other reason” one of ordinary skill in the art “would have been motivated to modify Grunenwald.” Prelim. Resp. 17 (citing Pet. 26–30). Patent Owner further contends that Petitioner has not shown that one of ordinary skill in the art would have understood that accessing the genetic material in the nuclei would allow the transposase complex to contact and tagment open chromatin. Prelim. Resp. 19. Patent Owner argues that Petitioner fails to explain how Grunenwald’s *in vivo* tagmentation method would have been combined with the incompatible *in vitro* nuclei isolation procedure for lysed cells taught in Song. *Id.* at 20 (citing Pet. 3, 28–29, 30; Ex. 1004, 3).

c) *[1B] Contacting a cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments*

Petitioner contends that Grunenwald “discloses the claimed transposase complex that comprises a transposase and at least two adaptors (e.g., tags, tag portions, or tag domains) that combine with polynucleotides of a cell nucleus (e.g., target DNA) to tagment said polynucleotides.”

Pet. 33. Petitioner further contends that Grunenwald's Figure 2 "demonstrates the transposase complex contacting the target DNA, and simultaneously fragmenting and tagging it, resulting in 5'-tagged DNA fragments." Pet. 34 (citing Ex. 1002 ¶ 158).

In particular, Petitioner contends that the claimed "open chromatin" limitation is met because "Grunenwald expressly discloses that the target DNA contacted by the insertional enzyme complex may 'comprise[] or consist[] of genomic DNA, subgenomic DNA, [or] **chromosomal DNA**'" Pet. 35 (citing Ex. 1003 ¶ 146). According to Petitioner, a person of ordinary skilled in the art "would have been aware that chromosomal DNA is chromatin, and so in embodiments wherein the contacted nucleic acid is chromosomal DNA, chromatin is contacted with the insertional enzyme complex." Pet. 35 citing Ex. 1002 ¶ 146). According to Petitioner, in Grunenwald's "embodiments wherein the contacted nucleic acid is chromosomal DNA, chromatin is contacted with the transposase complex" and "[t]his will necessarily include the regions of 'open chromatin' that are accessible to the transposase complex." Pet. 35–36 (citing Ex. 1002 ¶¶ 146, 155–157).

Patent Owner contends that Petitioner's cited passages in Grunenwald make no mention regarding transposase contacting the nucleus. Prelim. Resp. 22 (citing Pet. 34; Ex. 1003 ¶ 17, Fig. 2 (arguing that "Figure 2 further specifies that it relates to fragmenting *by in vitro* transposition.")). Patent Owner contends that Petitioner's reliance on its expert's declaration is misplaced because the declaration fails to "address what Grunenwald teaches or say anything about contacting a cell nuclei." Prelim. Resp. 22 (citing Pet. 34; Ex. 1002, ¶ 158).

Patent Owner particularly contends that Petitioner takes Grunenwald's disclosure regarding "chromosomal DNA" out of context to extrapolate that the cited art discloses the claimed "open chromatin" limitation. Prelim. Resp. 27 (citing Pet. 35). Patent Owner argues that Grunenwald does not disclose contacting chromatin, let alone open chromatin. *See, e.g.*, Prelim. Resp. 25 n.6 ("Figure 2 [of Grunenwald] shows a transposase inserting transposon ends into double stranded DNA 'In Vitro,' but shows **no chromatin**"). According to Patent Owner, "***Grunenwald nowhere mentions 'chromatin'***" (which, as defined by the '207 patent, is the complex of molecules including proteins and polynucleotides "as found in a nucleus of a eukaryotic cell." Prelim. Resp. 28 (quoting Ex. 1001, 12:58–64)). Patent Owner argues that the '736 patent, which Grunenwald incorporates by reference as describing *in vivo* transposition, "is focused on ***prokaryotes*** (with ***no chromatin***)." Prelim. Resp. 34–35 (citing Ex. 2013, 3:50–55).

Patent Owner additionally argues that, in attempting to show obviousness by Grunenwald and Song, Petitioner erroneously relies on disclosures from different embodiments of Grunenwald. Prelim. Resp. 37–38.

d) [1C] Performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

As set forth above, Petitioner contends that Grunenwald teaches generating a sequencing library of tagged DNA fragments from a plurality of cells, thus disclosing the claimed "tagged nucleic acid molecules" limitation. Pet. 24 (citing Ex. 1003 ¶¶ 2, 18, 71, 121, 146; Fig. 13); Pet. 39. Petitioner contends that Grunenwald teaches "subjecting the tagged nucleic acid molecules to additional reactions after tagmentation and prior to sequencing, to produce a sequencing library." Pet. 39 (citing Ex. 1003 ¶¶ 15, 17).

Patent Owner does not challenge Petitioner's contentions that Grunenwald discloses the limitations recited in [1C] of claim 1 of the '207 patent. Prelim. Resp. 39.

2. *Analysis*

Having considered the parties' positions and evidence of record, summarized above, we are not persuaded by Petitioner's contention that the Grunenwald discloses "contacting a cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments." *See* Pet. 31 ("Grunenwald discloses this limitation.").

At best, Petitioner equates Grunenwald's disclosure of chromosomal DNA with the recitation of claim 1 for "regions of open chromatin." In particular, Petitioner contends that Figure 2 of Grunenwald "demonstrates the insertional enzyme complex contacting *the target DNA*, and simultaneously fragmenting and tagging it, resulting in 5'-tagged DNA fragments." Pet. 34 (emphasis added; citing Ex. 1002 ¶ 158); *see also id.* at 35 (reproducing Ex. 1003, Fig. 2). Petitioner then asserts that the target DNA in Figure 2 are "regions of open chromatin." *Id.* at 35. This is so, according to Petitioner, because (1) "Grunenwald expressly discloses that the target DNA contacted by the insertional enzyme complex may "comprise[] or consist[] of genomic DNA, subgenomic DNA, [or] **chromosomal DNA**" EX1003 at [0146] (emphasis added); and (2) a person of ordinary skilled in the art "would have been aware that chromosomal DNA is chromatin, and so in embodiments wherein the contacted nucleic acid is chromosomal DNA, chromatin is contacted with the insertional enzyme complex." Pet. 35 (quoting Ex. 1003 ¶ 146 and citing Ex. 1002 ¶ 155).

Petitioner's position that "chromosomal DNA is chromatin" is not supported by the cited evidence. *Id.* The Petitioner-cited paragraph 146 of Grunenwald includes a parenthetical of exemplary "chromosomal DNA" that was omitted from the quotation appearing in the Petition. The parenthetical, which immediately follows "chromosomal DNA," states "(e.g., from an isolated chromosome or a portion of a chromosome, e.g., from one or more genes or loci from a chromosome)." Ex. 1003 ¶ 146. Petitioner's assertion that Grunenwald's "chromosomal DNA is chromatin" cannot be squared with the fact that Grunenwald explicitly states that "chromosomal DNA" may be from, for example, a single gene. *Id.*

Further, paragraph 146 also states that "the target DNA comprises or consists of eukaryotic and/or prokaryotic dsDNA." Ex. 1003 ¶ 146. Thus, as Patent Owner points out, the target DNA in Grunenwald is not necessarily from a eukaryotic cell, and only eukaryotic cells contain chromatin. *See* Ex. 1001, 12:54–56 ("The term 'chromatin,' as used herein, refers to a complex of molecules including proteins and polynucleotides (e.g. DNA, RNA), *as found in a nucleus of a eukaryotic cell.*" (emphasis added)); *see also* Ex. 1002, 22 (Dr. Cooper reproducing Figure 2 from Exhibit 1036 showing the "Organization of Eukaryotic Chromosomes");¹ Prelim Resp. 27.

We understand Grunenwald's reference to "chromosomal" to be describing the *source* of the DNA, i.e., from a chromosome as opposed to, for example, mitochondria, which is also a potential source enumerated in paragraph 146. Our understanding is supported by the context provided by

¹ Exhibit 1036 is an online course titled *DNA Packaging in Eukaryotes and Prokaryotes* (March 15, 2023) and available at <https://courses.lumenlearning.com/wmbiology1/chapter/reading-dna-packaging-in-eukaryotes-andprokaryotes/>.

the full sentence of paragraph 146 from which Petitioner's quotation was taken. It states the following:

In some embodiments, the target DNA comprises or consists of genomic DNA, subgenomic DNA, chromosomal DNA (e.g., from an isolated chromosome or a portion of a chromosome, e.g., from one or more genes or loci from a chromosome), mitochondrial DNA, chloroplast DNA, plasmid or other episomal-derived DNA (or recombinant DNA contained therein), or double-stranded cDNA made by reverse transcription of RNA using an RNA-dependent DNA polymerase or reverse transcriptase to generate first-strand cDNA and then extending a primer annealed to the first-strand cDNA to generate dsDNA.

Ex. 1003 ¶ 146.

The Petitioner-cited testimony of Dr. Cooper also does not support Petitioner's position that "chromosomal DNA is chromatin." *See* Pet. 35 (citing Ex. 1003 ¶ 155). Paragraph 155 of Dr. Cooper's Declaration states the following:

155. A POSA would have further understood that that Grunenwald necessarily discloses using that transposon complex to contact a cell nucleus of the plurality of cell nuclei. Specifically, Grunenwald teaches using the transposon complex to contact target DNA such as chromosomal DNA and that this method may be performed in vivo on a live cell by electroporating the enzyme complex directly into the cell. *Id.* at [0146]; [0157]. Furthermore, as noted in the '207 Patent, in a cell in vivo, chromatin is the complex of DNA and proteins found in the nucleus of the cell. EX1001 at 12:58-64.

Ex. 1002 ¶ 155. This testimony is not persuasive in view of (1) Grunenwald's statement that "chromosomal DNA" may be that of a single gene and that it may be from a prokaryotic cell, which would lack chromatin and (2) Dr. Cooper supports his testimony by pointing to Grunenwald's incorporation by reference of the '736 patent, which reports demonstrated success only with "nonnucleated target systems, such as bacterial cells." *See*

Ex. 1003 ¶ 146 (“For example, in some embodiments, the target DNA comprises or consists of eukaryotic and/or prokaryotic dsDNA.”); Ex. 1036, 2 (side by side illustration of a eukaryotic cell and a prokaryotic cell, with the only the former having “Chromatin”); Ex. 3001, 7:39–40.

Petitioner relies on Song to modify Grunenwald for its disclosure of a method for isolating cell nuclei. Pet. 26. We have considered Petitioner’s contentions and evidence in this regard and determine that, while Song may teach the isolation of cell nuclei as a source of DNA, the combination fails to sufficiently explain why a person of ordinary skill in the art would have sought to conduct the recited *in vitro* tagmentation method inside a preserved cell nucleus in order to target open chromatin.

We recognize that Petitioner relies on Grunenwald’s *in vivo* embodiment to argue, e.g., that the cells contain chromatin and that the chromatin in the nucleus is tagmented. Pet. 28–29; *see also* Pet. 3 (referring to Grunenwald teaching “applying tagmentation to living cells *in vivo*”) (emphasis original). Song, however, is not performed *in vivo*, but rather is performed on lysed cells. Ex. 1004, 3. Thus, even assuming that Petitioner is correct that Grunenwald’s *in vivo* embodiment would inherently make the cellular DNA in the nuclei accessible for its tagmentation process (Pet. 28; Ex. 1002 ¶¶ 134–135), Petitioner fails to explain how or why a person of ordinary skill in the art would have sought to maintain the integrity of the nuclear membrane of lysed cells when performing Grunenwald’s tagmentation process so as to target open chromatin.

In sum, we are not persuaded that Grunenwald expressly or inherently discloses *in vitro* tagmentation of regions of open chromatin as required by claim 1 by virtue of the fact that it discloses contacting “chromosomal DNA (e.g., from an isolated chromosome or a portion of a chromosome, e.g., from

one or more genes or loci from a chromosome)” with transposase. Ex. 1003 ¶ 146. Additionally, we are not persuaded that Song’s disclosure of isolated nuclei as a source of DNA cures that deficiency of Grunenwald.

3. Conclusion As To Claim 1, And By Extension, All Claims and Grounds

There is not a reasonable likelihood that Petitioner would prevail in proving that claim 1 would have been obvious over the combination of Grunenwald and Song. For the same reason, there is not a reasonable likelihood that Petitioner would prevail in proving that any of claims 2–16, and 22–24 would have been obvious over the combination of Grunenwald and Song, as each of these claims ultimately depends from claim 1 or otherwise require elements not taught or suggested by the combination of Grunenwald and Song as discussed above with regard to claim 1.

Petitioner includes two additional grounds of unpatentability under 35 U.S.C. § 103 challenging dependent claims 13–21 and 25–29. Pet. 54–66. However, none of the additional references relied upon in these grounds (O’Geen and Adey) is relied upon by Petitioner in way that could cure the deficiency of Grunenwald and Song discussed above, namely, failing to teach or suggest an insertion enzyme complex contacting “regions of open chromatin” as required by the claims.

III. CONCLUSION

The Petition fails to show there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. *See* 35 U.S.C. § 314(a); 37 C.F.R. § 42.108.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and no trial is instituted.

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