

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

IPR2023-00878
Patent 10,150,995 B1

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

Opinion for the Board filed by *Administrative Patent Judge* FITZPATRICK.

Opinion dissenting filed by *Administrative Patent Judge* SAWERT.

FITZPATRICK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner, Parse Biosciences, Inc., filed a Petition to institute an *inter partes* review of all claims, namely claims 1–23, of U.S. Patent No. 10,150,995 B1 (“the ’995 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 8 (“Prelim. Resp.”).

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

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that 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.

A. Related Matters

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

B. Real Parties In Interest

Each party identifies itself as the sole real party in interest. Pet. 4; Paper 6, at 1 (explaining that Patent Owner is the exclusive licensee of the '995 patent).

C. The '995 Patent

The '995 patent is titled “Transposition of Native Chromatin for Personal Epigenetics.” Ex. 1001, code (54). According to the '995 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 12:54–60.

The '995 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 1:24–26. The '995 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 1:26–31. However, according to the '995 patent, those prior art methods have “limitations [that] are problematic.” *Id.* at 1:31–35.

The '995 patent discloses “a method for analyzing chromatin.” *Id.* at 14:23.

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 1:55–62.

The '995 patent's filing date is July 24, 2018. *Id.*, code (22).

However, it claims priority, through a parent continuation application No. 14/784,250 (now U.S. Patent 10,059,989 B2) to a provisional application filed May 23, 2013.¹ Ex. 1001, codes (60), (63), 1:6–13. The Petition does not challenge the asserted priority date of May 23, 2013. *See* Pet. 12 (“[T]he priority date of the '995 Patent is no earlier than the date of . . . May 23, 2013.”).

D. The Challenged Claims

Review is sought for all of the claims of the '995 patent, namely claims 1–23. Claim 1 is the sole independent claim and reproduced below:

1. A method for analyzing a biological sample, comprising:
 - (a) contacting chromatin of a genome region of said biological sample with an insertional enzyme complex to produce tagged nucleic acid molecules, wherein said insertional enzyme complex does not comprise an

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the '029 patent claims priority to a provisional application filed after the effective date of these AIA amendments, we apply the AIA version of 35 U.S.C. § 102 and § 103.

antibody specific to a protein that is part of said chromatin; and

- (b) performing a nucleic acid assay on said tagged nucleic acid molecules or derivatives thereof, to provide sequence information of said tagged nucleic acid molecules or derivatives thereof.

Ex. 1001, 43:25–37.

C. The Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §	Basis
1, 3, 5, 6, 10–23	102	Grunenwald ²
2	103	Grunenwald, O’Geen ³
4, 6–8	103	Grunenwald, Okino ⁴
9	103	Grunenwald, Pitt ⁵
17–20	103	Grunenwald, Adey ⁶
1, 3, 5, 6, 10–23	103	Grunenwald, Okino
2	103	Grunenwald, O’Geen, Okino
17–20	103	Grunenwald, Adey, Okino

Pet. 5–6.

² US 2010/0120098 A1, published May 13, 2010 (“Grunenwald,” Ex. 1003).

³ 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. 1005).

⁴ WO 2010/065266 A1, published June 10, 2010 (“Okino,” Ex. 1004).

⁵ William G. Pitt, Dr. et al., *Ultrasonic Drug Delivery – A General Review*, EXPERT OPIN DRUG DELIV, 37–56 (2004) at <https://pubmed.ncbi.nlm.nih.gov/16296719/> (“Pitt,” Ex. 1006).

⁶ 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,” Ex. 1009).

II. ANALYSIS

A. Claim Construction

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

Petitioner proposes constructions of four limitations: “insertional enzyme complex,” “nucleic acid insert element,” “adapter sequence,” and “barcode sequence.” Pet. 21–25. Patent Owner, for its part, states that “[n]o terms require construction for considering institution.” Prelim. Resp. 16.

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 ’995 patent states that “[t]he insertional enzyme can be a transposase.” Ex. 1001, 3:41–42. There is no dispute that Grunenwald discloses the use of a transposase and, thus, an insertional enzyme complex. *See* Pet. 27 (citing Ex. 1003 ¶¶98, 161); Prelim. Resp. 34 (“Grunenwald defines ‘transposase’ to include any transposase, thus including those that comprise antibodies that are specific to a protein that is part of said chromatin.” (citing Ex. 1003 ¶93)).

Although neither party has proposed that we do so, we provide an express construction of the term “chromatin.” The ’995 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, 12:54–60. This is the meaning that we apply in this Decision.

B. Ground 1

Petitioner asserts that Grunenwald anticipates independent claim 1, as well some of the dependent claims. Pet. 25. “Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference.” *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009).

Patent Owner argues that Grunenwald fails to anticipate claim 1, which failure undermines the entire Petition. Prelim. Resp. 16–17 (“Petitioner has failed to show that Grunenwald discloses each and every limitation as arranged in the claims, including, e.g., ‘contacting chromatin of a genome region,’ and thus cannot meet its burden as to any claim in Ground 1.” (quoting claim 1)), 38 (“Petitioner cannot meet its burden as to Grounds 2–8 for the same reasons Petitioner cannot meet its burden for Ground 1.”). Accordingly, we turn first to claim 1.

1. Claim 1

Patent Owner argues that Grunenwald does not anticipate because it fails to disclose “contacting chromatin of a genome region . . . with an

insertional enzyme complex,” as recited in claim 1. Prelim. Resp. 18–38. Patent Owner does not dispute that Grunenwald discloses contacting target DNA with an insertional enzyme complex (transposase). However, Patent Owner argues that Grunenwald does not disclose contacting chromatin, let alone chromatin of a genome region. *See, e.g.*, Prelim. Resp. 19 n.5 (“Figure 2 [of Grunenwald] shows a transposase inserting transposon ends into double stranded DNA ‘*In Vitro*,’ but ***shows no chromatin or histones.***”), 27 (arguing that the Petition “does not even attempt to identify any disclosure *in Grunenwald*” of the “genome region” limitation of claim 1). Patent Owner additionally argues that, in attempting to show anticipation by Grunenwald, Petitioner erroneously relies on disclosures from different embodiments of Grunenwald. *Id.* at 28, 36–38.

We turn now to Petitioner’s showing with respect to this limitation.

Petitioner first states 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. 29 (emphasis added; citing Ex. 1002 ¶154); *see also id.* at 30 (reproducing Ex. 1003, Fig. 2). Petitioner then asserts that the target DNA in Figure 2 “is ‘chromatin of a genome region of said biological sample.’” *Id.* at 30. 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 skill 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. 30 (quoting Ex. 1003 ¶146 and citing Ex. 1002 ¶146).

Petitioner’s position, that “chromosomal DNA is chromatin” is not supported by the cited evidence. 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.

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 (Declaration of Gregory Cooper, Ph.D., reproducing Figure 2 from Exhibit 1036 showing the “Organization of Eukaryotic Chromosomes”).⁷

⁷ 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/>.

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 the full sentence of paragraph 146 of Grunenwald 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" and appears to be a typographical error. *See* Pet. 30 (citing Ex. 1002 ¶146).⁸ It appears that Petitioner intended to cite instead to paragraph 139 of Dr. Cooper's Declaration, which states the following:

139. First, it is my opinion that that Grunenwald explicitly discloses ["contacting chromatin . . . with an insertional enzyme complex"]. Grunenwald teaches tagmentation on "chromosomal DNA." EX1003 at [0146]. A POSA would understand that chromosomal DNA exists in the form of chromatin, and whether in a cell or isolated if the method

⁸ Paragraph 146 of Dr. Cooper's Declaration is directed to the "**genome region**" limitation of claim 1. Ex. 1002 ¶146.

disclosed in Grunenwald is being performed on chromosomal DNA it is being performed on chromatin.

Ex. 1002 ¶139. This testimony is not persuasive in view of 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. *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 only the former having "Chromatin").

In sum, we are not persuaded that Grunenwald expressly discloses "contacting chromatin" 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. Petitioner provides no other explanation for its contention that Grunenwald expressly discloses this claim limitation.⁹

⁹ The Dissent states that "[i]t is not clear—at least on this record and in the absence of expert testimony from Patent Owner—that an ordinarily skilled artisan would have understood 'chromosomal DNA' in Grunenwald as having been stripped of the proteins comprising chromatin." Dissent 2. However, it would be Petitioner's burden unquestionably to prove that the prior art teaches a limitation of the claim. 35 U.S.C. § 316(e) ("In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence."). Thus, it would be Petitioner's burden to prove its assertion that Grunenwald's "chromosomal DNA is chromatin." Pet. 30. To be clear, it would not be Patent Owner's burden to prove that Grunenwald's reference to "chromosomal DNA" would be understood by a person of ordinary skill in the art to not be chromatin.

This is not the end of our analysis, however, as Petitioner also asserts that Grunenwald *inherently* discloses the “contacting chromatin” limitation. *See* Pet. 31 (“To the extent Grunenwald is deemed to not explicitly disclose contacting chromatin, this limitation inherently disclosed.”); *see also Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (“A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference.”). This is so, according to Petitioner, because “Grunenwald discloses that its methods of using an insertional enzyme complex to tag and fragment DNA can be applied to chromosomal DNA *in vivo*, which necessarily requires contacting chromatin.” *Id.* (citing Ex. 1003 ¶¶146, 157). The Petition reproduces the first two sentences of paragraph 157, which state the following:

In 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).

Pet. 31 (quoting Ex. 1003 ¶157).

Patent Owner counters that Petitioner has not established inherent disclosure of “contacting chromatin.” Prelim. Resp. 28–34. According to Patent Owner, “contacting chromatin” is not inevitable when introducing transposase into a host cell *in vivo* as disclosed in Grunenwald because Grunenwald does *not* specify the “host cell” being eukaryotic as opposed to prokaryotic. *Id.* at 31.

We agree with Patent Owner that the evidence of record does not establish that the target DNA disclosed by Grunenwald necessarily would be eukaryotic. In fact, the patent that Grunenwald incorporates by reference as describing such an *in vivo* transposition, i.e., U.S. Patent No. 6,159,736 (“the ’736 patent,” Ex. 1045), reports demonstrated success only with “non-nucleated target systems, such as bacterial cells.” Ex. 1045, 7:39–40. “In particular, the synaptic complexes have been introduced into *E. coli* cells (strain MG1655) and productive transposition has been observed.” *Id.* at 7:40–43. Although the ’736 patent does not rule out application of its method to eukaryotes, Patent Owner is correct that the ’736 patent “is focused on *prokaryotes*.” Prelim. Resp. 32 (citing Ex. 1045, 3:50–55); *see* Ex. 1045, 7:39–44 (stating that its “method is demonstrated to work in non-nucleated target systems, such as bacterial cells” but also that “[n]o scientific impediment is known to exist that would prevent use of the method in nucleated cells”).

Also, Petitioner states that Grunenwald’s “*in vivo* embodiment is accomplished by electroporating the cell to allow the transposome^[10] to enter the cell,” but makes no mention of a nucleus, let alone how the transposome might enter a nucleus of a eukaryotic cell where chromatin would be present. Pet. 31; *see also* Prelim. Resp. 33 (“Petitioner does not assert, let alone establish, that Grunenwald necessarily electroporates the *cell nucleus*.”). In any event, the dispositive point is that Grunenwald’s disclosure

¹⁰ A transposome contains transposase. *See* Ex. 1003 ¶94 (describing a “transposome complex” or “transposition composition” containing transposase).

that the “insertion of a transposon end into target DNA according to the present invention can also be carried out in vivo” (Ex. 1003 ¶146) is not limited to cells that possess chromatin. Consequently, Petitioner has not shown that “contacting chromatin” is inherently disclosed.

*2. 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 is anticipated by Grunenwald.

For the same reason, there is not a reasonable likelihood that Petitioner would prevail in proving that any of claims 3, 5, 6, 10–23 is anticipated by Grunenwald, as each of these claims ultimately depends from claim 1.

Petitioner includes seven additional grounds of unpatentability under 35 U.S.C. § 103. Pet. 5–6. However, none of the additional references relied upon in these grounds (O’Geen, Okino, Pitt, and Adey) is relied upon by Petitioner in way that could cure the deficiency of Grunenwald failing to disclose an insertional enzyme complex “contacting chromatin.”

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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SAWERT, *Administrative Patent Judge*, dissenting.

I respectfully dissent from the majority’s denial of institution based on its determination that Grunenwald fails to disclose an insertional enzyme complex “contacting chromatin.” On this record, I would have determined that Petitioner has sufficiently shown for institution that Grunenwald satisfies the “contacting chromatin” claim limitation. Grunenwald teaches that “target DNA” may be from eukaryotic organisms and comprise or

consist of “chromosomal DNA.” Ex. 1003 ¶ 146. Dr. Cooper testifies that “[c]hromosomal DNA exists in the form of chromatin naturally, even when isolated,” Ex. 1002 ¶ 145, and that an ordinarily skilled artisan would have understood that “whether in a cell or isolated if the method disclosed in Grunenwald is being performed on chromosomal DNA it is being performed on chromatin,” *id.* ¶ 139. It is not clear—at least on this record and in the absence of expert testimony from Patent Owner—that an ordinarily skilled artisan would have understood “chromosomal DNA” in Grunenwald as having been stripped of the proteins comprising chromatin. I would have allowed the parties to litigate this issue during trial.

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