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Paper 8
Entered: December 19, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

IPR2023-01033
Patent 10,738,357 B2

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

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

Opinion dissenting filed by *Administrative Patent Judge* FITZPATRICK.

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 1–30 of U.S. Patent No. 10,738,357 B2 ("the '357 patent," Ex. 1001). Paper 1 ("Pet."). 10X Genomics, Inc., ("Patent Owner") filed a Preliminary Response to the Petitioner. Paper 6 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314 and 37 C.F.R. § 42.4. For the reasons set forth below, we exercise our discretion under 35 U.S.C. § 325(d) and decline to institute an *inter partes* review.

B. Real Parties in Interest

Each party identifies itself as the sole real party in interest. Pet. 5; Paper 5, 1 (explaining that Patent Owner is the exclusive licensee of the '357 patent).

C. Related Matters

The parties indicate that the '357 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 IPR2023-01030 against U.S. Patent No. 10,619,207. Pet. 7; Paper 5, 1.

D. The '357 patent (Ex. 1001)

The '357 patent is titled "Transposition of Native Chromatin for Personal Epigenomics." Ex. 1001, code (54). According to the '357 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 12:61–67.

The '357 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 1:29–31. The '357 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 1:31–36. However, according to the '357 patent, those prior art methods have "limitations [that] are problematic." *Id.* at 1:36–41.

The '357 patent discloses "a method for analyzing polynucleotides such as genomic DNA." *Id.* at 1:59–60.

> 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 1:60–67.

The '357 patent's filing date is May 21, 2019. *Id.*, code (22). However, it claims priority, through parent continuation application No. 16/160,719 (now U.S. Patent 10,337,062 B2); parent continuation application No. 16/043,784 (now U.S. Patent 10,150,995 B2); 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), 1:7–17. The Petition does not challenge the asserted priority date of

May 23, 2013. *See* Pet. 12 ("[T]he priority date of the '357 patent is no earlier than the date of . . . May 23, 2013.").

E. The Challenged Claims

Petitioner challenges claims 1–30. Representative independent claims 1 and 2 are reproduced below.

> 1. A composition, comprising:
>
> a permeabilized cell nucleus comprising:
>
> a) a plurality of polynucleotide molecules; and
>
> b) an insertional enzyme complex comprising an insertional enzyme and
>
> an insert element comprising a predetermined sequence.
>
> 2. A composition, comprising:
>
> a permeabilized cell nucleus comprising:
>
> a) chromatin comprising genomic DNA and a plurality of DNA binding proteins, wherein the chromatin comprises a plurality of open chromatin regions; and
>
> b) an insertional enzyme complex comprising an insertional enzyme and
>
> an inert element comprising a predetermined sequence, wherein the insertional enzyme complex is bound to one of said open chromatin regions.

Ex. 1001, 45:2–19.

F. 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, Okino et al., WO 2010/065266 A1, published June 10, 2010 ("Okino").

Ex. 1005, Abdelaty Saleh et al., *An efficient chromatin immunoprecipitation (ChIP) protocol for studying histone*

modifications in Arabidopsis plants, NATURE PROTOCOLS 1018–1025 (2008) ("Saleh").

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").

Ex. 1060, 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").

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

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–30 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–28, 30	103	Grunenwald, Okino
2	29	103	Grunenwald, Okino, Saleh, Song
3	16	103	Grunenwald, Okino, Adey

H. 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 two limitations: "insertional enzyme complex" and "nucleic acid insert element." Pet. 21. Patent Owner, for its part, states that "[n]o terms require construction for considering institution." Prelim. Resp. 18.

We determine that neither of the two limitations identified by Petitioner requires an express construction for purposes of this Decision. It bears mentioning, however, that the '357 patent states that "[t]he insertional enzyme can be a transposase." Ex. 1001, 3:47–48. There is no dispute that Grunenwald discloses the use of a transposase and, thus, an insertional enzyme complex. *See* Pet. 16 (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 '357 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, 12:61–67. This is the meaning that we apply in this Decision.

I. Level of Ordinary Skill in the Art

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. 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 above, which does not appear to be inconsistent with the level of skill reflected in the asserted prior art.

J. 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

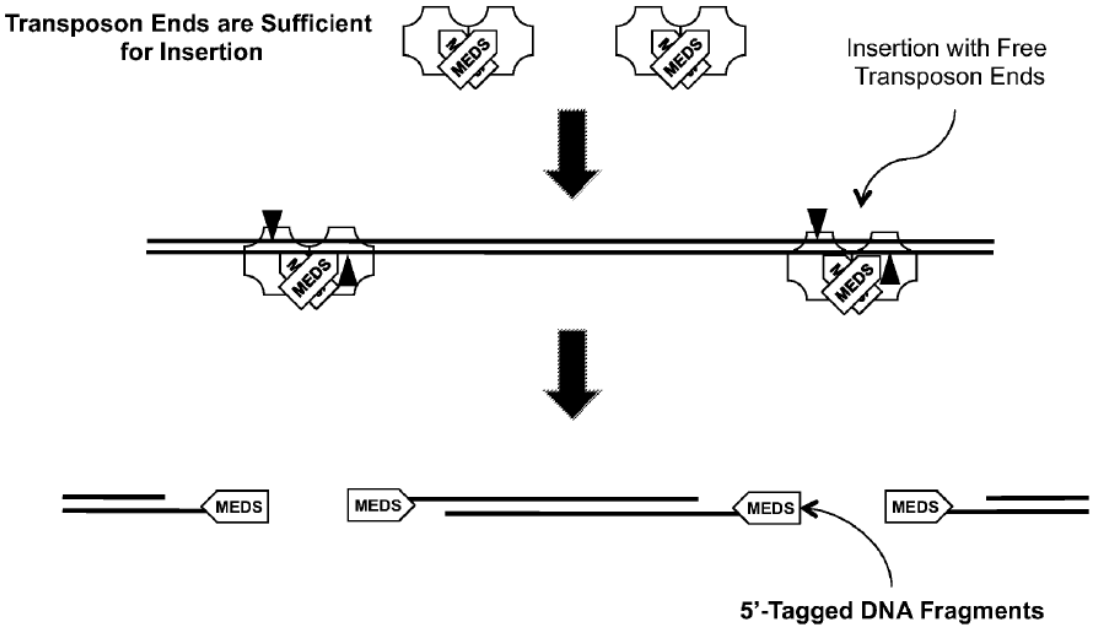

Figure 2 (above) depicts fragmentation and tagging of target DNA by insertion of transposon ends in a transposition reaction. *Id.*

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." IPR2023-00878, Paper 9, 13.

2. Okino (Ex. 1004)

Okino is titled "CHROMATIN STRUCTURE DETECTION." Ex. 1004, code (54). Okino "provides for methods for analyzing chromosomal DNA," such as "determining the accessibility of a DNA region on a chromosome to a DNA modifying agent, optionally correlating the accessibility to chromatin structure." Ex. 1004 ¶ 5.

Okino discloses the technique of "'permeabilizing' a cell membrane" by "reducing the integrity of a cell membrane to allow for entry of a modifying agent into the cell." *Id.* ¶ 34. Okino discloses agents for permeabilizing or disrupting cell membranes, such as lysolipids, which include "lysophosphatidylcholine (also known in the art as lysolecithin) or monopalmitoylphosphatidylcholine." *Id.* ¶ 72.

Figure 2 of Okino, reproduced below, illustrates a schematic representation of the assay in which culture media is aspirated and a permeabilization/digestion buffer is added. *Id.* Thereafter, "nuclease diffuses into the cell, enters the nucleus and digests accessible chromatin, but inaccessible chromatin (represented as a thick line towards the bottom of the Figure) is not digested." *Id.*

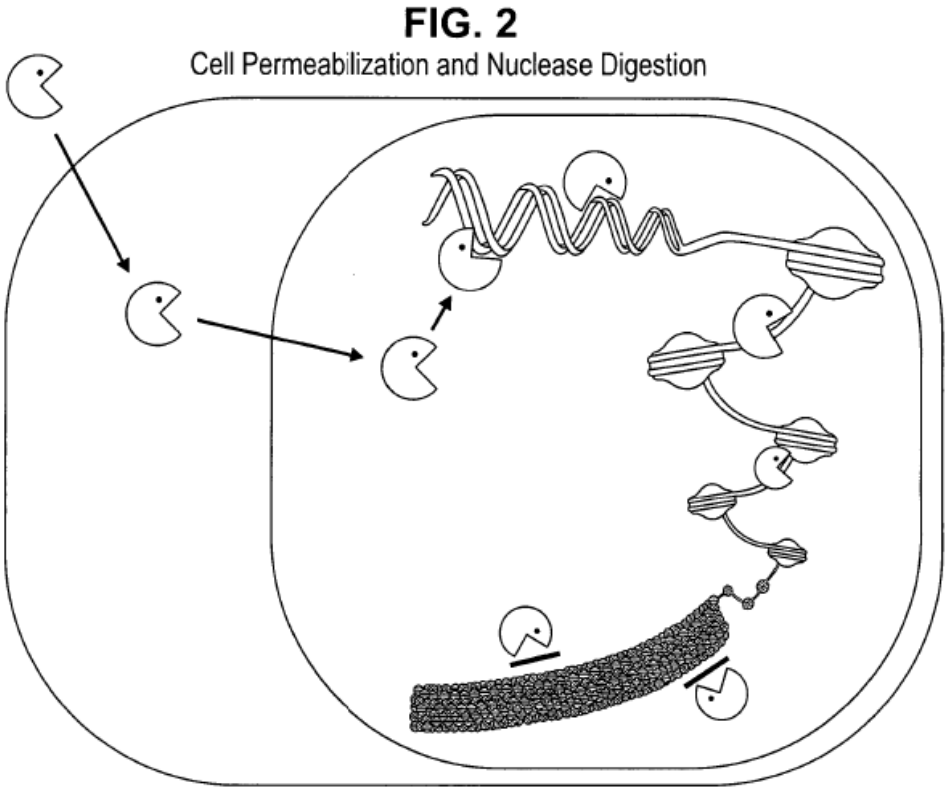

Figure 2 (above) depicts a schematic representation of Okino's assay. *Id.*

Okino teaches that the technique "allows for analysis of chromatin structure by . . . quantifying the extent of modification in various loci. The extent of modification at a particular locus reflects the accessibility of that portion of the chromosome to the modifying agent, and thus reflects the state of the chromatin." *Id.* at 64. Okino further teaches that "DNA regions that are more accessible to DNA modifying agents are likely in more 'loose' chromatin structures." *Id.* ¶ 66. In one embodiment, Okino discloses that a "variety of eukaryotic cells can be used in the present invention," such as "animal cells." *Id.* ¶ 67.

3. Saleh (Ex. 1005)

Saleh describes a method for fragmenting and tagging DNA in preparation for sequencing known as chromatin immunoprecipitation, or ChIP. Ex. 1005, Abstract. Saleh describes that ChIP allows for the study of

DNA-histone interactions through DNA preparation and subsequent sequencing or array study. *Id.* In ChIP, Saleh discloses that the first step is "cross-linking" DNA and proteins in vivo in a cell. *Id.* at 1.

Saleh describes that the first step consists of using formaldehyde to bind the DNA to associated proteins and freeze the interactions in a "snapshot." *Id.* at 5. Saleh discloses that the now-bound chromatin is subsequently isolated and sheared by isolating nuclei of the cell. *Id.* at 4. Saleh describes that DNA can then be extracted and sheared using sonication, or sound waves, to fragments of an appropriate length for tagging and sequencing. *Id.* at 4–5. According to Saleh, fragment size may be checked through gel electrophoresis, which allows seeing the relative size of DNA fragments. *Id.* at 5. After ensuring fragments are appropriately sized, Saleh describes that the bound proteins are contacted with antibodies to permit immunoprecipitation, or the pulling of proteins out of solution. *Id.* at 5. Saleh describes that the proteins are then un-linked from DNA and digested, and the DNA is precipitated and subject to further analysis. *Id.* at 5–6.

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.

5. Song (Ex. 1060)

Song is an article titled "DNase-seq: A High-Resolution Technique for Mapping Active Gene Regulatory Elements across the Genome from Mammalian Cells." Ex. 1004. Petitioner relies on Song for its disclosure for lysing cell membranes to isolate nuclei. Pet. 20–21, 57–62. 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. This allows researchers to identify the "most active regulator regions from potentially any cell type." *Id.*

II. ANALYSIS

A. 35 U.S.C. § 325(d)

Patent Owner argues that the Petition should be denied under 35 U.S.C. § 325(d). Prelim. Resp. 45–64. In determining whether to deny institution under § 325(d), we use

> the following two-part framework: (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential). The *Becton, Dickinson* factors provide useful insight into how to apply the framework under 35 U.S.C. § 325(d). *Id.* at 9 (referencing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph)).

Under § 325(d), we consider whether the art and arguments have been previously presented to the Office during proceedings, such as examination of the underlying patent application, pertaining to the challenged patent. *Advanced Bionics*, Paper 6, 7. Previously presented art includes art made of record by the Examiner, and art provided to the Office by an applicant, such as on an Information Disclosure Statement ("IDS"), in the prosecution history of the challenged patent. *Id.* at 7–8.

1. Whether the same or substantially the same art or arguments previously were presented to the Office

Under the first part of the *Advanced Bionics* framework, we consider "whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office." *Id.* at 8. We evaluate *Becton, Dickinson* factors (a), (b), and (d) to determine whether Petitioner has demonstrated material error. *Id.* at 10. Those factors are:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination; and
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8, 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

During prosecution, the Applicant submitted an Information Disclosure Statement identifying cited art Grunenwald in the first non-provisional application in the '357 patent's family before the same Examiner of the '357 patent. Ex. 2001, 295. Additionally, there is no dispute that the cited art of Okino, Adey, and Song were also before the Examiner. Pet. 66; Prelim. Resp. 46; Ex. 1001, code (56).

Regarding Saleh, Patent Owner argues the Petitioner relies upon "Saleh . . . as a reference for Ground 2 (which covers just claim 29), and this is insufficient to stave off §[]325(d) denial." Prelim. Resp. 51. Patent Owner further argues that Saleh is cumulative of art that was before the

Examiner because Song teaches isolating cell nuclei and Song was before the Examiner. *Id.* at 53 (citing Pet. 57–62, 66).

Having considered the parties' positions and evidence of record with regard to Saleh, summarized above, we find Patent Owner to have the better position. We first note that Petitioner's failure to conduct *any* analysis of whether its art was cumulative is, by itself, fatal under *AB* part one. *See* Pet. 66 (limiting its discussion to the assertion that "Saleh was not considered by the Examiner at all during prosecution"). Second, we also agree with Patent Owner that Saleh is cumulative of art that was before the Examiner, and Song in particular, because Song teaches isolating cell nuclei and Song was before the Examiner. Pet. 66; Prelim. Resp. 46; Ex. 1001, code (56). Further to that point, we note that Petitioner, in its Ground 2, relies on Saleh and Song in the alternative for a similar teaching. *See* Pet. 57 (asserting that claim 29 is rendered obvious by a combination of prior art references that include Saleh and/or Song); *id.* (asserting that both Saleh and Song teach isolation of cell nuclei).

In view of the above, we conclude that the prior art relied upon in the Petition is substantially the same art that was previously presented to the Office. Accordingly, the first part of the *Advanced Bionics* framework is satisfied. Because we determine that the same, or substantially the same, art was before the Examiner during examination, we need not consider *Becton, Dickinson* factor (d), and we turn to the second step of the *Advanced Bionics* framework.

2. Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims

Under the second part of the *Advanced Bionics* framework, we consider "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics*, Paper 6, 8. "An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Id.* at 8 n.9. We evaluate *Becton, Dickinson* factors (c), (e), and (f) to determine whether Petitioner has demonstrated material error. *Id.* at 10. Those factors are:

> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; . . . (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, Paper 8 at 17–18.

During the prosecution of the patent, the Examiner rejected the claims as, *inter alia*, obvious over Grunenwald in view of Jouvenot and further in view of Audit. *See* Ex. 1007, 152. The Examiner relied on Grunenwald for its tagmentation method. *Id.* at 152–155. The Examiner found that Grunenwald teaches "a composition comprising target DNA with a transposase and a transposon end or transposon end comprising a transferred strand that has a tag domain in its 5' portion," but found that "Grunenwald differs from the instant invention" because it does not expressly teach that the composition or reaction mixture is "comprise[d] of permeabilized cell nucleus." *Id.* at 152–153, 155.

The Examiner relied on Jouvenot for its method of permeabilizing the cell membrane "in such a way such that it will not disrupt the structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is not destroyed." Ex. 1007, 155–156. The Examiner found that a person of ordinary skill in the art would "have been motivated to modify the composition of Grunenwald to encompass permeabilized cell nucleus as taught by Jouvenot for the obvious benefit of allowing for entry of endonuclease into the nuclease and additionally for the benefit of allowing for chromatin structure analysis and/or epigenetic events in DNA regions of interest to detected." *Id.* at 156. The Examiner additionally found that Jouvenot discloses permeabilization of the cell by the use of nonionic detergents, particularly NP40 and Tween 20. *Id.*

In response to the Examiner's obviousness rejection, Applicant distinguished the rejected claims from the cited art by arguing that the cited references teach a "multi-step approach" and at no point does that approach result in a "composition comprising a permeabilized cell nucleus comprising the elements recited in the pending claims," specifically, "an insertional enzyme complex and an insert element comprising at least one nucleic acid comprising a predetermined sequence." *Id.* at 198–199 (emphasis removed); *see also id.* at 200 ("There is simply no guidance or teaching in *Jouvenot* that would lead one of ordinary skill in the art to apply *Gruenwald*'s teaching to a cell nucleus."). The claims were amended to expressly recite *a permeabilized cell nucleus* comprising an insertional enzyme complex comprising an insertional enzyme. *Id.* at 214.

The Examiner issued a notice of allowance stating the following reasons for the allowance:

> the prior art either alone or in combination, do not teach or suggest a composition comprising a *cell nucleus* comprising a plurality of polynucleotide molecules and an insertional enzyme complex comprising an insertion enzyme and an insert element comprising a predetermine[d] sequence. No prior art either alone or in combination teach[es] the composition further comprising open chromatin regions.

See id. at 224 (emphasis added).

Petitioner asserts the Examiner materially erred by "not considering the relevant teachings in Grunenwald and Okino, or in Grunenwald and Okino in combination with Saleh." Pet. 67. In particular, Petitioner contends that

> the Examiner erred by failing to acknowledge the teachings in [(1)] Grunenwald regarding application of tagmentation to living cells *in vivo* that disclose transposition tagging on chromosomal target DNA and [(2)] Okino that disclose permeabilization of the cell and nuclear membrane by the use of nonionic detergents, particularly NP40 and Tween 20.

Id. at 68.

In response, Patent Owner contends that

> Petitioner's only allegation is that the Examiner erred "by not considering the relevant teachings in Grunenwald and Okino, or in Grunenwald and Okino in combination with Saleh," arguing the Examiner "did not discuss or cite any passage or disclosure of Okino" and did not discuss Grunenwald's single in vivo reference. Pet.67. . . . But Petitioner entirely fails to show how that in vivo embodiment was overlooked (given the Examiner's thorough analysis) or how it would expressly disclose the permeabilized cell nucleus the Examiner found to be missing. Pet. 67–68. Thus, Petitioner fails to assert, let alone explain, why the Examiner's conclusion as to patentability would have differed based on these additional cumulative references and arguments. Pet. 67–68.

Prelim. Resp. 47–48 (footnote omitted); *see also id.* at 60–61 ("Petitioner does not even attempt to explain how the Examiner's decision would have differed if it had 'acknowledged' these disclosures from both Grunenwald and Okino."). Patent Owner further contends that

> [Okino] is plainly cumulative of Jouvenot, which was affirmatively asserted by the Examiner. For example, Petitioner asserts Okino discloses "'methods of permeabilizing' a cell membrane that 'will not disrupt the structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is destroyed.'" Pet.24 (citing EX1004, ¶71). Petitioner also argues that "[c]ritically, the permeabilization agent used in Okino is a detergent, such as the common NP40 or Tween detergents." Pet.26 (citing EX1004, ¶12). But (while Petitioner ignores this) the Examiner *found and asserted the same teachings* in Jouvenot, stating that "Jouvenot teaches that permeabilizing of the cell membrane occurs in such a way such that it will not disrupt the structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is not destroyed [0055]. *Jouvenot teaches wherein such agents used to permeabilize the cells comprise of NP40, Tween 20* or Triton X-100." EX1007, 155-156. These are nearly verbatim statements of the disclosures argued by Petitioner, and there can be no dispute that Okino and Jouvenot are cumulative.

Prelim. Resp. 50.

Having considered the parties' positions and evidence of record, summarized above, we find Patent Owner to have the better position. *See* Prelim. Resp. 54–64. In particular, we have considered Petitioner's argument that Grunenwald discloses an in vivo method using electroporation to permit a transposase to access the cell, and that "a [person of ordinary skill in the art] would have considered other alternatives to gain access and/or improve access to the genetic material in the cell nucleus." Pet. 29; *see also id.* at 60 ("a [person of ordinary skill in the art] would have been motivated to combine the insertional enzyme complex as used in vivo in

Grunenwald with the permeabilization techniques taught in Okino to permit the insertional enzyme complex to enter the cell and nucleus.").

That argument fails to sufficiently explain how the person of ordinary skill in the art would have combined Grunenwald's in vivo tagmentation method with the in vitro procedure for disrupting cell membranes taught in Okino to arrive at the claimed composition comprising a permeabilized cell nucleus. Ex. 1004 ¶ 71. In its Ground 1, for example, Petitioner appears to rely exclusively on Grunenwald and Okino's in vitro embodiments to support its obviousness argument that (1) a person of ordinary skill in the art "would understand the reference to a 'permeabilized cell nucleus' to encompass, *inter alia*, cellular nuclei that result from treatment of cells with standard lysis buffers so as to lyse the cells and permeabilize the nuclear envelope," (2) Okino teaches "methods of permeabilizing" a cell membrane, and (3) "a person of skill in the art would have been motivated to combine Okino's permeabilized cell nuclei with Grunenwald" because "Grunenwald teaches that just about any source of DNA may be used in its tagmentation method." Pet. 23–24, 27–28. Okino's in vitro embodiments relied upon by Petitioner appear, on their face, to be entirely different embodiments from Grunenwald's in vivo tagmentation method that uses electroporation to permeabilize the cell membrane. *See* Ex. 1003, 151–158 ("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."). Petitioner fails to explain how Grunenwald's in vivo tagmentation method would have been combined with the in vitro cell permeabilization method disclosed in Okino.

We also recognize that Okino discloses simultaneously permeabilizing a cell membrane and contacting it with DNA modifying

agents." Ex. 1002 ¶ 146; Ex. 1004, 5. We do not recognize, however, any material error on the part of the Examiner for failing to find that a person of ordinary skill would have been motivated to combine Grunenwald's in vivo embodiments with Okino's in vitro embodiments, and to reject the challenged claims, directed to compositions, in an obviousness ground on that basis. Petitioner fails to provide the necessary analysis that would be required to show why the person of ordinary skill would have been motivated to combine the in vivo and in vitro embodiments of the cited prior art to achieve the compositions of the challenged claims.

Moreover, we agree with the Examiner that "Grunenwald differs from the instant invention in that the reference does not expressly teach wherein the composition or reaction mixture of the methods disclosed therein comprise of a permeabilized cell nucleus." Ex. 1007, 155. To that point, Petitioner fails to show how a person of ordinary skill in the art would apply Grunenwald's method to chromatin, a nucleus, or a eukaryotic cell in vivo (let alone one with a permeabilized cell nucleus). For example, even to the extent Grunenwald mentions in vivo transposition, it does not address any transposition of chromosomal DNA of the nucleus of a eukaryotic cell (Grunenwald is not limited to eukaryotic cells, the only cellular location where chromatin exists) or using an insertional enzyme complex within an intact nucleus. Ex. 1003 ¶ 157. Grunenwald Paragraph 157 does not mention a nucleus or "chromatin" (the complex of molecules including proteins and polynucleotides "as found in a nucleus of a eukaryotic cell" (Ex. 1001, 12:61–63)). Petitioner points to no indication in that paragraph that an insertional enzyme complex contacts chromatin or concerns anything involving a permeabilized cell nucleus. Furthermore, we agree with Patent Owner that Petitioner has not otherwise "established that Grunenwald

discloses contacting a cell nucleus and that Okino discloses permeabilizing a cell nucleus" such that a person of ordinary skill in the art would have been motivated to achieve the cited compositions comprising a permeabilized cell nucleus, and adopt its reasoning as our own. Prelim. Resp. 41; *see also id.* at 26–31 ("Petitioner does not address whether its contention is that these buffers, as used in Okino, would lyse rather than permeabilize the cellular membrane or the nuclear membrane").

We accordingly determine that Petitioner fails to identify a material error by the Office in its earlier consideration of the art we discuss above.

3. Summary

We conclude that (1) substantially the same art was previously presented to the Office, and (2) Petitioner has not demonstrated that the Office erred. We therefore conclude that it is appropriate to exercise discretion under 35 U.S.C. § 325(d) to deny the Petition.

III. CONCLUSION

For the foregoing reasons, we exercise discretion under 35 U.S.C. § 325(d) to deny institution of an *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

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

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

IPR2023-01033
Patent 10,738,357 B2

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

FITZPATRICK, *Administrative Patent Judge*, dissenting.

I respectfully dissent from the majority's Decision denying institution.

I would not exercise discretion to deny under 35 U.S.C. § 325(d). Further, I would institute trial, as there is a reasonable likelihood Petitioner would prevail with respect to at least one challenged claim. 35 U.S.C. § 314(a).

As relied upon by Petitioner, Okino teaches permeabilization of a eukaryotic cell and nucleus such that a nuclease may enter the nucleus and

digest open chromatin[1] while not digesting inaccessible chromatin. *See* Pet. 24–26 (citing Ex. 1004 ¶¶44, 71, 72, 75, Fig. 2; Ex. 1002 ¶148); *see also* Ex. 1004 ¶44 (describing Figure 2, stating: "The culture media is aspirated and a permeabilization/digestion buffer is added. The nuclease diffuses into the cell, enters the nucleus and digests accessible chromatin, but inaccessible chromatin (represented as a thick line towards the bottom of the Figure) is not digested."). The Office either failed to appreciate this teaching by Okino or failed to recognize its significance in combination with Grunenwald.

In allowing the claims, the Examiner stated:

> While the teaching of Jouvenot (US 20110306042; citation previously made or record) discloses a permeabilizing cell membrane such that the structure of genomic DNA of the cells including nucleosomal or chromatic structure are not disrupt [0055], the prior art either alone or in combination, do not teach or suggest a composition comprising a cell nucleus comprising a plurality of polynucleotide molecules and an insertional enzyme complex comprising an insertion enzyme and an insert element comprising a predetermine sequence. No prior art either alone or in combination teach the composition further comprising open chromatin regions.

Ex. 1007, 2.

[1] Okino does not mention "open chromatin" but clearly discusses it using different terms, "euchromatin" and "accessible chromatin." Ex. 1004 ¶43 ("Chromatin is classified into two main groups, *euchromatin*, where the DNA is loosely packaged, accessible and generally, but not always, transcriptionally competent, and heterochromatin, where the DNA is tightly packaged, inaccessible and generally, but not always, transcriptionally silent." (emphasis added)), ¶44 ("The nuclease diffuses into the cell, enters the nucleus and digests *accessible chromatin*, but inaccessible chromatin . . . is not digested." (emphasis added)).

The first sentence suggests to me that the Office did not appreciate that a combination of Grunenwald and Okino teach such a composition, with Grunenwald teaching targeting DNA with "an insertional enzyme complex comprising an insertional enzyme and an insert element comprising a predetermined sequence" and Okino teaching "a permeabilized cell nucleus comprising: a) a plurality of polynucleotide molecules," as recited in claim 1.

Further, the second sentence suggests to me that the Office did not appreciate, as relevant to independent claim 2, for example, that Okino explicitly teaches that the permeabilized cell nucleus has both accessible (open) and inaccessible chromatin, and that the nuclease can digests the open chromatin only.

For the above-stated reasons, I respectfully dissent from the majority's Decision denying institution.

IPR2023-01033
Patent 10,738,357 B2

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