

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.

Petitioner,

v.

10X GENOMICS, INC.

Patent Owner.

Case No. IPR2023-_____
U.S. Patent No. 10,150,995

**PETITION FOR *INTER PARTES* REVIEW
OF
U.S. PATENT NO. 10,150,995**

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PETITIONER’S EXHIBIT LIST

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EX1004	PCT Patent Publication No. WO 2010/065266 A1 to Okino <i>et al.</i> (“Okino”).
EX1005	Henriette O’Geen et al., <i>Using ChIP-Seq Technology to Generate High-Resolution Profiles of Histone Modifications</i> , 791 <i>Methods in Molecular Biology</i> , 265-286 (2011) (“O’Geen”).
EX1006	William G. Pitt, Dr. et al., <i>Ultrasonic Drug Delivery – A General Review</i> , <i>Expert Opin Drug Deliv</i> , 37-56 (2004) at https://pubmed.ncbi.nlm.nih.gov/16296719/ (“Pitt”).
EX1007	Prosecution File History of U.S. Patent No. 10,150,995
EX1008	Fraz Syed, 19 <i>Second-Generation Sequencing Library Preparation: In Vitro Tagmentation via Transposome Insertion</i> , <i>Tag-based Next Generation Sequencing</i> 311-321 (1st Ed. 2012) (“Syed”).
EX1009	Andrew Adey et al., <i>Rapid, Low-input, Low-bias Construction of Shotgun Fragment Libraries by High-density in vitro Transposition</i> , <i>Genome Biology</i> 1-17 (2010) (“Adey”).
EX1010	Megan L McCloskey et al., <i>Encoding PCR Products with Batch-Stamps and Barcodes</i> , 45 <i>Biochemical Genetics</i> , 761-767 (2007) (“McCloskey”).
EX1011	William J. Dower, Jeff F. Miller and Charles W. Ragsdale, <i>High Efficiency Transformation of E.coli by High Voltage Electroporation</i> , 16 <i>Nucleic Acids Research</i> 6127–6145 (1988) (“Dower”).
EX1012	Gerald Schochetman et al, <i>Polymerase Chain Reaction</i> , 158 <i>J. of Infectious Diseases</i> 1154-1157 (1988) (“Schochetman”).

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EX1013	Peter E. Brodelius, Christoph Funk, and Raymond D. Shillito, Permeabilization of Cultivated Plant Cells by Electroporation for Release of Intracellularly Stored Secondary Products, 7 Plant Cell Reports 186-188 (1988) (“Brodelius”).
EX1014	Jeffrey M. Becker, 15 Determination of β -Galactosidase in Permeabilized Yeast Cells, <i>Biotechnology A Laboratory Course</i> 131-134 (2nd Ed. 1996) (“Becker”).
EX1015	J. Sambrook, E.F. Fritsch, T. Maniatis, <i>Molecular Cloning: A Laboratory Manual</i> (Ford et al, eds., 2d ed. 1989).
EX1016	J. Gehl, <i>Electroporation: theory and methods, perspectives for drug delivery, gene therapy and research</i> , 177 Acta Physiologica Scandinavica 437-447 (2003) (“Gehl”).
EX1017	Jin Liu et al., <i>Non-invasive Assessment and Control of Ultrasound-Mediated Membrane Permeabilization</i> , 15 Pharmaceutical Research 918-924 (1998) (“Liu”).
EX1018	Terez Márián et al., <i>Hypo-osmotic Shock Induces an Osmolality-dependent Permeabilization and Structural Changes in the Membrane of Carp Sperm</i> , 41.2 Journal of Histochemistry & Cytochemistry 291-297 (1993) (“Márián”).
EX1019	Melissa A. Melan, <i>Overview of Cell Fixation and Permeabilization</i> , 34 Immunocytochemical Methods and Protocols 55-66 (1995) (“Melan”).
EX1020	10X’s Supplemental Brief in Opposition to Parse’s Motion to Dismiss, <i>10X Genomics, Inc. and The Board of Trustees of the Leland Stanford Junior University v. Parse Biosciences, Inc.</i> , C.A. No. 22-1117-JHS (Dec 15, 2022 D. Del.)(No.33).
EX1021	Henderson’s Dictionary of Biology (Eleanor Lawrence ed., 14th ed., 2008).
EX1022	David S. Johnson et al., Genome-Wide Mapping of in Vivo Protein-DNA Interactions, <i>Science Express</i> 1-70 (2007) (“Johnson”).
EX1023	Curriculum Vitae of Gregory Cooper

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EX1024	Transcript of Motion Hearing Before Honorable Joel H. Slomsky United States District Court Judge, <i>10X Genomics, Inc. and The Board of Trustees of the Leland Stanford Junior University v. Parse Biosciences, Inc.</i> , C.A. No. 22-1117-JHS (Nov. 29, 2022 D. Del.) (No. 27).
EX1025	Bruce Alberts, et al., “Chapter 6 How Cells read the Genome: From DNA To Protein”, <i>Molecular Biology of the Cell</i> , Garland Science 299-335 (4th ed. 2002).
EX1026	David H. Persing, <i>Polymerase Chain Reaction: Trenches to Benches</i> , J. of Clinical Microbiology 1281-1285 (1991) (“Persing”).
EX1027	Kazuki Kurimoto et al., <i>An improved single-cell cDNA amplification method for efficient high-density oligonucleotide microarray analysis</i> , 34(5) Nucleic Acids Research 1-17 (2006) (“Kurimoto”).
EX1028	Shigeyuki Esumi et al., <i>Method for single-cell microarray analysis and application to gene-expression profiling of GABAergic neuron progenitors</i> , 60 Neuroscience Research 439-451 (2008) (“Esumi”).
EX1029	Tweet by Jason Buenrostro, co-inventor of the 995 Patent (August 26, 2022) at https://twitter.com/JD_Buenrostro/status/1563327469293551618
EX1030	Clyde A. Hutchinson, <i>DNA sequencing: bench to bedside and beyond</i> , 35(18) Nucleic Acids Research 6227-6237 (2007) (“Hutchinson”).
EX1031	Elaine R. Mardis, <i>Next-Generation DNA Sequencing Methods</i> , 9 Annual Review Genomics and Human Genetics 387-402 (2008) (“Mardis”).
EX1032	Jay Shendure and Hanlee Ji, <i>Next-Generation DNA Sequencing</i> , 26(10) Nature Biotechnology 1135-1145 (2008) (“Shendure”).
EX1033	Elaine R. Mardis, <i>The impact of next-generation sequencing technology on genetics</i> , 24(3) Trends in Genetics 133-141 (2008) (“Mardis 2”).
EX1034	Robert A. Holt and Steven J.M. Jones, <i>The new paradigm of flow cell sequencing</i> , 18(6) Genome Research 839-846 (2008) (“Holt”).

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EX1035	National Human Genome Research Institute, <i>Nucleotide</i> (March 21, 2023) at https://www.genome.gov/genetics-glossary/Nucleotide
EX1036	Lumen, <i>DNA Packaging in Eukaryotes and Prokaryotes</i> (March 15, 2023) at https://courses.lumenlearning.com/wm-biology1/chapter/reading-dna-packaging-in-eukaryotes-and-prokaryotes/
EX1037	Epigentek, Antibodies for Histone Modifications (March 15, 2023) at https://www.epigentek.com/catalog/antibodies-for-histone-modifications-lp-49.html
EX1038	National Human Genome Research Institute, <i>Polymerase Chain Reaction</i> (March 21, 2023) at https://www.genome.gov/genetics-glossary/Polymerase-Chain-Reaction
EX1039	Athina Gkazi, <i>An Overview of Next-Generation Sequencing</i> , Technology Networks Genomics Research at Figure 2 (March 17, 2021) at https://www.technologynetworks.com/genomics/articles/an-overview-of-next-generation-sequencing-346532
EX1040	Rami Sukarieh, <i>Relocalization of eIF4E by its binding partners upon stress</i> , Figure 2 (August 2009) at https://www.researchgate.net/publication/41663010_Relocalization_of_eIF4E_by_its_binding_partners_upon_stress
EX1041	Dr. Samanthi, <i>Difference Between Chromatin and Nucleosome</i> , Figure 01 (March 31, 2023) at https://www.differencebetween.com/difference-between-chromatin-and-vs-nucleosome/#:~:text=Nucleosome%20can%20be%20defined%20as,a%20basic%20unit%20of%20chromatin
EX1042	S. Clancy et al., <i>Translation: DNA to mRNA to Protein</i> , Nature Education (2008), at https://www.nature.com/scitable/topicpage/translation-dna-to-mrna-to-protein-393/

Exhibit #	Description
EX1043	Illumina. (2017). Nextera XT Troubleshooting Guide. Technical Note. Illumina. Retrieved from https://www.illumina.com/content/dam/illumina-marketing/documents/products/technotes/nextera-xt-troubleshooting-technical-note.pdf
EX1044	Anjali Shah, <i>Chromatin Immunoprecipitation Sequencing (ChIP-Seq) on the SOLiD™ system</i> , Nature America, Inc. I-III (2009) (“Shah”).
EX1045	U.S. Patent No. 6,159,736
EX1046	Scheduling Order, <i>10X Genomics, Inc. and The Board of Trustees of the Leland Stanford Junior University v. Parse Biosciences, Inc.</i> , C.A. No. 22-1117-JHS (Mar. 2, 2023 D. Del.) (No. 48).
EX1047	Federal Judicial Caseload Statistics (2022), at https://www.uscourts.gov/statistics-reports/analysis-reports/federal-judicial-caseload-statistics
EX1048	Epicentre Biotechnologies, Nextera™ DNA Sample Prep Kit (Illumina-compatible) (June 12, 2012), at https://web.archive.org/web/20120622102355/http://nextgen.mgh.harvard.edu/attachments/Nextera%20Protocol.pdf
EX1049	Docket Navigator, <i>Motion Success for Stay Pending IPR in Delaware District</i> (March 31, 2023).
EX1050	Beáta G Vértessy and Judit Tóth, <i>Keeping Uracil Out of DNA: Physiological Role, Structure and Catalytic Mechanism of dUTPases</i> , Acc Chem Res. 1-20 (2009) (“Vértessy”).
EX1051	Declaration of Sylvia D. Hall-Ellis, Ph.D.

I. INTRODUCTION

Parse Biosciences, Inc. (“Petitioner”) requests review of Claims 1-23 of U.S. Patent No. 10,150,995 (“’995 Patent”), which issued on December 11, 2018 and is assigned to The Board of Trustees of the Leland Stanford Junior University.

The ’995 Patent pertains to a molecular biology technique known as “tagmentation.” Briefly, “tagmentation” entails using an enzyme, called a transposase, to fragment a DNA molecule into smaller chunks that are suitable for sequencing. Concurrent with DNA fragmentation, the transposase enzyme also adds “tags” to the DNA molecules that are necessary for the DNA to be sequenced with modern instrumentation. The term “tagmentation” is thus a combination of the words “tagging” and “fragmentation,” reflecting the simultaneous execution of the “tagging” and “fragmentation” processes.

Importantly, “tagmentation” was not new, but was rather a well-established prior art process. The ’995 Patent even acknowledges, for instance, that tagmentation had not only been published, but was so well developed that it had already been the subject of commercial product offerings that could be “readily adapted” for the alleged invention. *See* EX1001 at 14:23-38.

What, then, is the alleged invention of the ’955 Patent, if not tagmentation? To the extent there is any alleged novelty in the ’995 Patent, it is nothing more than the trivial idea of using the prior art “tagmentation” process with living cells so as

to fragment and tag DNA as it exists in its naturally-occurring form, known as “chromatin.” For instance, in parallel district court litigation, Patent Owner acknowledged that tagmentation has long been known, but that it was supposedly new to apply tagmentation to a cell:

Although engineered insertional enzymes having sequencing adaptor molecules had been used to tagment isolated DNA fragments, prior to the ATAC-seq Patents, such engineered insertional enzymes had not been introduced into a cell nucleus to perform tagmentation inside the cell nucleus to interrogate areas of open chromatin.

EX1020 at 19 (emphasis in original); *see also* EX1024 at 106:6-13 (“[T]agmentation was being used as a way of doing that fragmenting process. And it was being used on DNA that had already been purified, it wasn't being used on a cell. Right?”).

Yet, there is nothing inventive or novel about applying tagmentation to a cell. Any such contention that this is inventive is negated by the earliest patent filings on the tagmentation process, such as the Grunenwald reference. Grunenwald unambiguously contemplates applying tagmentation to living cells *in vivo* by permeabilizing a cell so the machinery of tagmentation be introduced into the cell:

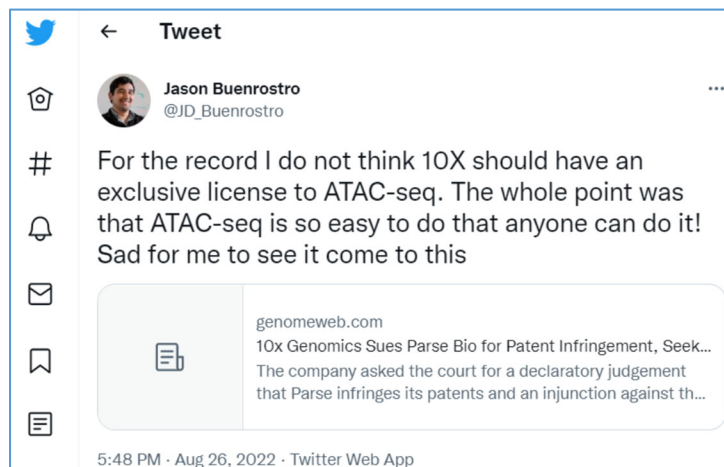
In some embodiments, the insertion of a transposon end into target DNA according to the present invention can also be carried out in vivo. If transposition is carried out in vivo, transposition into the target DNA is preferably achieved by electroporating a synaptic

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).

EX1003 at [0157].

As proven herein and in the accompanying declaration of Dr. Gregory Cooper, the application of tagmentation *in vivo* to living cells will unavoidably involve chromatin and Grunenwald thus anticipates and/or renders obvious every claim of the '995 Patent. In allowing the claims of the '995 Patent, however, the Examiner performed no analysis of Grunenwald, and certainly did not consider the disclosure of the *in vivo* embodiment taught in Grunenwald. See EX1007.144-146. The Board should now take this opportunity to correct this oversight.

Indeed, any suggestion that the claimed invention of the '995 Patent is novel or inventive is put to rest by the primary inventor, Dr. Jason Buenrostro. He and the other inventors termed the application of prior art tagmentation to chromatin “ATAC-seq,” which is short for “Assay for Transposase Accessible Chromatin followed by high-throughput sequencing.” EX1001 at 24:38-39. In a tweet shortly after Patent Owner filed a lawsuit against Petitioner based on *inter alia* the '995 Patent, he lamented the litigation and confirmed that the application of “tagmentation” to chromatin was “so easy that anyone can do it!”



EX1029. Because the alleged inventions in the '995 Patent are not new and reflect nothing more than the previously disclosed application of tagmentation to living cells, the claims of the '995 Patent should be cancelled.

II. MANDATORY NOTICES

A. Real Party-in-Interest

The real party-in-interest is Parse Biosciences, Inc.

B. Related Matters

As of the filing date of this Petition, the '995 Patent is involved in litigation in *10x Genomics v. Parse Biosciences, Inc.*, 22-cv-01117 (D. Del. filed Aug. 8, 2022).

C. Grounds for Standing

Petitioner certifies that the '995 Patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting *inter partes* review challenging the patent claims on the grounds identified in this Petition.

D. Lead and Back-Up Counsel and Service Information

Petitioner provides the following designation of Lead and Back-Up Counsel.

Lead Counsel	Back-Up Counsel
Derek C. Walter Registration No. 74,656 (derek.walter@weil.com) Postal & Hand-Delivery Address: Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 T: 650-802-3934 F: 650-802-3100	Adrian C. Percer Registration No. 46,986 (adrian.percer@weil.com) Postal & Hand-Delivery Address: Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 T: 650-802-3124 F: 650-802-3100 William Sutton Ansley Registration No. 67,828 (sutton.ansley@weil.com) Postal & Hand-Delivery Address: Weil, Gotshal & Manges LLP 2001 M Street NW, Suite 600 Washington, DC 20036 T: 202-682-7018 F: 202-857-0940

III. IDENTIFICATION OF CHALLENGE

Petitioner presents the following challenges to the claims of the '995 Patent:

- **Ground 1:** Claims 1, 3, 5-6, and 10-23 of the '995 Patent are unpatentable under 35 U.S.C. § 102 as being anticipated by Grunenwald (US 2010/0120098 (EX1003)).
- **Ground 2:** Claim 2 of the '995 Patent is unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Grunenwald (EX1003) in view of O'Geen ("Using ChIP-Seq Technology to

Generate High-Resolution Profiles of Histone Modifications” (EX1005)).

- **Ground 3:** Claims 4 and 6-8 are unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Grunenwald (EX1003) in view of Okino (WO 2010/065266 A1 (EX1004)).
- **Ground 4:** Claim 9 is unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Grunenwald (EX1003) in view of Pitt (“Ultrasonic Drug Delivery – A General Review” (EX1006)).
- **Ground 5:** Claims 17-20 are unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Grunenwald (EX1003) in view of Adey (“Rapid, Low-input, Low-bias Construction of Shotgun Fragment Libraries by High-density *in vitro* Transposition” (EX1009)).
- **Ground 6:** Claims 1, 3, 5-6, and 10-23 of the ’995 Patent are unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Grunenwald (EX1003) and Okino (EX1004).
- **Ground 7:** Claim 2 of the ’995 Patent is unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Grunenwald (EX1003) in view of O’Geen (EX1005) and Okino (EX1004).
- **Ground 8:** Claims 17-20 are unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Grunenwald (EX1003) in view of Adey (EX1009) and Okino (EX1004).

IV. TECHNOLOGICAL BACKGROUND

A. DNA and RNA

Deoxyribonucleic acid, or DNA, is a double-stranded molecule having a chain of bases or “nucleotides.” EX1002 ¶¶ 40-41. Each nucleotide comprises of four

types of bases: adenine (“A”), cytosine (“C”), guanine (“G”), and thymine (“T”). *Id.* ¶ 41. The order of these bases constitute genetic information, which can be copied to a ribonucleic acid (“RNA”) strand, by a process called transcription. *Id.* ¶ 46.

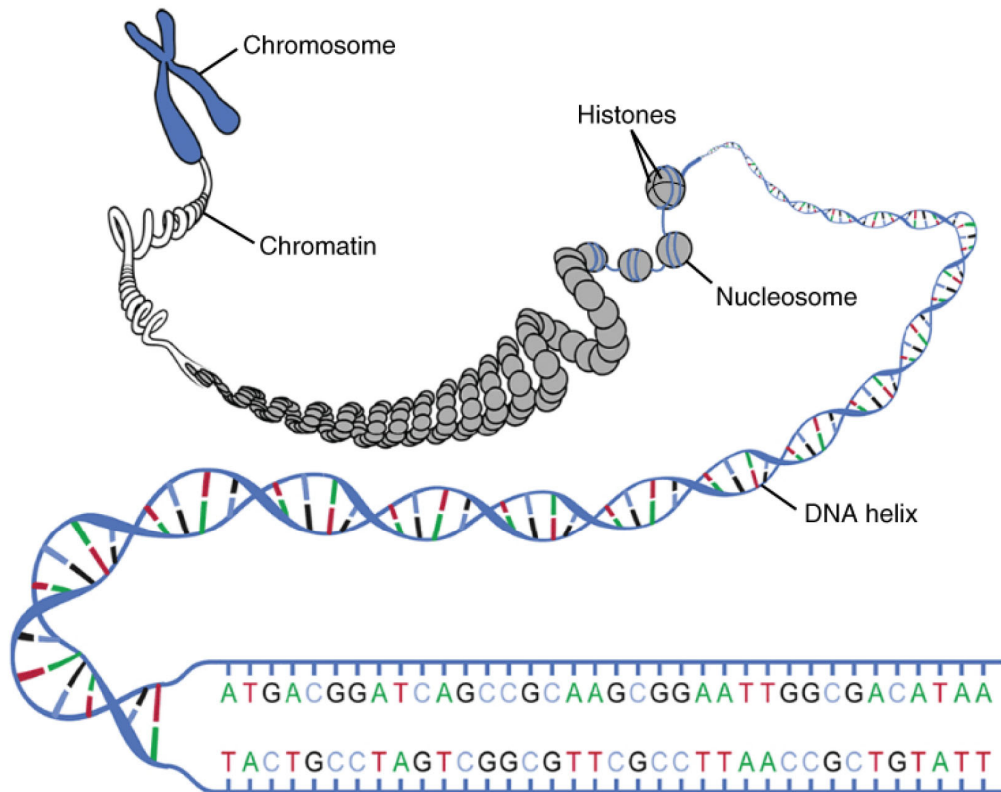
RNA is a molecule similar to DNA, where the nucleotides in RNA are adenine, cytosine, guanine, and uracil. Uracil and thymine are functionally equivalent including for both information storage and transmission. *Id.* ¶¶ 43-44. EX1044.001. A specific type of RNA—messenger RNA (“mRNA”)—is read by ribosomes to make proteins. EX1002 ¶ 46. mRNA is critical to the study of epigenetics, or gene expression, because it shows the portions of DNA being copied for the production of proteins—*i.e.*, which genes are expressed. *Id.* ¶ 49.

B. DNA Packaging

For all of the DNA in a cell to fit inside of the nucleus of a cell, it must be very tightly packaged. EX1002 ¶ 51. This packaging is achieved with the aid of proteins called “histones,” which act as scaffolding around which the DNA is coiled. A histone protein with DNA coiled around it is a “nucleosome.” The collection of nucleosomes together is known as “chromatin.” *Id.* ¶¶ 54-55.

Chromatin is further packaged and condensed into chromosomes. *Id.* ¶ 52. This format for packaging DNA is shown in the figure below, which shows that an

individual chromosome is made up of chromatin, which, in turn, consists of DNA wrapped around histones:



EX1041 at Figure 01

The DNA packaging depicted above is not static, but is rather dynamic, changing in the cell depending on the phase of the cell's life cycle. EX1002 ¶ 59. For example, at one point in time a portion of chromatin may be considered "closed" when the DNA in that portion is tightly coiled around a histone, but at another point in time the same chromatin portion may be considered "open," when the DNA is not coiled, or not as tightly coiled, around the histone. *Id.* ¶ 59-60.

This accessibility of chromatin is directly associated with gene expression. *Id.* ¶ 60. While open chromatin regions are loosely packaged and hence more accessible to the cellular machinery for transcription, closed chromatin regions are tightly packaged and less accessible. *Id.*

C. Sequencing and Tagmentation

Nucleic acid sequencing, loosely speaking, is the process of determining the sequence of nucleotides in a polynucleotide such as DNA. EX1002 ¶ 61. Amongst the nucleic acid sequencing technologies, Next Generation Sequencing (“NGS”) emerged in the early 2000s. EX1033.002. NGS is a type of high-throughput sequencing technology that uses parallel sequencing of many fragments of DNA, enabling processing and detection of millions of sequence reads in a single run. EX1033.003. NGS platforms have a common workflow including the steps of “library preparation” (*i.e.*, making a collection of nucleic acid fragments), amplification, and sequencing. EX1002 ¶ 62.

Importantly, many NGS platforms are so-called “short read” sequencing platforms. In such platforms, one can generate only a short string of DNA sequence information from a nucleic acid molecule, typically only a couple of hundred nucleotides in length. The NGS platforms that are by far most commonly used in industry and academia, such as those sold by Illumina, fall into this “short read” category. For this reason, prior to sequencing, it is commonly essential for

DNA to be broken up (*i.e.*, fragmented) into small chunks so that it is suitable for the sequencing instrument. EX1002 ¶ 63.

Historically, this was done through a process known as chromatin immunoprecipitation. *See, e.g.*, EX1022. In this process, chromatin is treated with antibodies to pull DNA out of solution, at which point it could be fragmented by either digestion with restriction enzymes or by sonication. EX1005.005.

However, library preparation, including the necessary fragmentation, can also be, and often is, accomplished by “tagmentation,” which was developed by researchers as early as 2010 to reduce the time and cost of preparing DNA libraries for NGS. EX1002 ¶ 64; EX1009.002; EX1008.003. Tagmentation is a one-step reaction where accessible DNA is fragmented and tagged for analysis. EX1008.003. A specific type of enzyme—transposase—can carry out this single-step reaction. EX1008.004. Oligonucleotide tags can be discrete segments of DNA with pre-defined lengths and sequences such that each tag is identifiable during sequencing, but tags may serve a variety of other purposes. EX1002 ¶ 64; EX1009.002; EX1010.002.

D. Permeabilization

To gain access to chromatin nested inside of a cell, the cell membrane has to first be made permeable. The process by which openings are created in the cell membrane to allow entry of reagents into the cell is generally known as

“permeabilization.” EX1002 ¶ 82. Permeabilization techniques have been developed to minimally perturb the genomic material of the cell to keep the DNA of interest intact and associated with the cell after permeabilization so that it can be studied. EX1002 ¶ 82; EX1014.003.

Electroporation was an established physical method of permeabilization as early as 2003. EX1016.001. Electroporation uses short electrical pulses to temporarily create pores in the cell membrane. EX1016.002. By applying an external electric field that just exceeds the capacitance of cell membrane, a transient and reversible breakdown of the cell membrane can be triggered. EX1016.001-002. This transient state of permeability had been widely used to introduce virtually any molecules into the cell, including antibodies, oligonucleotides, DNA, dyes and drugs. EX1016.001. Electroporation had proven to be a useful method of permeabilization both *in vitro* and *in vivo*, and researchers had optimized electroporation protocols to ensure delivery of molecules while preserving cell viability. EX1002 ¶ 83; EX1016.001.

Ultrasonication is another physical method of permeabilization known as early as 1998. EX1017.001. Ultrasonication employs ultrasound to transiently permeabilize cell membranes. EX1002 ¶ 84; EX1017.001. Application of ultrasound temporarily increases the permeability of cell membrane by acoustic cavitation, where acoustic cavitation involves the creation, oscillation, and collapse

of gas bubbles. EX1017.001. By 1998, it was well-known that ultrasonication can facilitate transportation of large molecules, like DNA and proteins, into cells. EX1017.001.

Permeabilization techniques can also be chemical. Detergents such as saponin, Triton X-100, and NP40 were commonly used permeabilization agents as early as 1994. EX1019.006-007. Detergents act on membrane by dissolving the components of the membranes, thereby creating openings on the membranes and rendering the membranes permeable. EX1002 ¶ 86. Among them, saponin acts by interacting with membrane cholesterol, and Triton X-100 and NP40 act by solubilizing lipids and integral membrane proteins. EX1019.006.

V. OVERVIEW OF THE '995 PATENT

A. Priority Date of the '995 Patent

The '995 Patent, which was filed on July 24, 2018, identifies a provisional application, which was filed on May 23, 2013. EX1001 at (60). Thus, the priority date of the '995 Patent is no earlier than the date of this provisional application—May 23, 2013.

B. Overview of the Challenged Claims and Specification

The '995 Patent pertains to applying the prior art tagmentation technique to open chromatin, and sequencing the resulting tagged chromatin fragments. Exemplary Claim 1 of the '995 Patent is as follows:

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 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.

Step (a) of Claim 1 of the '995 Patent recites using an “insertional enzyme complex” on open chromatin to generate fragmented and tagged genomic nucleic acid molecules. EX1001 at Claim 1.

The '995 Patent defines the term “insertional enzyme complex” to mean a complex comprising an insertional enzyme (e.g., a transposase) and a payload of DNA tag sequences. EX1001 at 13:19-26; *see id.* at 15:61-63 (explaining that the insertional enzyme can be a transposase). But as explained above, tagmentation—using a transposase to tag a target polynucleotide sequence with tag sequences—had been known and widely used in the art as of the filing of the '995 Patent. *See* Section IV.C, *supra* (explaining tagmentation has been known since 2010).

Indeed, the specification of the '995 Patent readily admits that tagmentation had long since been published and was even the subject of commercial product

offerings that could be “readily adapted” for the alleged invention of the ’995 Patents:

Methods for tagmenting isolated genomic DNA are known in the art (see, e.g., Caruccio *Methods Mol. Biol.* 2011 733: 241-55; Kaper et al, *Proc. Natl. Acad. Sci.* 2013 110: 5552-7; Marine et al, *Appl. Environ. Microbiol.* 2011 77: 8071-9 and US20100120098) and are commercially available from Illumina (San Diego, Calif.) and other vendors. Such systems may be readily adapted for use herein.

EX1001 at 14:23-38.

Independent claim 1 additionally recites in step (b) the conventional process of sequencing the tagged nucleic acid molecules. EX1001 at Claim 1. As explained above, however, methods for sequencing nucleic acid molecules, including next-generation sequencing, had also been known and widely practiced in the art before the earliest priority date of the ’995 Patent. Section IV.C, *supra*. The ’995 Patent thus admits that sequencing techniques were well-known in the prior art and commercialized. EX1001 at 14:62:67.

As further documented herein *infra*, the ’995 Patent’s dependent claims further recite nothing more than aspects of genetic analysis that had also long been well-known in the art.

C. Prosecution History Overview

During prosecution, the Applicant submitted an Information Disclosure Statement (IDS) identifying Grunenwald (US 2010/0120098 (EX1003)). EX1007.098. In the Notice of Allowance, the Examiner indicated that the IDS, which identified Grunenwald, was acknowledged and considered. EX1007.144. The Examiner, however, did not cite or discuss Grunenwald. In the Reasons for Allowance, the Examiner noted that:

[T]he art supports techniques which involves the use of insertional complex that comprises an antibody specific to a protein that is part of the chromatin, such as via chromatin immunoprecipitation[,] as a main tool for investigating transposition in epigenetic studies. See for example Park et al., Nature 10, 669-680, 2009; see entire reference especially Figure 1 (citation made of record on IDS filed 7/24/2018) and Jelinek et al (US 20160115474, effective filing date May 2013) both of which requires transpososome-antibody complex associated with chromatin for subsequent analysis.

EX1007.145. The Applicant later submitted another IDS identifying the Chinese national designation for Okino. EX1007.167. While Okino was included in the IDS, there was no indication that the Examiner evaluated Okino in any depth at all. Okino was not the basis for any substantive action by the Examiner. Adey, while cited in the specification of the '995 Patent, was also not the basis for any substantive

action by the Examiner. The Examiner did not issue any rejections during the prosecution of the '995 Patent. The '995 Patent issued on December 11, 2018.

VI. LEVEL OF ORDINARY SKILL IN THE ART OF THE '995 PATENT

A person of ordinary skill in the art ("POSA") relating to the '995 Patent would have had (1) a Masters degree and/or Ph.D. in molecular biology, genetics, chemistry, engineering, or a related discipline and at least two years of post-Masters, postdoctoral, or industry experience or (2) a Bachelor of Science in such disciplines and at least five years of academic or industry experience (including any experimental work toward a graduate degree), relating to DNA sample preparation techniques (including electroporation and permeabilization), tagmentation, amplification methods, and DNA sequencing technologies (including next generation sequencing). EX1002 ¶ 90.

As documented above, all aspects of the claims of the '995 Patent reflect techniques and competencies that would have been part of the toolkit of the ordinary skilled artisan. *See supra* Part IV. In particular, the ordinary skilled artisan in 2013 would have been familiar with and would have fully understood the following concepts and techniques:

- The format of DNA packaging in living cells.
- The dynamic nature of DNA packaging in living cells.
- Next generation sequencing techniques, and methods of preparing nucleic acid for sequencing.

- The tagmentation process, and commercially available products for carrying out tagmentation.
- Methods of permeabilizing cells for nucleic acid analysis.
- Epigenetic analysis and techniques therefore.

Id.; *see also* EX1002 ¶¶ 88-91.

VII. THE CITED PRIOR ART

A. Grunenwald

U.S. Patent Publication 2010/0120098 (“Grunenwald”), entitled “Transposon End Compositions And Methods For Modifying Nucleic Acids,” was published on May 13, 2010. EX1003.001. Grunenwald is prior art under 35 U.S.C. § 102(a).

Grunenwald discloses methods of using transposase enzymes to generate libraries of tagged DNA fragments for sequencing and analysis. *See, e.g.*, EX1003 at [0017]. According to one method, Grunenwald teaches incubating the DNA with transposase and what it calls “transposon end compositions.” *Id.* at [0162]; *see also id.* at [0093]-[0094].

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.* at [0103]. Grunenwald explains that as a result of this incubation, the

transposase enzyme can fragment the DNA while simultaneously inserting tags into the DNA fragment. *Id.* at [0093].

Grunenwald teaches that the target DNA for fragmenting and tagging may be derived from any *in vivo* or *in vitro* source, such as “one or multiple cells, tissues, organs or organisms, whether living or dead, or from any biological or environmental source (e.g., water, air, soil).” *Id.* at [0146]. According to Grunenwald, the DNA derived from these sources may be selected from a variety of types of DNA. *Id.*

Critically, Grunenwald further teaches that its methods of transposition fragmentation and tagging may be carried out *in vivo*, directly on target DNA found in a host cell, by “electroporating a synaptic complex of a transposase and a suitable transposon end composition into the host cell.” *Id.* at [157]. A POSA reading these disclosures would have understood that performing transposition fragmentation and tagging on chromosomal target DNA within a host cell would mean that Grunenwald’s methods were applicable to chromatin in the nucleus of the cell. EX1002 ¶ 98.

B. O’Geen

Using ChIP-Seq Technology to Generate High-Resolution Profiles of Histone Modifications by Henriette O’Geen, Lorigail Echipare, and Peggy J. Farnham

(“O’Geen”) was published in *Epigenetics Protocols* in 2011. EX1051.031; EX1005.003. O’Geen is prior art under 35 U.S.C. § 102(a).

O’Geen teaches a prior art method of fragmenting and tagging DNA in preparation for sequencing and using that sequence information to determine epigenetic features of the DNA, known as chromatin immunoprecipitation and sequencing (ChIP-Seq). EX1005.005.

C. Okino

PCT Application Publication No. WO 2010/065266 A1 titled “Chromatin Structure Detection” (“Okino”) was filed on November 13, 2009 and published on June 10, 2010. EX1004.001. Okino claims priority to U.S. Provisional Application No. 61/119,280. Okino is prior art under 35 U.S.C. § 102(a).

Okino is directed to the study of chromatin structure through the use of a “DNA modifying agent,” which may be any molecule that “alters DNA in a detectable matter,” such as an enzyme that breaks the DNA, or an enzyme that introduces or removes a moiety bound to the DNA. EX1004 at [0035]. Okino teaches that this is done in two steps: first, a cell is simultaneously permeabilized and contacted with a DNA modifying agent, and second, the DNA sequence information is detected. EX1004 at [0005].

D. Pitt

Ultrasonic Drug Delivery – A General Review by William G. Pitt, Ghaleb A. Hussein, and Bryant J. Staples (“Pitt”) was published in *Expert Opinion on Drug Delivery* in 2004. EX1051.040; EX1006.001. Pitt is prior art under 35 U.S.C. § 102(a).

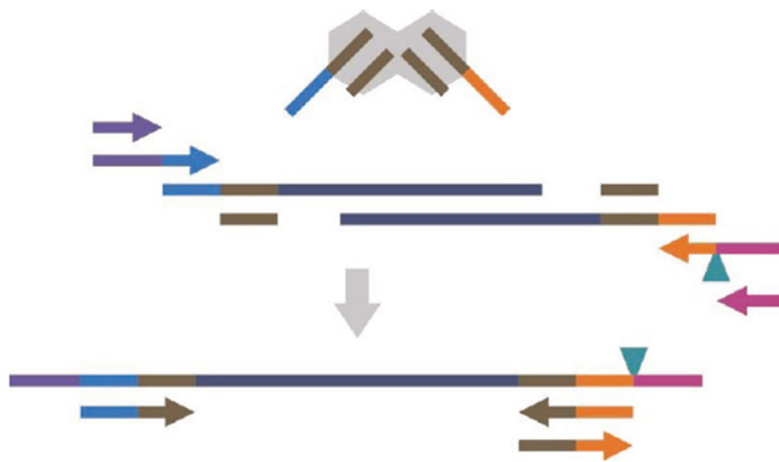
Pitt provides a review of the state of the art as early as 2004 for ultrasonic delivery of various types of molecules, including proteins. EX1006.010. Pitt notes that “proteins have very different transport and solubility characteristics in tissues, and thus their delivery is much more complex.” EX1006.010. Despite these challenges, Pitt teaches that low frequency ultrasound may be used to permeabilize cells and allow the delivery of proteins. EX1006.010. Further, Pitt specifically teaches the delivery of “thrombolytic enzymes,” proteins that are able to maintain their activity after ultrasonication is used to permeabilize a cell. EX1006.011.

E. Adey

Rapid, Low-input, Low-bias Construction of Shotgun Fragment Libraries by High-density In vitro Transposition by Andrew Adey, Hilary G Morrison, Asan, Xu Xun, Jacob O Kitzman, Emily H Turner, Bethany Stackhouse, Alexandra P MacKenzie, Nicholas C Caruccio, Xiuqing Zhang and Jay Shendure (“Adey”) was

published in Genome Biology in 2010. EX1051.036; EX1009.001. Adey is prior art under 35 U.S.C. § 102(a).

Adey describes a prior art method of tagmentation using Epicentre's Nextera™ Technology—a transposase-based process for preparing DNA libraries by simultaneously fragmenting and tagging genomic DNA. Specifically, Adey discloses using a transposase to insert distinct adapter sequences. EX1009.002. As depicted in Figure 1 (b), the transposome complex comprises the transposase enzyme (two grey hexagons), a sequence to assist the transposase to fragment DNA (brown), and two different adaptors (mild blue/orange):



EX1009.002 at Figure 1

VIII. CLAIM CONSTRUCTION

This Petition analyzes the claims using the ordinary and customary meaning in light of the specification and prosecution history. 37 C.F.R. § 42.100(b).

A. “Insertional Enzyme Complex”

The '995 Patent defines the term “insertional enzyme complex” as follows: “The term ‘insertional enzyme complex,’ as used herein, refers to a complex comprising an insertional enzyme and two adaptor molecules (the ‘transposon tags’) that are combined with polynucleotides to fragment and add adaptors to the polynucleotides.” EX1001 at 13:19-26. This definition is consistent with the plain and ordinary meaning of the term as understood by a POSA. EX1002 ¶ 124.

B. “Nucleic Acid Insert Element”

The plain and ordinary meaning of a “nucleic acid insert element” in the context of the '995 Patent is a nucleic acid for insertion in a polynucleotide by an insertional enzyme, such as transposase. EX1002 ¶ 125. This meaning is consistent with plain language of the claim term. EX1001 at claims 13, 17. Moreover, the '995 Patent specification describes that an “insert element” may comprise a nucleic acid sequence and can be part of a composition also including a polynucleotide and an insertional enzyme. *See* EX1001 at 3:59-3:67, 4:19-26, 22:24-30, 22:44-48, 22:26-67. The insert element can also be “bound to the insertional enzyme and the insertional enzyme bound to the polynucleotide.” EX1001 at 4:7-8.

C. “Adapter Sequence”

The plain and ordinary meaning of an “adapter sequence” is the sequence of an adapter, which in the ’995 Patent refers to a tag. EX1002 ¶ 126. Indeed, the ’995 Patent uses the term “adaptor” interchangeably with “tag.”

For example, when defining an “insertional enzyme complex,” the ’995 Patent states that the complex comprises “an insertional enzyme”—*e.g.*, a transposase—“and two *adaptor molecules* (the ‘transposon *tags*’).” EX1001 at 13:19-22. This description continues by explaining that the insertional enzyme complex is “combined with polynucleotides to fragment and *add adaptors* to the polynucleotides.” *Id.*

A POSA would have understood that this disclosure of the insertional enzyme complex fragmenting and adding adaptors is equivalent to the insertional enzyme complex fragmenting and tagging, as described throughout the ’995 Patent. *See, e.g.*, EX1001 at Abstract (“...treating chromatin...with an insertional enzyme complex to produce *tagged* fragments...”) (emphasis added); *id.* at 2:20-25 (“...combining the isolated nuclei with the insertional enzyme complex, wherein the combining results in...production of the *tagged* fragments of genomic DNA”) (emphasis added); *id.* at 2:45-50 (“...inserting a plurality of molecular *tags* with an insertional enzyme into the polynucleotide...”) (emphasis added); *id.* at 14:23-27 (“...treating chromatin isolated from a population of cells with an insertional

enzyme complex to produced *tagged* fragments of genomic DNA”) (emphasis added); EX1002 ¶ 126.

Moreover, the use of the term “adaptor” in the ’995 Patent specification is consistent with it being a tag. For example, the ’995 Patent explains one process by using tagging and adding adaptors interchangeably: “chromatin is tagmented (*i.e.*, cleaved and *tagged* in the same reaction) using an insertional enzyme such as Tn5 or MuA that cleaves the genomic DNA in open regions in the chromatin and *adds adaptors* to both ends of the fragments.” EX1001 at 14:27-31. The ’995 Patent only uses the term “adaptor” to refer to an element tagged to a polynucleotide.

Although the ’995 Patent also refers to a “sequencing adaptor,” this is just one type of tag or adaptor. See EX1001 at 16:26-30 (“The molecular tags can comprise sequencing adaptors....”).

D. “Barcode Sequence”

The ’995 Patent defines the term “barcode sequence” as follows:

The term “barcode sequence” or “molecular barcode,” as used herein, refers to a unique sequence of nucleotides used to a) identify and/or track the source of a polynucleotide in a reaction and/or b) count how many times an initial molecule is sequenced (e.g., in cases where substantially every molecule in a sample is tagged with a different sequence, and then the sample is amplified).

EX1001 at 12:26-32. This definition is consistent with the plain and ordinary meaning of the term as understood by a POSA. EX1002 ¶ 127.

IX. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground 1: Claims 1, 3, 5-6, and 10-23 Are Unpatentable Under 35 U.S.C. § 102 As Anticipated By Grunenwald

1. Claim 1:

a. [1A] A method for analyzing a biological sample, comprising:

To the extent the preamble is limiting, Grunenwald discloses this claim limitation.

Grunenwald discloses methods for analyzing a biological sample—specifically, by analyzing its DNA. Grunenwald discloses methods of tagging and fragmenting DNA “for use in a variety of processes, including processes for metagenomics analysis of DNA in environmental samples, copy number variation (CNV) analysis of DNA, and comparative genomic sequencing (CGS), including massively parallel DNA sequencing (so-called ‘next generation sequencing[’]).” EX1003 at Abstract; *see also id.* at [0159], [0208] (“the tagged DNA fragments are used as templates for DNA sequencing”).

Grunenwald also explains that in “some embodiments, the method further comprises the step of amplifying and/or sequencing the library of the tagged circular ssDNA fragments,” and in “some embodiments, the method further comprises the

step of sequencing DNA that is complementary to the target DNA obtained by amplification of the tagged circular ssDNA fragments or the di-tagged linear ssDNA fragments.” *Id.* at [0312].

Grunenwald further teaches a variety of biological samples for analysis from which the DNA is derived. Specifically, Grunenwald teaches that the DNA may be derived from any *in vivo* or *in vitro* source, such as “one or multiple cells, tissues, organs or organisms, whether living or dead, or from any biological or environmental source. *Id.* at [0146]

b. [1B] contacting chromatin of a genome region of said biological sample with an insertional enzyme complex to produce tagged nucleic acid molecules

Grunenwald teaches this claim element.

First, Grunenwald discloses an “insertional enzyme complex.” As explained in Section VIII.A, *supra*, the ’995 Patent defines the “insertional enzyme complex” as “a complex comprising an insertional enzyme and two adaptor molecules (the ‘transposon tags’) that are combined with polynucleotides to fragment and add adaptors to the polynucleotides.” EX1001 at 13:19-26. The ’995 Patent further states that this “insertional enzyme can be transposase.” *Id.* at 3:41-42. Thus, “insertional enzyme complex” encompasses a complex comprising transposase and two transposon tags that are combined with polynucleotides to fragment and tag the polynucleotides. *See* EX1002 ¶ 142.

Grunenwald discloses this complex, which has a transposase and two transposon tags: “a single *transposome composition* comprising a stable complex formed between the transposase and the transposon end composition.” EX1003 at [0161] (emphasis added) (further explaining that “it will be understood that any method that describes the use of a transposase and a transposon end composition could also use a transposome composition”).

Grunenwald explains that a “transposon end composition” may comprise multiple tags:

A “transposon end composition” means a composition comprising a transposon end (*i.e.*, the minimum double-stranded DNA segment that is capable of acting with a transposase to undergo a transposition reaction), optionally plus additional sequence *or sequences*[] 5’-of the transferred transposon end sequence and/or 3’-of the non-transferred transposon end sequence. For example, a transposon end attached to a tag is a “transposon end composition.”

EX1003 at [0098]. According to this passage, Grunenwald’s transposon end composition may have a “sequence or sequences,” which are tags for the 5’ end of the transferred polynucleotide strand and the 3’ of the non-transferred polynucleotide strand. EX1002 ¶ 143; *see also* EX1003 at [0102] (explaining that the transposon end composition may include a “transposon end sequence” plus a “tag [that] can have one or more other tag portions or tag domains.”).

In addition, Grunenwald discloses that each tag of a transposon end composition “can have one or more other tag portions or tag domains,” which a POSA would have understood also teaches the tags of the ’995 Patent’s insertional enzyme complex. EX1003 at [0102]; *see also id.* at [0103] (defining “tag portion” and “tag domain” as “a portion or domain of a tag that exhibits a sequence for a desired intended purpose or application.”); EX1002 ¶ 143. These tag domains can include, for example, “one or more of 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” EX1003 at [0103]. Further, Grunenwald teaches that “one tag domain can comprise two or more other tag domains....” *Id.* at [0115]. Thus, Grunenwald discloses a transposome complex comprising a transposase and at least two tags.

As Grunenwald explains, this complex comprising a transposase and at least two tags is combined with polynucleotides to fragment and add adaptors to the polynucleotides. For example, Grunenwald discloses that one embodiment of the invention is a “method for generating a library of tagged DNA fragments,” with the method comprising in part “incubating the target DNA in an in vitro transposition reaction with at least one transposase and transposon end composition with which the transposase forms a transposition complex. . . under conditions and for sufficient time wherein multiple insertions into the target DNA occur, each of which results in

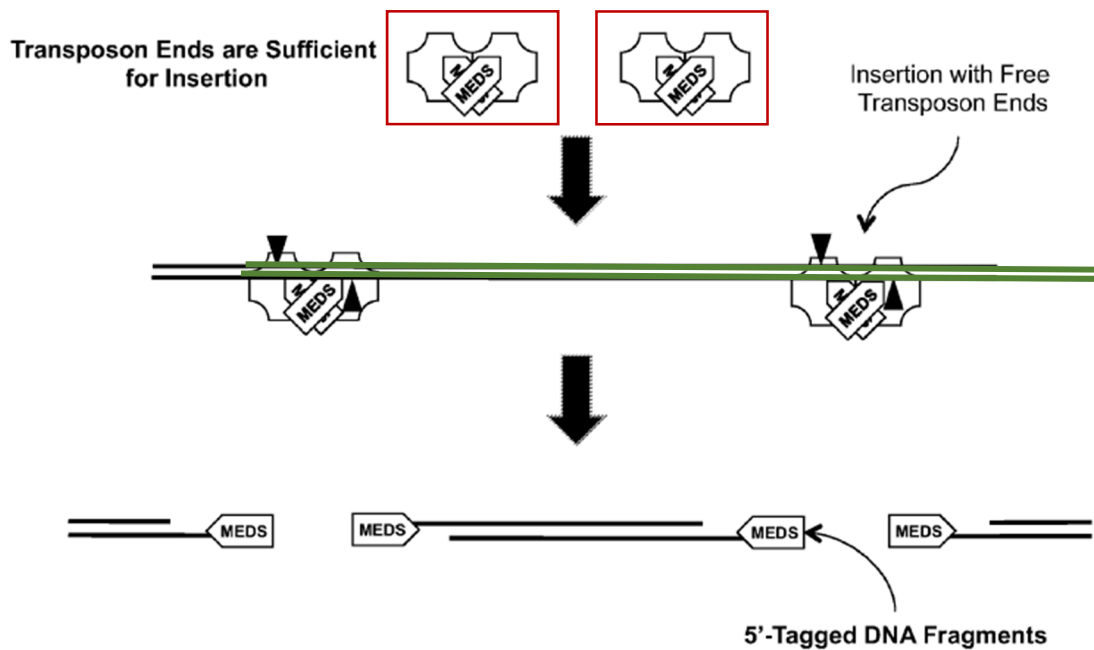
joining of a first tag comprising or consisting of the transferred strand to the 5' end of a nucleotide in the target DNA, thereby fragmenting the target DNA and generating a population of annealed 5'-tagged DNA fragments.” EX1003 at [0161].

Grunenwald therefore discloses the claimed “insertional enzyme complex” (*e.g.*, the transposome) that comprises a transposase and at least two adaptors (*e.g.*, tags, tag portions, or tag domains) that combine with polynucleotides (*e.g.*, target DNA) to fragment and tag it.

Second, Grunenwald discloses that the insertional enzyme complex contacts nucleic acid “to produce tagged nucleic acid molecules.” The explanation of how the insertional enzyme complex fragments and tags polynucleotides is noted above, but it is also described throughout Grunenwald’s disclosure. *See, e.g.*, EX1003 at [0017] (summarizing portions of the invention).

For example, Figure 2 of Grunenwald, reproduced below, showcases the disclosure of this limitation. *See* EX1003 at [0060]. In this figure, the two parallel lines highlighted in green represent the target DNA and the transposomes (which are the claimed insertional enzyme complex) are boxed in red. This schematic demonstrates the insertional enzyme complex contacting the target DNA, and simultaneously fragmenting and tagging it, resulting in 5'-tagged DNA fragments. *See* EX1002 ¶ 154.

FIG. 2 Fragmenting by In Vitro Transposition



EX1003 at Figure 2

Third, Grunenwald teaches that the nucleic acid contacted with the insertional enzyme complex is “chromatin of a genome region of said biological sample.” 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). A POSA 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. EX1002 ¶ 146.

To the extent Grunenwald is deemed to not explicitly disclose contacting chromatin, this limitation inherently disclosed. A prior art reference “may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Here, 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. See EX1003 at [1046], [0157].

This *in vivo* embodiment is accomplished by electroporating the cell to allow the transposome to enter the cell:

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).

EX1003 at [0157]. Because chromosomal DNA in a cell is necessarily packaged in the form of chromatin, and genomic DNA is necessarily part of the chromatin, Grunenwald inherently discloses performing its method of contacting chromatin of a genome region of a biological sample with the insertional enzyme complex to produce tagged nucleic acid molecules. See EX1002 ¶ 147-149.

Indeed, Patent Owner has argued in parallel litigation that the allegedly novel aspect of the '995 Patent is to simply apply "tagmentation" "on a cell," or to introduce the relevant enzymes "into a cell nucleus to perform tagmentation inside the cell to interrogate open areas of chromatin." EX1020 at 19; EX1024 at 106:6-14. In other words, the alleged invention is achieved simply by taking measures to introduce the enzymes for tagmentation into a cell. As documented above, this is *exactly* what Grunenwald teaches.

Importantly, the '995 Patent does not disclose any special measures that must be taken to practice the alleged invention other than the use of standard techniques to introduce enzymes into the cell. And, far from providing any nuance on this issue, the '995 Patent simply discloses an open-ended laundry list of permeabilization techniques (including "hypotonic shock and/or ultrasonication") without any special guidance on how they ought to be employed. *See, e.g.*, EX1001 at 3:19-23, 16:48-58. In fact, the '995 Patent teaches that permeabilization is only required in "some cases." *Id.* at 16:48-58. The working example in the '995 Patent does not even bother to describe specifically how permeabilization was achieved. *See id.* at 33:12-54.

Beyond the use of well-known permeabilization techniques, the '995 Patent not once suggests that any steps need to be taken to practice tagmentation on chromatin. Thus, the overriding message that is acknowledged in the '995 Patent

itself is that so long as one can introduce the tagmentation enzymes into a cell (using standard techniques), the invention will necessarily and inherently work. As inventor Jason Buenrostro stated in his tweet, the alleged invention is “so easy that anyone can do it!” EX1029.

Thus, Grunenwald discloses this limitation. In particular, Grunenwald discloses the use of standard electroporation to introduce the enzymes for a tagmentation into a cell, which will necessarily and inherently lead to contacting chromatin of a genome region of with an insertional enzyme complex to produce tagged nucleic acid molecules. The '995 Patent does not specify any novel or inventive steps needed to apply the method of tagmentation on chromatin. In fact, it actually points out that “methods for tagmenting isolated genomic DNA are known in the art” and that those systems “may be readily adapted for use” in the invention, contemplating that if one can introduce the insertional enzyme complex into the cell, the invention will necessarily work. EX1001 at 14:31-38. It is this ease of use that led one of the inventors to tweet that the method is “so easy anybody can do it!” EX1029.

- c. **[1C] wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part said chromatin; and**

Grunenwald discloses this claim element.

To disclose a negative limitation, a prior art reference need not specify the negative limitation in the disclosure; rather, if a prior art reference does not require the use of a limitation, it is sufficient to disclose a negative limitation. *See, e.g. WAG Acquisition, LLC. V. WebPower, Inc.*, 781 Fed. Appx. 1007, 1013 (Fed. Cir. 2019) (“While [the prior art reference] does not specify that a pointer is *not* used, nothing in the record suggests that a pointer *must* be used.”).

Nothing in Grunenwald suggests that an antibody specific to a protein that is part of the chromatin must be used. On the contrary, Grunenwald discloses multiple embodiments that do not use an antibody specific to a protein that is part of the chromatin. For example, Grunenwald discloses:

incubating the target DNA with a transposase and transposon end or transposon end composition comprising a transferred strand that has a tag domain in its 5' portion, under conditions in which a transposition reaction is catalyzed by the transposase, and wherein the target DNA is fragmented to generate a plurality of target DNA fragments and a transferred strand of the transposon end or transposon end composition is joined to 5' ends of each of a plurality of the target DNA fragment, to produce a plurality of 5' tagged target DNA fragments.

EX1003 at [0018]. At no point does Grunenwald state that an antibody specific to a protein that is part of said chromatin is required to carry out the method disclosed

in the embodiment. This is true for subsequent embodiments disclosed by Grunenwald. *See, e.g.*, EX1003 at [0019]–[0057].

As confirmation that the embodiments in Grunenwald do not involve an antibody specific to a protein that is part of the chromatin, consider the references to an antibody that are included in Grunenwald. Although Grunenwald references the term “antibody” seven times throughout the specification, these disclosures do not describe an antibody that is part of an insertional enzyme complex or that is specific to a protein in the target DNA. EX1003 at [0109], [0117], [0212], [0216], [0217], [0229]. As explained in the accompanying declaration of Dr. Cooper, the disclosures of the use of an antibody are for various purposes such as capture of a tagged DNA molecule and assisting in isolation and purification of tagged DNA, not antibodies specific to a protein that is part of the chromatin. EX1002 ¶¶ 150-169.

Because Grunenwald discloses methods for contacting chromatin with an insertional enzyme complex that does not require the use of an antibody specific to a protein that is part of the chromatin, Grunenwald discloses this claim limitation.

- d. [1D] 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.**

Grunenwald discloses this claim element.

Grunenwald discloses using tagged DNA fragments as “templates in a DNA sequencing or an amplification reaction,” and that in embodiments wherein tagged

circular single-strand DNA (ssDNA) fragments are generated, the “step of amplifying and/or sequencing the library of tagged circular ssDNA fragments.” EX1003 at [0037], [0312]. Sequencing is a type of nucleic acid assay, and is used to determine the sequence information of the tagged nucleic acid molecules. EX1002 ¶¶ 170-171.

Further, Grunenwald discloses the addition of nucleic acid tags needed to carry out DNA sequencing, including “Roche 454A and 454B sequencing tags, ILLUMINA™ SOLEXA™ sequencing tags, Applied Biosystems’ SOLID™ sequencing tags, the Pacific Biosciences’ SMRT™ sequencing tags, Pollonator Polony sequencing tags, or the Complete Genomics sequencing tags.” EX1003 at [0021]. These sequences are added through the tagging process described above in Section IX.A.1.b, and the addition would be for the purpose of performing an assay to determine the sequence information of the tagged DNA. EX1002 ¶ 172.

2. Claim 3: The method of claim 1, wherein said biological sample is a cell or a nucleus.

Disclosed. *See supra* Section IX.A.1.a.

3. Claim 5: The method of claim 3, further comprising permeabilizing said cell or said nucleus to permit said insertional enzyme complex to access said chromatin.

Grunenwald discloses claim 5.

Grunenwald discloses permeabilizing said cell or said nucleus to permit said insertional enzyme complex to access said chromatin. Grunenwald discloses that

when the transposition reaction is carried out *in vivo*, the insertional enzyme complex (e.g., the transposome comprising the transposase with tags) can be placed into the cell by electroporation. EX1003 at [0157]. Electroporation is a technique well known in the art to permeabilize and allow molecules to pass a cell membrane. EX1002 ¶¶ 83, 177-178. Thus, Grunenwald's disclosure of tagging and fragmenting DNA with an insertional enzyme complex *in vivo* via electroporation teaches permeabilizing said cell or said nucleus to permit the insertional enzyme complex to enter the cell or nucleus and access the DNA, which in a host cell is organized as chromatin. EX1002 ¶¶ 177-178.

4. Claim 6: The method of claim 5, wherein said permeabilizing is configured to minimally perturb said chromatin of said cell or said nucleus.

Grunenwald discloses claim 6.

Grunenwald teaches that permeabilizing is configured to minimally perturb said chromatin of said cell or said nucleus. As noted above, Grunenwald discloses electroporation as a method of permeabilization. *See* Section IX.A.1.c, *supra*. Electroporation is a method of permeabilization well-known and used commonly in the art. EX1002 ¶ 180. It would have been known to a POSA that electroporation minimally perturbs the chromatin of the cell or nucleus. *Id.*

Indeed, the particular method of electroporation disclosed in Grunenwald is drawn from another prior art reference. EX1003 at [0157] (incorporating by

reference the electroporation protocol found in U.S. Patent No. 6,159,736); *see also* EX1045 at 7:14-17 (incorporating by reference an electroporation protocol found in Dauer et al.). The taught method of electroporation is configured to minimally perturb the chromatin of the nucleus by only altering the permeability of the cell membrane to allow a transposase and the associated payload to enter the cell without causing any damage to the chromatin within. EX1002 ¶¶ 181-188.

Further, Grunenwald describes an embodiment in which the transposition reaction is carried out *in vivo*. EX1003 at [0157]. In such an embodiment, the method of permeabilization, e.g., electroporation, must be configured to minimally perturb the chromatin because the cell and chromatin in the cell must remain intact for the method to function. EX1002 ¶ 180.

5. Claim 10: The method of claim 1, wherein said insertional enzyme comprises a transposase.

Disclosed. *See* Section IX.A.1.b, *supra*.

6. Claim 11: The method of claim 10, wherein said transposase is a Tn5 transposase or derived from a Tn5 transposase.

Grunenwald teaches that its *in vivo* electroporation transposition method (*see* Section IX.A.1.b, *supra*) is “exemplified by employing a transposition complex formed *by a hyperactive Tn5 transposase* and a suitable Tn5-type transposon end composition.” EX1003 at [0157]; EX1002 ¶ 195.

7. **Claim 12: The method of claim 11, wherein said transposase is a hyperactive Tn5 transposase.**

Disclosed. *See supra* Section IX.A.4.

8. **Claim 13: The method of claim 1, wherein said insertional enzyme complex comprises a first nucleic acid insert element comprising a first adapter sequence.**

Grunenwald discloses claim 13.

First, Grunenwald discloses an insertional enzyme complex that comprises a nucleic acid insert element. As explained above in Section IX.A.1.b, Grunenwald discloses a transposome (*i.e.*, an insertional enzyme complex) comprising a transposase (*i.e.*, an insertional enzyme) and a transposon end composition comprising multiple tags. *See* EX1003 at [0098], [0102], [0161], Figs. 1-2. These tags are nucleic acid insert elements because they are nucleic acids for insertion in a polynucleotide by an insertional enzyme—*i.e.*, transposase. EX1002 ¶¶ 199-204.

Second, Grunenwald discloses a nucleic acid insert element “comprising a first adapter sequence.” Specifically, Grunenwald discloses a transposome comprising tags, which comprise a sequence. *See* Section IX.A.1.b, EX1003 at [0098], [0102], [0161], Figs. 1-2. Therefore, Grunenwald discloses a tag that is a nucleic acid insert element comprising an adapter, or tag, sequence. EX1002 ¶¶ 205-207.

9. Claim 14: The method of claim 13, wherein said first adapter sequence comprises a first sequencing adapter sequence.

Grunenwald discloses claim 14.

As discussed in Section IX.A.1.b above, Grunenwald discloses that tags (*i.e.*, the claimed adapter sequence) may comprise one or more portions, or domains, “that exhibit[] a sequence for a desired intended purpose or application.” *See* EX1003 at [0103]. Grunenwald further teaches that one type of tag domain for use with its disclosed methods is “a sequencing tag domain.” EX1003 at [0103], [0110].

Further, Grunenwald teaches that the sequencing tag domain may comprise “Roche 454A and 454B sequencing tags, ILLUMINA™ SOLEXA™ sequencing tags, Applied Biosystems’ SOLID™ sequencing tags, the Pacific Biosciences’ SMRT™ sequencing tags, Pollonator Polony sequencing tags, or the Complete Genomics sequencing tags.” *Id.* at [0021], [0194], Claims 7, 13, 15, 21. This domain, being a short sequence of DNA to facilitate sequencing of the fragmented and tagged DNA, is the sequencing adapter sequence. EX1002 ¶ 210.

10. Claim 15: The method of claim 13, wherein said first adapter sequence comprises a barcode sequence.

Grunenwald discloses claim 15.

Grunenwald discloses an adapter sequence comprising a barcode sequence. Specifically, Grunenwald discloses that the tag inserted with a transposase may comprise an “address tag domain.” EX1003 at [0103]. An address tag domain

“exhibits a sequence that permits identification of a specific sample,” which a POSA would have understood to be the claimed barcode sequence. *Id. at* [0113]; EX1002 ¶ 212; *compare* EX1001 at 12:26-32 (stating that the “barcode sequence” is “used to ...identify and/or track the source of a polynucleotide in a reaction...”).

11. Claim 16: The method of claim 13, wherein said first adapter sequence comprises a first primer sequence.

Grunenwald discloses claim 16.

Specifically, Grunenwald discloses a tag comprising an amplification tag domain. EX1003 at [0103]. In Grunenwald, an amplification tag domain is a “tag domain that exhibits a sequence for the purpose of facilitating amplification of a nucleic acid to which said tag is appended.” EX1003 at [0111]. For example, the amplification tag domain “provides a priming site for a nucleic acid amplification reaction using a DNA polymerase.” EX1003 at [0111]. The priming site on the tag domain is the claimed primer sequence. EX1002 ¶ 218.

12. Claim 17: The method of claim 13, wherein said insertional enzyme complex further comprises a second nucleic acid insert element comprising a second adapter sequence.

Grunenwald discloses claim 17.

Grunenwald discloses an insertional enzyme complex that comprises a second nucleic acid insert element comprising a second adapter sequence. For example, Grunenwald teaches that a transposon end composition may comprise, in addition to the transposon end, an “additional sequence *or sequences* 5’-of the transferred

transposon end sequence and/or 3' of the non-transferred transposon end sequence.” EX1003 at [0098]. Moreover, Grunenwald discloses an insertional enzyme complex comprising at least two tags. *See* EX1003 at [0102], [0161], Figs. 1-2. For example, in one working example Grunenwald teaches that “‘A-MEDS Transposomes’ and ‘B-MEDS Transposomes’ were formed by pre-incubating 12.5 μ M TSase with 12.5 μ M A-MEDS or 12.5 μ M B-MEDS transposon end compositions, respectively, for 60 minutes at 37°C.” EX1003 at [0425]. The second tag is a second nucleic acid insert element comprising a second adapter sequence for the same reasons that the first tag satisfies this limitation. *See supra* Section IX.A.8.

Alternatively, in embodiments where the tag comprises multiple tag domains (*i.e.*, a sequencing tag domain and an amplification tag domain), each tag domain would be a separate nucleic acid insert element. Further, the tag domain, being a short sequence of DNA added for a desired intended purpose, is an adapter sequence. EX1002 ¶ 221; *see supra* Section IX.A.8. Grunenwald discloses that the tag domain sequences “can be used to accomplish any desired purposes.” EX1003 at [0331]. In these embodiments, where “one or more tag domain sequences” are the additional sequences being used to accomplish a desired purpose, a second tag domain sequence (*e.g.*, a second nucleic insert element) acts as a second adapter sequence. EX1003 at [0331]; EX1002 ¶ 222.

13. Claim 18: The method of claim 17, wherein said second adapter sequence comprises a second sequencing adapter sequence.

Grunenwald discloses claim 18.

As discussed above in Section IX.A.12, Grunenwald discloses a second adapter sequence. Moreover, for the same reasons that Grunenwald discloses that the first adapter sequence comprises a first sequencing adapter sequence, Grunenwald discloses that the second adapter sequence comprises a second sequencing adapter sequence. *See supra* Section X.A.9.

14. Claim 19: The method of claim 17, wherein said second adapter sequence comprises a barcode sequence.

Grunenwald discloses claim 19.

As discussed above in Section IX.A.12, Grunenwald discloses a second adapter sequence. Moreover, for the same reasons that Grunenwald discloses that the first adapter sequence comprises a barcode sequence, Grunenwald discloses that the second adapter sequence comprises a barcode sequence. *See supra* Section X.A.10.

15. Claim 20: The method of claim 17, wherein said second adapter sequence comprises a second primer sequence.

Grunenwald discloses claim 20.

As discussed above in Section IX.A.12, Grunenwald discloses a second adapter sequence. Moreover, for the same reasons that Grunenwald discloses that

the first adapter sequence comprises a first primer sequence, Grunenwald discloses that the second adapter sequence comprises a second primer sequence. *See* Section *supra* IX.A.11.

16. Claim 21: The method of claim 1, further comprising subjecting said tagged nucleic acid molecules to one or more reactions.

Grunenwald discloses claim 21.

First, as explained above in Section IX.A.1.b, Grunenwald discloses tagged nucleic acid molecules.

Second, Grunenwald discloses subjecting tagged nucleic acid molecules to one or more reactions, including, for example, a PCR reaction, which is an amplification reaction. *See* EX1003 at [0022], [0123]; *see also* EX1002 ¶ 231.

17. Claim 22: The method of claim 21, wherein said one or more reactions comprise a nucleic acid amplification reaction.

Disclosed. *See supra* Section IX.A.16.

18. Claim 23: The method of claim 22, wherein said nucleic acid amplification reaction is configured to add one or more functional sequences to said tagged nucleic acid molecules or derivatives thereof, wherein said one or more functional sequences are compatible with a selected next generation sequencing platform.

Grunenwald discloses claim 23.

First, Grunenwald discloses “tagged nucleic acid molecules.” *See supra* Section IX.A.1.b.

Second, Grunenwald discloses a “nucleic acid amplification reaction,” including one using a DNA polymerase to generate a strand based on a template strand. *See supra* Section IX.A.16; EX1003 at [0123]; *see also* EX1002 ¶¶ 233-235.

Third, Grunenwald discloses that the “nucleic acid amplification reaction is configured to add one or more functional sequences to said tagged nucleic acid molecules or derivatives thereof.” For example, Grunenwald discloses that in some embodiments, the method of generating a library of tagged DNA fragments further comprises “amplifying the library of tagged DNA fragments comprising di-tagged DNA fragments, tagged circular ssDNA fragments, or fantail DNA fragments.” EX1003 at [0198]. In some of these embodiments, the “5’ portion of the first PCR primer or the 5’ portion of the second PCR primer” may comprise or consist of “first or second sequencing tags, respectively, for generation of templates for next-generation sequencing for a particular sequencing platform.” EX1003 at [0201]; EX1002 ¶ 236.

Fourth, Grunenwald discloses that the “one or more functional sequences are compatible with a selected next generation sequencing platform.” For example, Grunenwald teaches that exemplary sequencing tag domains may comprise “Roche 454A and 454B sequencing tags, ILLUMINA™ SOLEXA™ sequencing tags, Applied Biosystems’ SOLID™ sequencing tags, the Pacific Biosciences’ SMRT™

sequencing tags, Pollonator Polony sequencing tags, or the Complete Genomics sequencing tags.” EX1003 at [0021]. When one of the aforementioned sequencing tag domains is added to a fragmented and tagged sample of DNA, it renders that sample compatible with one of the next generation sequencing platforms. EX1002 ¶ 236.

B. Ground 2: Claim 2 Is Unpatentable Under 35 U.S.C. § 103 Over O’Geen in View Of Grunenwald

1. Claim 2: The method of claim 1, further comprising generating a representation of epigenetic features of said genome region at least in part by mapping said sequence information to said genome region.

a. The Combination of O’Geen and Grunenwald Teaches This Limitation

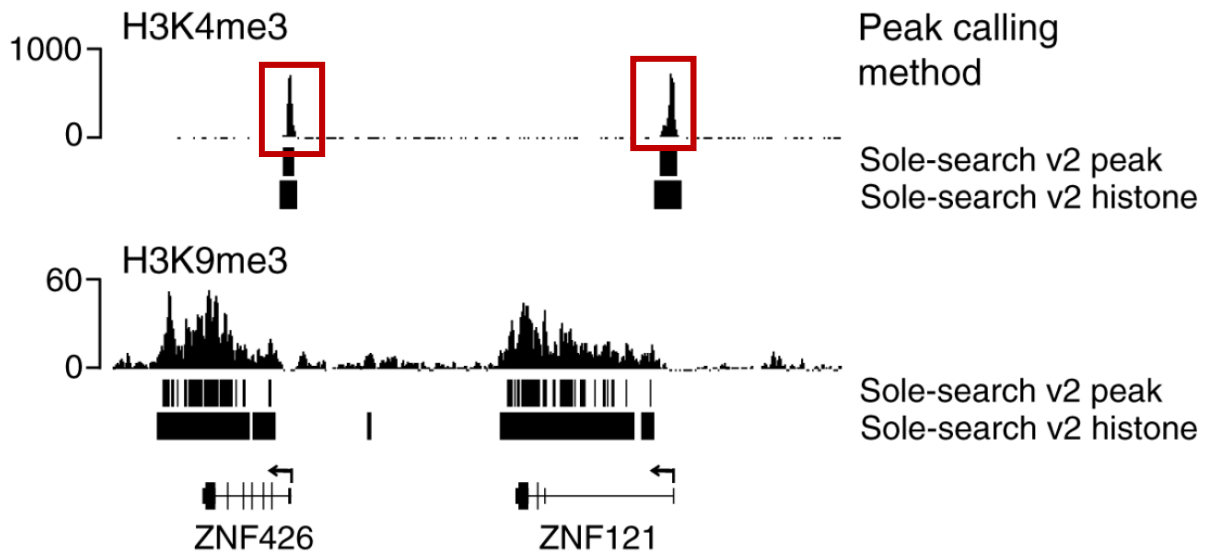
The combination of O’Geen and Grunenwald discloses and renders obvious claim 2.

First, as explained in Section IX.A.1, *supra*, Grunenwald discloses each and every limitation of claim 1.

Second, O’Geen discloses “generating a representation of epigenetic features of said genome region at least in part by mapping said sequence information to said genome region.” O’Geen teaches that “technologies allow the genome-wide visualization of the information encoded in the epigenome,” including, for example, “the chromatin immunoprecipitation (ChIP) assay,” which “allows investigators to characterize DNA-protein interactions in vivo.” EX1005.004. O’Geen

“describe[]s in detail the steps involved in performing ChIP assays,” including steps for fragmenting and tagging section of chromatin, sequencing, and mapping tags to the human genome to identify epigenetic features of the genome. EX1005.009, .014, .024, Fig. 1 (depicting the steps of a ChIP-seq assay).

More specifically, O’Geen teaches that “short tags (~25-50 nts) are mapped to the human genome, the tags that map uniquely to only one location in the genome are selected, these unique tags are extended to the average size of the library fragments (~200 nt), and then the extended fragments are grouped into consecutive bins running the length of each chromosome.” EX1005.19. O’Geen explains that “peak calling methods” can then be used to identify epigenetic features such as target sites and binding patterns. EX1005.19. For example, O’Geen explains that one of the disclosed peak calling methods “correctly identifies sharp peaks for H3K4me3, and also calls broad regions occupied by H3K9me3,” which is depicted in Figure 3:



EX1005.019 at Figure 3 (red highlighting added)

O’Geen further explains that “mono- or trimethylation of lysine 4 on histone H3 (H3K4me1 or **H3K4me3**)...are associated with open chromatin” and that H3K4me3 “mark[s] gene promoter regions....” EX1005.004-005. Thus, O’Geen discloses “generating a representation of epigenetic features of said genome region” (*e.g.*, O’Geen’s Figure 3 that identifies peaks for H3K4me3) “at least in part by mapping said sequence information to said genome region” (*e.g.*, O’Geen’s disclosure that “short tags (~25-50 nts) are mapped to the human genome”).

Thus, the combination of Grunenwald and O’Geen discloses each and every limitation of claim 2.

b. It Would Have Been Obvious to a POSA to Combine O’Geen’s and Grunenwald’s Teachings

It would have been obvious to combine O’Geen’s methods of determining epigenetic features of a genome by mapping sequence reads to the genome with Grunenwald’s methods of fragmenting and tagging chromatin.

First, O’Geen and Grunenwald are analogous art. Both references are in the field of genetics and molecular biology, and particularly concern methods of DNA tagging and fragmenting for sequencing and analysis. EX1002 ¶¶ 251-252. Further, both references cover the preparation of chromatin for analysis. *See, e.g.*, EX1003 at Abstract; [0146]; [0157]; EX1005.004.

Second, a POSA would have combined O’Geen with Grunenwald, because O’Geen identifies problems of the ChIP-seq method to which Grunenwald teaches the solution. O’Geen discloses that the “biggest limitations to histone ChIP assays are the specificity of the antibody and the variability between different lot numbers of the same antibody.” EX1005.23. This resulted in a very small number of validated assays for ChIP-seq, and limited its usefulness as a tool to investigate epigenetic features of chromatin. *Id.*; EX1002 ¶ 253. A POSA would have been aware of these limitations and sought to overcome them. EX1002 ¶ 253.

Grunenwald teaches a solution to this problem. Rather than using immunoprecipitation and sonication as taught by O’Geen to fragment and tag chromatin, Grunenwald uses the method of tagmentation described above. *See*

supra Section VII.A. A POSA would have understood that unlike immunoprecipitation, tagmentation as taught by Grunenwald does not face the same issues caused by antibody specific and variability between different lot numbers of the same antibody. EX1002 ¶ 255.

Notably, during prosecution of the '995 Patent, the Examiner found that the point of novelty for the '995 Patent claims was its use of tagmentation over chromatin immunoprecipitation, but as Grunenwald shows, this idea was not new. EX1007.145. A POSA would have recognized the advantages of Grunenwald's method of tagging and fragmenting and would have had a reason to modify O'Geen's method of epigenetic analysis with these teachings.

Third, a POSA would have had a reasonable expectation of success in combining the references. Both the ChIP-seq method taught by O'Geen and the tagmentation method taught by Grunenwald ultimately result in sequencing fragmented DNA samples. EX1002 ¶ 256; *see, e.g.*, EX1005.17-18, EX1003 at [0312]. As was taught in O'Geen, the use of sequencing data to generate a map of the epigenetic features of the DNA was well-known in the art. *See, e.g.*, EX1005.005-006. Therefore, a POSA seeking to generate such a map through sequencing would have a reasonable expectation of success applying Grunenwald's preparation methods to build a sequencing library that could be used as taught in O'Geen.

Thus, the combination of Grunenwald and O’Geen teach and render obvious the method of claim 2.

C. Ground 3: Claims 4 and 6-8 Are Unpatentable Under 35 U.S.C. § 103 Over Grunenwald in View Of Okino

1. Claim 4: The method of claim 3, further comprising lysing said cell or nucleus.

a. The Combination of Grunenwald and Okino Teaches This Limitation

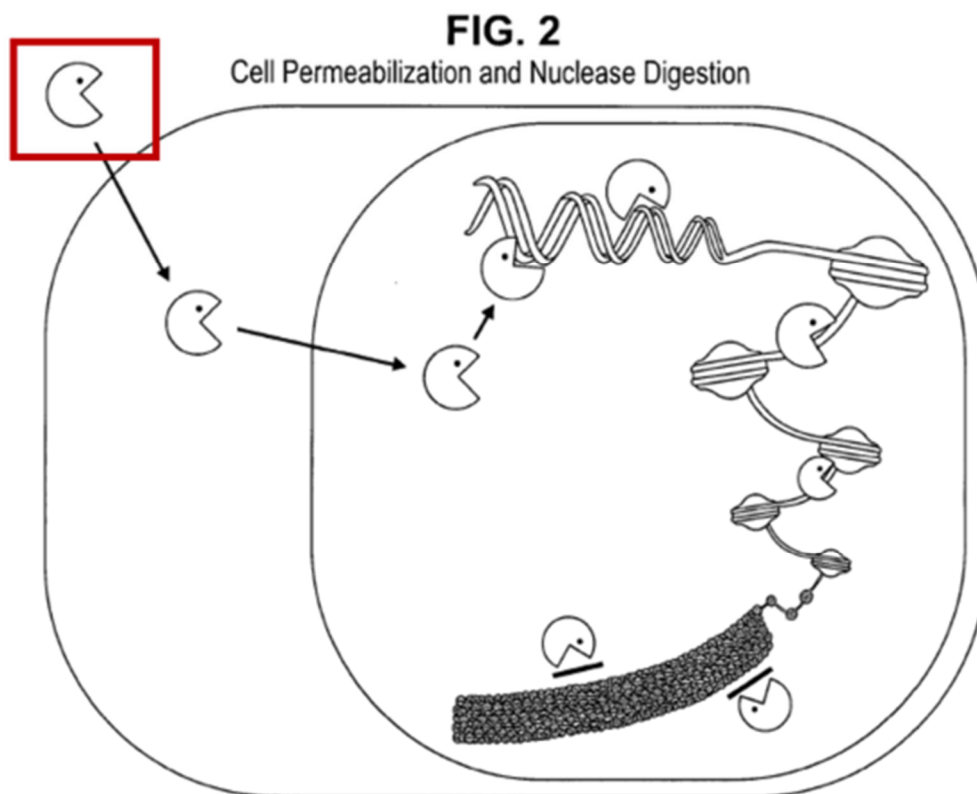
The combination of Grunenwald and Okino discloses and renders obvious claim 4.

First, as explained in Section IX.A.2, *supra*, Grunenwald discloses each and every limitation of claim 3.

Second, Okino discloses “further comprising lysing said cell or nucleus.” Okino teaches a method of in vivo modification of chromatin to study its structure. EX1004 at [0064]. This is accomplished in two steps. Initially, the cell is permeabilized and simultaneously contacted with a “DNA modifying agent,” which may be a protein or other molecule. EX1004 at [0005], [0065]. A physical characteristic, based on the modification, is then detected through a method such as sequencing. EX1004 at [0005].

Figure 2 of Okino, reproduced below, demonstrates the contacting and modifying step. In this figure, an example of a DNA modifying agent such as a restriction enzyme is highlighted in red. The DNA modifying agent is able to enter

the cell and nucleus to access the chromatin being studied; certain areas of chromatin are more accessible than others, with inaccessible areas indicated by a black bar. The accessible areas are modified.



EX1004 at Fig. 2 (annotated with a red box).

Okino teaches that after the modification step the modified DNA can be isolated. In teaching isolation, Okino discloses that “standard cell lysis reagents can be used to lyse cells.” EX1004 at [0105]. The DNA extracted and isolated from a lysed cell is then subject to an assay to detect a physical characteristic, such as sequencing to determine sequence. EX1004 at [0109].

Thus, the combination of Grunenwald and Okino discloses each and every limitation of claim 4.

b. It Would Have Been Obvious to a POSA to Combine Grunenwald's and Okino's Teachings

It would have been obvious to combine Grunenwald's methods of fragmenting and tagging chromatin with Okino's cell lysis step.

First, Grunenwald and O'Geen are analogous art. Both references are in the field of genetics and molecular biology. EX1002 ¶¶ 93, 100. Further, both references cover the study of chromatin through DNA modification and subsequent sequencing. *See, e.g.*, EX1003 at Abstract; EX1004 at [0005].

Second, a POSA interested in studying the DNA that is tagmented in Grunenwald's *in vivo* embodiment would be aware of the need to extract and isolate that DNA prior to sequencing. EX1002 ¶ 268. Lysing the cell for these purposes was one well-known, routine and commonly-used method. EX1002 ¶ 269.

Third, a POSA would have had a reasonable expectation of success in combining the references. Grunenwald teaches a method for the modification of chromatin through tagmentation, analogous to the methods of chromatin modification taught in Okino. *See supra* Sections IV.C, VII.C; *see also* EX1002 ¶ 266. A POSA performing Grunenwald's *in vivo* tagmentation method, combined with the cell lysis step taught in Okino, would likely be successful in extracting and isolating the DNA in preparation for sequencing.

Therefore, the combination of Grunenwald and Okino teach and render obvious the method of claim 4.

2. Claim 6: The method of claim 5, wherein said permeabilizing is configured to minimally perturb said chromatin of said cell or said nucleus.

As demonstrated above, Claim 5 is anticipated by Grunenwald. *See supra* Section IX.A.3. To the extent Patent Owner contends otherwise, that the permeabilizing is configured to minimally perturb said chromatin of said cell or said nucleus would have been obvious because it is disclosed in Okino, and a POSA would have combined this disclosure with Grunenwald with a reasonable expectation of success.

For example, in teaching the permeabilizing step of the invention, Okino discloses that “methods of permeabilizing or disrupting the cell membrane will not disrupt the structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is destroyed,” thus minimally perturbing the chromatin in the cell. EX1004 at [0071]; EX1002 ¶ 274.

One method of permeabilization taught in Okino is electroporation, which “can be used to permeabilize a cell membrane such that a DNA modifying agent is introduced into the cell and can thus contact the genomic DNA.” EX1004 at [0075]. As discussed above, Grunenwald teaches electroporation when its method is performed *in vivo* on genomic DNA. *See supra* Section IX.A.4.

As explained above in Section IX.C.1, Grunenwald and Okino are analogous art, and thus a POSA interested in configuring a method of permeabilization to minimally perturb chromatin and enable delivery of a transposon complex would have been knowledgeable of the Grunenwald and Okino references. A POSA would have known at least from Grunenwald and Okino that electroporation is a method of permeabilization and that electroporation as a method would minimally perturb the chromatin, and so would be motivated to combine the Okino and Grunenwald references to achieve an expected result, i.e. that electroporation in a manner to minimally disrupt chromatin. EX1002 ¶¶ 274-276.

Therefore, the combination of Grunenwald and Okino teach and render obvious the method of claim 6.

3. Claim 7: The method of claim 5, wherein said cell or said nucleus is permeabilized with a reagent configured to permit said insertional enzyme complex to access said chromatin.

Claim 7 would have been obvious because such methods are disclosed in Okino and a POSA would have combined the disclosures of Okino with those of Grunenwald with a reasonable expectation of success. EX1002 ¶ 285.

Okino teaches a permeabilization step occurring simultaneously with a step of a DNA cleaving enzyme contacting the cell. EX1004 at [0005]. Okino teaches that this step may comprise “contacting the cell with an agent that permeabilizes the cell membrane.” *Id.* at [0011].

A POSA would have been motivated to incorporate the use of an agent to permeabilize the cell membrane with the *in vivo* transposition reaction taught in Grunenwald. Grunenwald teaches that transposition *in vivo* is preferably achieved by “electroporating a synaptic complex of a transposase and a suitable transposon end composition into the host cell,” wherein electroporating acts as a permeabilization step to facilitate access to chromatin for an insertional enzyme complex. EX1003 at [0157].

Okino teaches that “non ionic [*sic*] detergents are an exemplary class of agents that disrupt cell membranes.” EX1004 at [0073]. Okino also teaches that alternatively, electroporation “can be used to permeabilize a cell membrane such that a DNA modifying agent is introduced into the cell and can thus contact the genomic DNA.” *Id.* at [0075]. In solving the problem of permeabilization, there were a small, finite number of solutions that are available to a skilled artisan, including permeabilization by electroporation or by agent. EX1002 ¶ 284. The choice to permeabilize by agent or electroporation would have been a mere design choice to a POSA. *Id.*

A POSA, familiar with Okino and alternative methods of permeabilization taught in the art, would be motivated to use an agent in lieu of the electroporation taught in Grunenwald to achieve the expected result of permeabilizing a cell to better enable the transposon end composition and transposase to enter the cell. EX1002

¶ 285; *see, e.g., Uber Technologies, Inc. v. X One, Inc.*, 957 F.3d 1334, 1341 (Fed. Cir. 2020) (holding that where “a person of ordinary skill would have faced a simple design choice” between finite options, they would have been motivated to combine the teachings of prior art that disclosed those options).

Therefore, the combination of Grunenwald and Okino teach and render obvious the method of claim 7.

4. Claim 8: The method of claim 7, wherein said reagent comprises NP40, digitonin, tween, streptolysin, or a cationic lipid.

Claim 8 would have combined the disclosures of Okino with those of Grunenwald with a reasonable expectation of success. EX1002 ¶ 286.

As discussed above, Okino discloses the use of nonionic detergents to permeabilize the cell membrane. *See supra* Section X.C.2. Okino further discloses that exemplary nonionic detergents “include, but are not limited to, **NP40**, **Tween20**, and Triton X-100.” EX1004 at [0073] (emphasis added). As demonstrated above, the use of such reagents to permeabilize a cell membrane and permit an insertional enzyme complex to access chromatin would have been obvious to a POSA. A POSA would have had a reasonable expectation of success applying the use of the detergents described in Okino to the *in vivo* transposition reaction methods described in Grunenwald. EX1002 ¶¶ 289-291.

Therefore, the combination of Grunenwald and Okino teach and render obvious the method of claim 8.

D. Ground 4: Claim 9 Is Unpatentable Under 35 U.S.C. § 103 Over Grunenwald in View Of Pitt.

1. Claim 9: The method of claim 5, wherein said cell or said nucleus is permeabilized by hypotonic shock or ultrasonication.

a. The Combination of Grunenwald and Pitt Teaches This Limitation

The combination of Grunenwald and Pitt discloses and renders obvious claim 9.

First, Grunenwald discloses each and every limitation of, and therefore anticipates, claim 5. *See supra* Section IX.A.3.

Second, Pitt discloses that “low frequency ultrasound” is an effective method to permeabilize cells for the delivery of a protein. EX1006.010. Further, Pitt discloses that enzymes can be delivered into cells through ultrasonic permeabilization and maintain their activity. EX1006.011. For example, Pitt teaches the transport of enzymes such as tissue plasminogen activator (tPA), noting that “1 MHz ultrasound increased the rate of uptake” of tPA. *Id.*

Thus, the combination of Grunenwald and Pitt discloses and renders obvious each and every limitation of claim 9.

b. It Would Have Been Obvious to a POSA to Combine Grunenwald's and Pitt Teachings

It would have been obvious to combine Grunenwald's methods of fragmenting and tagging chromatin with Pitt's permeabilization step.

First, a POSA would have considered Grunenwald and Pitt analogous. Both references are in the field of molecular biology. EX1002 ¶ 299. Further, both references are directed to the delivery of enzymes into cells to permit an enzyme to perform an activity. *See, e.g.*, EX1003 at [0157] ("transposition into the target DNA is preferably achieved by electroporating a synaptic complex of a transposase and suitable transposon end composition into the cell."); EX1006.011 ('1 MHz ultrasound increased the rate of uptake and the depth of penetration of tPA into clots.').

Second, a POSA interested in the delivery of the insertional enzyme complex into the cell for Grunenwald's *in vivo* embodiment would have been aware of different methods of permeabilization. EX1002 ¶ 300. A POSA interested in studying the DNA that is tagged in Grunenwald's *in vivo* embodiment would be aware of the need to extract and isolate that DNA prior to sequencing. *Id.* Further, a POSA would have been aware of limitations in delivering proteins across the cell membrane, and Pitt specifically addresses ultrasonication as a potential solution to allow proteins to cross cell membranes. *See* EX1006.012. As discussed above, in solving the problem of permeabilizing a cell membrane for

protein delivery, there are a finite number of solutions. *See supra* Section IX.C.3. The choice to use ultrasonication over other methods is merely a design choice. A POSA would have been motivated to attempt ultrasonication as an alternative to the electroporation disclosed in Grunenwald. EX1002 ¶ 300.

Third, a POSA would have had a reasonable likelihood of success in combining the references. Grunenwald teaches the delivery of an insertional enzyme complex (e.g., a transposase and associated nucleic acids) directly into a cell in vivo. EX1003 at [0157]. Because Pitt discloses a method for the delivery of an enzyme into a cell in vivo, a POSA would reasonably expect that the method of permeabilization taught in Pitt would work with the method taught in Grunenwald to accomplish the same goal of delivering an insertional enzyme complex into a cell in vivo. EX1002 ¶ 301.

Therefore, the combination of Grunenwald and Pitt teach and render obvious the method of claim 9.

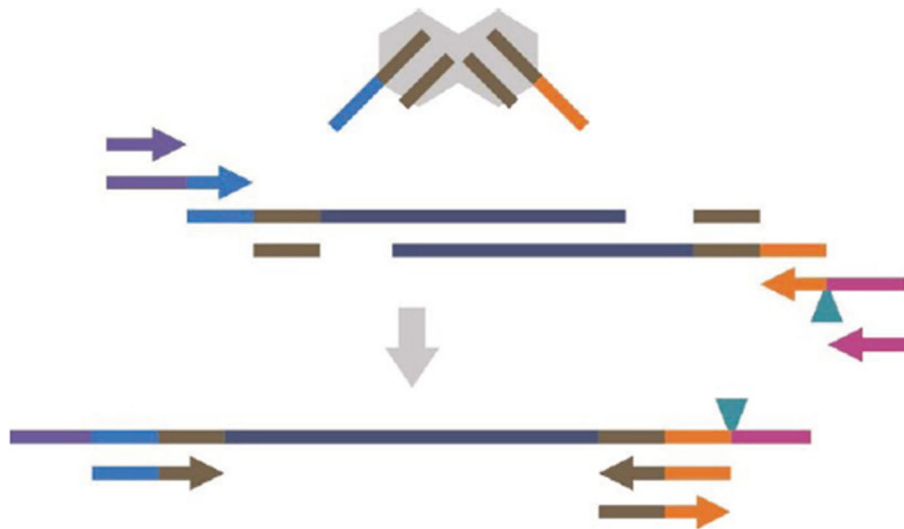
E. Ground 5: Claims 17-20 Are Unpatentable Under 35 U.S.C. § 103 Over Grunenwald in View Of Adey.

To the extent Patent Owner claims that Grunenwald does not anticipate claims 17-20, they are rendered obvious by the combination of Grunenwald and Adey.

Claim 17 recites the method of claim 13, “wherein said insertional enzyme complex further comprises a second nucleic acid insert element comprising a second adapter sequence.” Claims 18-20 depend from claim 17, and further recite that the

second adapter sequence is a second sequencing adapter sequence, a barcode sequence, or a second primer sequence. As explained above, Grunenwald discloses each and every limitation of claim 13. *See supra* Section XI.A.8. Further, Grunenwald discloses each and every limitation of claim 17; to the extent Patent Owner claims that Grunenwald does not anticipate claim 17, it would be rendered obvious by the combination of Grunenwald and Adey. *See supra* Section XI.A.12.

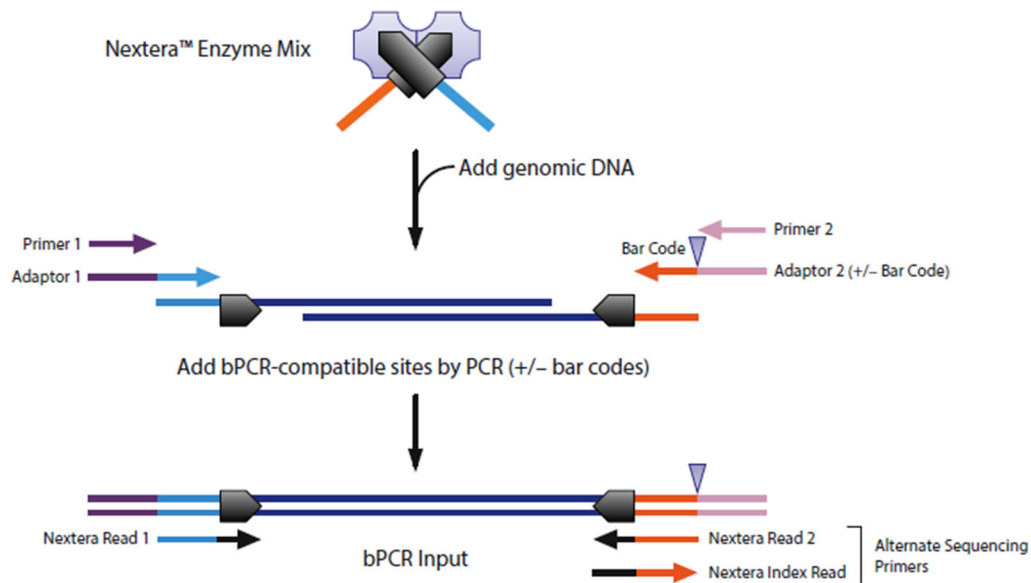
Adey discloses the limitation that “said insertional enzyme complex further comprises a second nucleic acid insert element comprising a second adapter sequence.” For example, in Figure 1(b), reproduced below, the transposome complex is composed of the two grey hexagons, which contain two different adaptors (blue/brown/orange). The complex is capable of simultaneously fragmenting and tagging genomic DNA (navy blue).



EX1009.002 at Figure 1(b) (modified)

As shown in Figure 1(b), Adey discloses the use of a first and a second adapter sequence, in which the two adapter sequences are different (as marked by different colors). Thus, the combination of Grunenwald and Adey discloses each and every limitation of Claim 17.

Adey further discloses that the second adapter sequence comprises a second sequencing adapter sequence, barcode sequence, or second primer sequence. Adey teaches that in the preparation of a library of fragments, genomic DNA is contacted with a Nextera™ enzyme mix. EX1009.014. This mix contains transposon ends with a variety of sequences, illustrated below in Figure 1 from the Nextera™ DNA Sample Prep Kit manual. In Figure 1, the transposase enzyme (two gray crosses) is shown carrying a payload of two adapters (blue and orange) which are sequencing adapters (labeled “Nextera Read 1” and “Nextera Read 2”). EX1048 at .002. In pink and purple, the nucleic acids labeled “Primer 1” and “Primer 2” are amplification primers that permit PCR to be conducted on tagged fragments. The small triangle represents a location for a barcode sequence to be inserted, and in embodiments the adapter would further comprise a barcode sequence. Adey, in its use of the Nextera™ Enzyme kit, did integrate a barcode sequence into the adapters. EX1009.016. Thus, the combination of Grunenwald and Adey discloses each and every limitation of claims 17-20.



EX1048.002 at Figure 1

Further, the combination of Grunenwald and Adey would have been obvious to a POSA.

First, Adey and Grunenwald would have been considered analogous art. Both references disclose the use of a transposase complex to accomplish tagmentation in preparation for sequencing, and a POSA interested in collecting sequence data for the purpose of generating a map of epigenetic features would have been aware of both references. EX1002 ¶ 312.

Second, a POSA would have been motivated to combine the references. Adey discloses a method of tagmentation using a particular kit, the Nextera™ kit, which uses two different adapters that contain different amplification primer sequences, sequencing primer sequences, and, optionally, a barcode sequence.

See, e.g., EX1009.004, 016. Grunenwald, in turn, teaches a method of tagmentation that can be applied directly to chromatin, either on isolated chromosomal DNA or in vivo on chromatin within a living cell. EX1003 at [0146], [0157]. A POSA seeking to prepare chromatin for sequencing would have found it obvious to try using the methods taught in Adey, particularly the use of the Nextera™ kit, for the tagmentation methods taught in Grunenwald. EX1002 ¶¶ 313-314.

Third, a POSA would have had a reasonable expectation of success in combining the references. The Nextera™ Enzyme kit disclosed in Adey was commercially available and, as references such as Adey show, the kit was successful in accomplishing tagmentation. *See, e.g.,* EX1009.014. It would have been predictable that combining an effective commercially available kit with Grunenwald's method to fragment and tag chromatin would yield the predictable result of successful tagmentation and preparation of chromatin for subsequent sequencing and analysis. EX1002 ¶ 315.

F. Grounds 6-8: Obviousness Of Claims 1-3, 5-6, And 10-23

Obviousness grounds 6-8 are identical in all respects to grounds 1, 2, and 5, respectively, except that they further include the disclosure of permeabilization techniques as disclosed in Okino, as detailed above in connection with Ground 3. *See supra* Section IX.C.

To the extent Patent Owner contends that the claims addressed in these grounds are not invalid as laid out in Grounds 1, 2, and 5 because Grunenwald's disclosure of electroporation fails to inherently lead to permeabilization of cells so as to contact chromatin and produce tagged nucleic acid molecules, the skilled artisan would have nonetheless been motivated to further utilize the permeabilization techniques set forth in Okino and would have had a reasonable expectation of successfully using these techniques. This is for the exact reasons set forth above in connection with Ground 3. *See supra* Part IX.C.1.a-b. For instance, the skilled artisan would have found it obvious to use the particular detergents set forth in claim 8 of the '995 Patent and as taught by Okino to achieve the claims addressed in this ground. *See supra* Part IX.C.1.4.

X. The Board Should Reach the Merits of This Petition

A. Section 325(d) Does Not Apply Here, and Even if it Does, the Examiner's Material Errors Warrant Reaching the Merits of This Petition

In deciding whether to exercise its discretion to deny institution under 35 U.S.C. § 325(d), the Board applies a two-part framework that considers six non-exclusive factors. *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential). As documented below, the same art and arguments presented herein were not previously presented to the Office in any meaningful or relevant way. In addition, the

Examiner erred by not considering the relevant teachings in Grunenwald alone or in combination with Okino or Adey. As such, application of *Becton* overwhelmingly confirms that the Board should not exercise its discretion to deny institution under § 325(d).

1. Factors (a), (b) and (d): The Office Has Not Considered the Same or Substantially the Same Art or Arguments

O’Geen and Pitt were not in front of the Examiner during prosecution. The Applicant identified Grunenwald and Okino, but the Examiner did not cite or discuss these references during prosecution. Grunenwald and Adey are mentioned in the specification of the ’995 Patent. Mention of a reference in a specification alone, however, does not justify denial under § 325(d), particularly where, as here, neither were cited or discussed by the Examiner during prosecution. *See 3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Paper No. 9 at 39-42 (P.T.A.B. June 11, 2019) (declining to apply § 325(d) where there was no evidence that the examiner substantively considered references that were of record during prosecution); *Limelight Networks, Inc. v. Akamai Tech., Inc.*, 2016 WL 8115506, at *5 (P.T.A.B. Dec. 30, 2016) (declining to exercise § 325(d) discretion because the Board was “not persuaded that merely referencing [references] in the ’102 patent’s specification necessarily is the same as presenting arguments with respect to those references”); *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486, Paper No.

10 at 15 (P.T.A.B. July 15, 2015); *Weber, Inc. v. Provisur Tech., Inc.*, 2020 WL 755049, at *4 (P.T.A.B. Feb. 14, 2020).

2. Factors (c), (e), and (f): The Examiner Erred by Not Considering the Art and Relevant Teachings Herein

Even if the Board determines that the same or substantially the same art or arguments were before the Office, the Examiner materially erred by not considering the relevant teachings in Grunenwald, Okino, and Adey.

In the Notice of Allowance, the Examiner did not discuss or cite any passage or disclosure of Grunenwald, Okino, or Adey. EX1007.139-146, 350-351. In such a case, where “the record of the Office’s previous consideration of the art is not well developed...a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).” *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 at 10 (P.T.A.B. Feb. 13, 2020); *see Kayak Software Corp. v. Int’l Bus. Machs. Corp.*, CBM2016-00075, Paper 16 at 11 (P.T.A.B. Dec. 15, 2016) (informative) (“where the prior art at issue was only cursorily considered that can weigh against exercising the discretion”). Moreover, the fact that these references “w[ere] not the basis of a rejection weighs strongly against exercising [the Board’s] discretion to deny institution.” *Cellco P’ship v. Huawei Device Co., Ltd.*, IPR2020-01117, Paper 10 at 13 (P.T.A.B. Feb. 3, 2021).

Here, the Examiner erred by failing to acknowledge the teachings in Grunenwald regarding application of tagmentation to living cells *in vivo* that disclose transposition tagging on chromosomal target DNA, Okino that disclose cell lysis, and permeabilization by the use of nonionic detergents, particularly NP40 and Tween 20, and Adey that disclose tagmentation with two tags. *Amber.IO, Inc. v. 72LUX, Inc.*, IPR2020-00015, Paper No. 8 at 20 (P.T.A.B. Apr. 1, 2020) (finding that the Examiner materially erred by failing to consider prior art references listed on IDS, when the Petitioner demonstrated that the references teach significant elements of the challenged claims). The Board should reach the merits of this petition and consider these relevant teachings in the first instance.

B. The *Fintiv* Factors Favor Institution

The factors set forth in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (P.T.A.B. Mar. 20, 2020) (“*Fintiv*”), for weighing discretionary denial when there is parallel, co-pending district court litigation also overwhelmingly favor institution.

The **first *Fintiv* factor**—whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted—is neutral. If instituted, Petitioner will seek stay in the district court litigation. As the court’s decision will come after institution, and is “based on a variety of circumstances and facts beyond [the Board’s] control and to which the Board is not privy.” *Sand Revolution II*,

LLC v. Continental Intermodal Grp. – Trucking, LLC, IPR2019-01393, Paper 24 at 7 (P.T.A.B. June 16, 2020) (informative).

Moreover, the District of Delaware grants majority of motions to stay pending IPR. EX1049; *see also, e.g., International Business Machines Corp. v. Rakuten Inc.*, No. 21-461-GBW, 2022 WL 17848779 (D. Del. Dec. 22, 2022) (granting defendant’s motion to stay after the Board instituted IPRs for the asserted patents). Thus, this factor is at least neutral.

The **second *Fintiv* factor**—proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision—favors institution. Currently, the trial date in the district court litigation is scheduled to start on December 2, 2024, which will be approximately 2 months after the anticipated final written decision in this IPR. EX1046.

But more realistically, it is far from certain that the district court trial will proceed as planned. There is a reasonable chance that the litigation may be stayed upon institution and/or ordinary delays in district court litigation may occur over the next 18 months. Indeed, the median time to trial for civil cases in the District of Delaware is 33.7 months, which would place trial in June 2025. EX1047.014. Thus, this factor favors institution.

The **third *Fintiv* factor**—investment in the parallel proceeding by the court and the parties—favors institution. The Board has found that the third factor favors

institution where in the parallel litigation, “the District Court has not issued any substantive orders,” “no claim construction orders have issued,” and “discovery is not complete, because...neither party had taken any depositions.” *Snap, Inc. v. SRK Tech. LLC*, IPR2020-00820, Paper 15, at 10–11 (PTAB. Oct. 21, 2020). This is all true for the district court litigation.

Fact discovery is ongoing. Further, expert discovery or dispositive motion briefing will not be completed until after the institution deadline. EX1046.012. Moreover, no claim construction brief has been filed by either party, and the claim construction hearing will not occur until February 21, 2024. EX1046.012. Furthermore, “the most burdensome parts of the case—filing and responding to pretrial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice—all lie in the future.” *CyWee Grp. Ltd. v. Samsung Elecs. Co. Ltd.*, No. 2:17-cv-00140-WCB-RSP, 2019 WL 11023976, at *6 (E.D. TEX Feb. 14, 2019). Thus, this third factor favors institution.

The **fourth *Fintiv* factor**—overlap between issues raised in the petition and in the parallel proceeding—favors institution. If instituted, Petitioner will stipulate to not pursuing, in the district court litigation, invalidity arguments based on any instituted IPR ground.

The **fifth *Fintiv* factor**—whether the Petitioner and the defendant in the parallel proceeding are the same party—is neutral. Petitioner is the defendant in

the district court litigation, but that is often the case for a patent asserted in district court and challenged at the Board.

Finally, the **sixth *Fintiv* factor**—other circumstances that impact the Board’s exercise of discretion, including the merits—also favors institution. This Petition presents a compelling merits case that all claims of the ’995 Patent are unpatentable, and therefore this factor weighs in favor of institution. *Fintiv*, IPR2020-00019, Paper 11 at 14–15.

Thus, in view of the facts presented in this Petition, the *Fintiv* factors do not support discretionary denial.

XI. CONCLUSION

For the reasons set forth above, Petitioner Parse Biosciences, Inc. respectfully requests *inter partes* review of the challenged claims of the ’995 Patent.

Dated: April 20, 2023

Respectfully submitted,

/Derek C. Walter/

Derek C. Walter

Lead Counsel for Petitioner

Reg. No. 74,656

Weil, Gotshal & Manges LLP

201 Redwood Shores Parkway

Redwood Shores, CA 94065

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 13,993 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: April 20, 2023

By: /Derek C. Walter/
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,150,995 WITH PARSE BIOSCIENCES, INC'S EXHIBIT LIST, POWER OF ATTORNEY AND EXHIBITS 1001-1051** are being served on April 20, 2023, via Priority Express Mail (Fed Ex) pursuant to 37 C.F.R. § 42.105 and § 42.6(e) to the Patent Owner at the address below:

Bozicevic, Field & Francis LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065

Patent Owner's Address of Record

Nicholas Groombridge
Jennifer H. Wu
Josephine Young
Jennifer Rea Deneault
PAUL, WEISS, RIFKIND,
WHARTON & GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019

*Additional Addresses Known as Likely to
Effect Service*

Dated: April 20, 2023

By: /Derek C. Walter/
Derek C. Walter
Lead Counsel for Petitioner
Reg. No. 74,656