

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR
UNIVERSITY,¹
Patent Owner

Case IPR2023-00878
Patent 10,150,995

**PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

¹ Petitioner listed 10x as the Patent Owner. While 10x, as exclusive licensee, is the real party-in-interest, The Board of Trustees of the Leland Stanford Junior University (“Stanford University”) is formally the Patent Owner.

LIST OF EXHIBITS

Exhibit	Description
EX2001	File History of App. No. 14/784,250
EX2002	U.S. Patent Pub. No. 2015/0111788
EX2003	U.S. Patent No. 9,080,211
EX2004	S. Ma & Y. Zhang, <i>Profiling chromatin regulatory landscape: insights into the development of ChIP-seq and ATAC-seq</i> , Molecular Biomedicine (2020)
EX2005	T Shashikant & C. Ettensohn, <i>Genome-wide analysis of chromatin accessibility using ATAC-seq</i> , Methods Cell. Biol. 151:219-235 (2019)
EX2006	A. Han, <i>Parse Biosciences Expands Single-Cell Product Line</i> , Global Research, genomeweb (Apr. 14, 2022), (available at https://www.genomeweb.com/sequencing/parse-biosciences-expands-single-cell-product-line-global-reach)
EX2007	Henderson's Dictionary of Biology (Eleanor Lawrence ed., 14th ed., 2008)
EX2008	Bruce Alberts, et al., <i>Molecular Biology of the Cell</i> , Garland Science (4th ed. 2002)
EX2009	U.S. Patent Pub. No. 2015/0337298
EX2010	File History of App. No. 16/418,796
EX2011	Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-01033, Pap.1, (May 25, 2023)
EX2012	U.S. Patent Pub. No. 2003/0032141
EX2013	Declaration of J. Steven Baughman
EX2014	Declaration of Sayem Osman

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Challenged Claims Are Directed To A Novel, Non-Obvious Invention...5	
III.	Petitioner’s References.....	12
	A. Grunenwald (EX1003).....	12
	B. O’Geen (EX1005)	13
	C. Okino (EX1004).....	15
	D. Pitt (EX1006).....	15
	E. Adey (EX1009).....	15
IV.	Claim Construction	16
V.	Ground 1: Petitioner’s Anticipation Analysis Is Legally Deficient	16
	A. Petitioner Fails To Clearly Identify The “Biological Sample” In Grunenwald	17
	B. Petitioner Fails To Show Grunenwald Discloses “Contacting Chromatin Of A Genome Region”	18
	1. Petitioner’s <i>Express</i> Disclosure Theory Fails	19
	(a) Contacting Chromatin.....	19
	(b) “Of a Genome Region”	27
	2. Petitioner Has Not Established Inherency	28
	(a) Contacting Chromatin.....	28
	(b) “Of a Genome Region”	34
	(c) Mixing and Matching Embodiments.....	36
VI.	Grounds 2-8: Petitioner’s Obviousness Analyses Are Flawed And Cannot Support A Finding Of Obviousness	38

A.	Petitioner Fails to Assert—Let Alone Prove—Its References are Analogous Art to the '995	39
B.	Petitioner’s Motivation To Combine And Reasonable Expectation Of Success Analyses Are Conclusory	40
C.	Ground 2: Petitioner’s Obviousness Analyses Lacks The Requisite Particularity For Additional Reasons	45
VII.	Institution Should Be Denied Under 35 U.S.C. §325(d)	47
A.	Advanced Bionics Part One Favors Denial	50
B.	Advanced Bionics Part Two Favors Denial	56
VIII.	Institution Should Be Denied Under 35 U.S.C. §314(a)	64
IX.	Conclusion	65

TABLE OF AUTHORITIES

	Page(s)
CASES	
<i>Adidas AG v. Nike, Inc.</i> , 963 F.3d 1355 (Fed. Cir. 2020)	45
<i>ADT LLC v. Vivint, Inc.</i> , IPR2022-00612, Pap.8 (Aug. 22, 2022)	60
<i>ADT LLC v. Vivint, Inc.</i> , IPR2022-00634, Pap.7 (Oct. 4, 2022)	46, 47
<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH</i> , IPR2019-01469, Pap.6 (Feb. 13, 2020)	<i>passim</i>
<i>Agrinomix, LLC v. Mitchell Ellis Prods., Inc.</i> , IPR2017-00525, Pap.8 (June 14, 2017)	51
<i>Alarm.com, Inc. v. Vivint, Inc.</i> , IPR2022-00728, Pap.6 (Nov. 1, 2022)	53
<i>Albaad Massuot Yitzhak, Ltd. v. Edgewell Pers. Care Brands, LLC</i> , IPR2017-00693, Pap.11 (July 17, 2017)	28, 31
<i>Allergan, Inc. v. Apotex Inc.</i> , 754 F.3d 952 (Fed. Cir. 2014)	30
<i>Apple Inc. v. Argina Tech. Ltd.</i> , IPR2023-00453, Pap.7 (June 14, 2023)	37
<i>Autel Intelligent Tech. Corp. v. Orange Elec. Co.</i> , IPR2021-01545, Pap.8 (Apr. 8, 2022)	53
<i>Becton, Dickinson and Co. v. B. Braun Melsungen AG</i> , IPR2017-01586, Pap.8 (Dec. 15, 2017)	48, 49, 50, 51
<i>Bioeq IP AG v. Genentech, Inc.</i> , IPR2016-01608, Pap.11 (Feb. 22, 2017)	32

<i>BlephEx, LLC v. Myco Indus., Inc.</i> , 24 F.4th 1391 (Fed. Cir. 2022)	16, 36
<i>Captioncall, LLC v. Ultratec, Inc.</i> , IPR2020-01215, Pap.6 (Jan. 27, 2021).....	16, 28, 36, 37
<i>Chevron Oronite Co. v. Infineum USA L.P.</i> , IPR2018-00923, Pap.9 (Nov. 7, 2018)	64
<i>Cisco Sys., Inc. v. C-Cation Techs., LLC</i> , IPR2014-00454, Pap.12 (Aug. 29, 2014)	27
<i>Cont'l Can Co. USA v. Monsanto Co.</i> , 948 F.2d 1264 (Fed. Cir. 1991)	29
<i>Crown Operations Int'l, Ltd. v. Solutia Inc.</i> , 289 F.3d 1367 (Fed. Cir. 2002)	29, 30
<i>CSL Behring LLC v. Bioverative Therapeutics Inc.</i> , IPR2018-01313, Pap.10 (Jan. 9, 2019).....	32
<i>Cuozzo Speed Techs., LLC v. Lee</i> , 579 U.S. 261 (2016).....	47
<i>Darfon Elecs. Corp. v. Shipman</i> , IPR2022-01008, Pap.11 (Dec. 2, 2022).....	53
<i>Deeper, UAB v. Vexilar, Inc.</i> , IPR2018-01310, Pap.7 (Jan. 24, 2019).....	65
<i>Elk Engineering SDN. BHD. v. Wilco Marsh Buggies & Draglines, Inc.</i> , IPR2020-00344, Pap.7 (June 23, 2020).....	46
<i>ESET, LLC v. Finjan, Inc.</i> , IPR2017-01738, Pap.57 (Jan. 24, 2019).....	29
<i>Eyenovia, Inc. v. Sydnexis, Inc.</i> , IPR2022-00963, Pap.7 (Nov. 8, 2022)	63
<i>Fujian Sanan Grp. Co. v. Epistar Corp.</i> , IPR2018-00971, Pap.9 (Nov. 20, 2018)	37

<i>Galderma Lab’ys, L.P. v. Teva Pharms. USA, Inc.</i> , 799 F. App’x 838 (Fed. Cir. 2020)	29
<i>Gilead Scis., Inc. v. Regents of the Univ. of Minn.</i> , IPR2017-01753, Pap.42 (Apr. 22, 2020)	32
<i>Google LLC v. Valtrus Innovations Ltd.</i> , IPR2022-01197, Pap.9 (Jan. 3, 2023)	63
<i>Health Care Logistics, Inc. v. Kit Check, Inc.</i> , IPR2019-00385, Pap.7 (June 3, 2019)	40
<i>In re Magnum Oil Tools Int’l, Ltd.</i> , 829 F.3d 1364 (Fed. Cir. 2016)	40
<i>In re Wesslau</i> , 353 F.2d 238 (CCPA 1965)	32
<i>Ivantis, Inc. v. Sight Scis., Inc.</i> , IPR2022-01533, Pap.14 (Mar. 27, 2023)	<i>passim</i>
<i>Kayak Software Corp. v. IBM</i> , CBM2016-00075, Pap.16 (Dec. 15, 2016)	53
<i>Keysight Techs., Inc. v. Centripetal Networks, Inc.</i> , IPR2022-01421, Pap.9 (Mar. 22, 2023)	51
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	4
<i>Live Nation Entertainment, Inc. v. Complete Entertainment Resources B.V.</i> , PGR2017-00038, Pap.11 (Jan. 16, 2018)	61
<i>Microsoft Corp. v. AlmondNet, Inc.</i> , IPR2022-01319, Pap.9 (Jan. 30, 2023)	49, 58, 64
<i>Microsoft Corp. v. ThroughPuter, Inc.</i> , IPR2022-00757, Pap.10 (Nov. 1, 2022)	56, 63
<i>Miltenyi Biomedicine GmbH v. The Trustees of the Univ. of Pa.</i> , IPR2022-00853, Pap.11 (Oct. 11, 2022)	53, 59

<i>Monolithic Power Sys., Inc. v. Volterra Semiconductor LLC</i> , IPR2020-01348, Pap.19 (Mar. 4, 2021)	52, 58, 60
<i>Motorola Mobility LLC v. Maxell, Ltd.</i> , IPR2022-01287, Pap.11 (Feb. 2, 2023)	48, 49, 52, 63
<i>Motorola Mobility LLC v. Maxell, Ltd.</i> , IPR2023-00110, Pap.7 (June 15, 2023)	25
<i>Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.</i> , IPR2020-00040, Pap.91 (May 7, 2021)	29
<i>Net MoneyIN, Inc. v. VeriSign, Inc.</i> , 545 F.3d 1359, 1369 (Fed. Cir. 2008)	16, 28, 37
<i>Pungkuk Wire Mfg. Co. v. Seong, Ki Chul</i> , IPR2016-00763, Pap.70 (Aug. 16, 2017)	29
<i>Salpeter v. ARP Wave, LLC</i> , IPR2019-01384, Pap.12 (Jan. 27, 2020)	4, 40
<i>Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.</i> , 66 F.4th 1373 (Fed. Cir. 2023)	3, 39
<i>Scanstrut, Inc. v. Nat’l Prods., Inc.</i> , IPR2020-01542, Pap.7 (Mar. 16, 2021)	45
<i>U.S. v. Dunkel</i> , 927 F.2d 955, 956 (7th Cir. 1991)	24
<i>U.S. Well Servs., LLC v. Haliburton Energy Servs., Inc.</i> , IPR2022-01163, Pap.9 (Dec. 20, 2022)	23-24, 41
<i>Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.</i> , 200 F.3d 795 (Fed. Cir. 1999)	16
<i>Xerox Corp. v. Bytemark, Inc.</i> , IPR2022-00624, Pap.9 (Aug. 24, 2022)	21, 25, 28, 36

STATUTES

35 U.S.C. §312(a)(3).....	45
35 U.S.C. §325(d)	<i>passim</i>

I. Introduction

10x Genomics, Inc. (“10x”) submits this §42.107² Preliminary Response to the above-captioned Petition (“Petition”/“Pet.”). The Board should deny the Petition because it fails to meet Petitioner’s burden to establish unpatentability of Claims 1-23 (the “Challenged Claims”) of U.S. Pat. No. 10,150,995 (the “’995 Patent”/“’995”).

First, Petitioner’s Ground 1, anticipation by Grunenwald—a reference on which all of Petitioner’s other Grounds depend³—is deficient. Petitioner first argues Grunenwald expressly discloses the claim requirement of “contacting chromatin of a genome region,” but then pivots to an inherency argument. Petitioner is wrong on both counts. Petitioner’s express disclosure argument for “contacting chromatin” relies solely on Grunenwald’s disclosure of “*chromosomal DNA*, e.g., from an isolated chromosome or portion of a chromosome.” But nowhere does Grunenwald mention chromatin, and even Petitioner’s own

² Unless stated, all statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates, and all emphases/annotations are added.

³ Petitioner’s Grounds 2-5 do not challenge claim 1 (and instead depend on Ground 1’s arguments to do so) and Grounds 6-8 are limited to adding “the disclosure of permeabilization techniques as disclosed in Okino.” Pet.64.

dictionary confirms chromatin and “chromosomal DNA” are not the same.

Petitioner also identifies no disclosure in Grunenwald that it even alleges teaches the requirement of contacting “chromatin *of a genome region*.”

For inherency, Petitioner fails to present any persuasive technical reasoning to explain its argument that Grunenwald inherently disclosed contacting chromatin of a genome region, and its mere conclusory assertions cannot meet its burden.

Pet.31-33. That (in Petitioner’s words) Grunenwald’s methods “*can* be applied to chromosomal DNA *in vivo*” does not mean they necessarily *were*; nor does

Petitioner point to *any* disclosure of the methods *actually being applied* to

chromosomal DNA *in vivo*. Pet.31. Further, even if Petitioner established

Grunenwald disclosed an *in vivo* chromosomal DNA embodiment, Petitioner

nevertheless failed to establish inherency of the contacting chromatin limitation.

Prokaryotes and eukaryotes have chromosomal DNA, and Petitioner fails to

acknowledge the fact that *prokaryotes do not have chromatin*. Petitioner has not

established and cannot establish that Grunenwald’s disembodied generic disclosure

of “chromosomal DNA (*e.g.*, from an isolated chromosome or a portion of a

chromosome, *e.g.*, from one or more genes or loci from a chromosome)”

necessarily, and thus inherently, refers to *chromatin* (found only in the nuclei and

not the cytoplasm of eukaryotic cells), let alone contacting chromatin *of a genome*

region. Indeed, to the extent Petitioner’s “genome region” inherency theory can be

understood at all (and it was Petitioner’s burden to detail and support), Petitioner relies on an unexplained, unsupported, double-inherency theory. Petitioner’s erroneous citations to its expert report regarding the “contacting chromatin of a genomic region” limitation only add confusion to its already-insufficient proof.

Second, Petitioner’s Grounds 2-8 present obviousness arguments based on Grunenwald and additional references. Petitioner’s obviousness Grounds do not even purport to fill the gaps of Grunenwald identified above. Moreover, those Grounds each have two threshold failures. First, Petitioner entirely fails to assert or analyze whether its references are analogous art *to the ’995* (instead discussing only whether they are analogous *to one another*). This failure impacts all seven obviousness grounds and requires denial, as the Federal Circuit recently confirmed. *See, e.g., Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373 (Fed. Cir. 2023) (reversing a Final Written Decision (“FWD”) for this failure). Even if this definitive failure were, *arguendo*, overlooked (and it cannot be), Petitioner’s obviousness theories would also fail because Petitioner’s motivation to combine and reasonable expectation of success arguments are not sufficiently supported. Petitioner provides nothing more than its own conclusory say-so that POSITA would have been motivated to combine any of its references, or would have had a reasonable expectation of success in doing so. But conclusory assertions are insufficient for obviousness. *Salpeter v. ARP Wave, LLC*, IPR2019-

01384, Pap.12, 16-17 (Jan. 27, 2020) (denying institution and stating that “[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements”) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

Third, while the Petition’s merits failures warrant denial, the circumstances here support denial under §325(d) as a threshold matter before those merits are ever reached. Grunenwald—the reference at the heart of each of Petitioner’s eight Grounds—was not only of record during prosecution—which alone would satisfy part one of the §325(d) analysis—but it was also discussed and ***incorporated by reference*** into the ’995. Similarly, Petitioner’s four secondary references were either before the Examiner, discussed in ’995’s specification, or cumulative of references before the Examiner. Petitioner’s allegation of “error” (for part two of the §325(d) analysis) is simply that the Examiner erred “by not considering the relevant teachings in Grunenwald,” including its “application of tagmentation to living cells *in vivo*.” Pet.67-68. But Petitioner does not prove the Examiner misunderstood or overlooked any teachings in Grunenwald, and fails to explain how the Examiner could have failed to consider Grunenwald ***when it was incorporated by reference into the ’995 itself***. Moreover, the Examiner acknowledged tagmentation in living cells in a rejection during prosecution of ’995’s parent application. EX2001, 380-382, 437-438. Petitioner simply ignores this prosecution history that directly contradicts its only allegation of “error.”

Thus, as a threshold matter, §325(d) denial is appropriate here to avoid squandering both the Board's and 10x's time and resources in rehashing arguments raised and resolved in prosecution.

II. Challenged Claims Are Directed To A Novel, Non-Obvious Invention

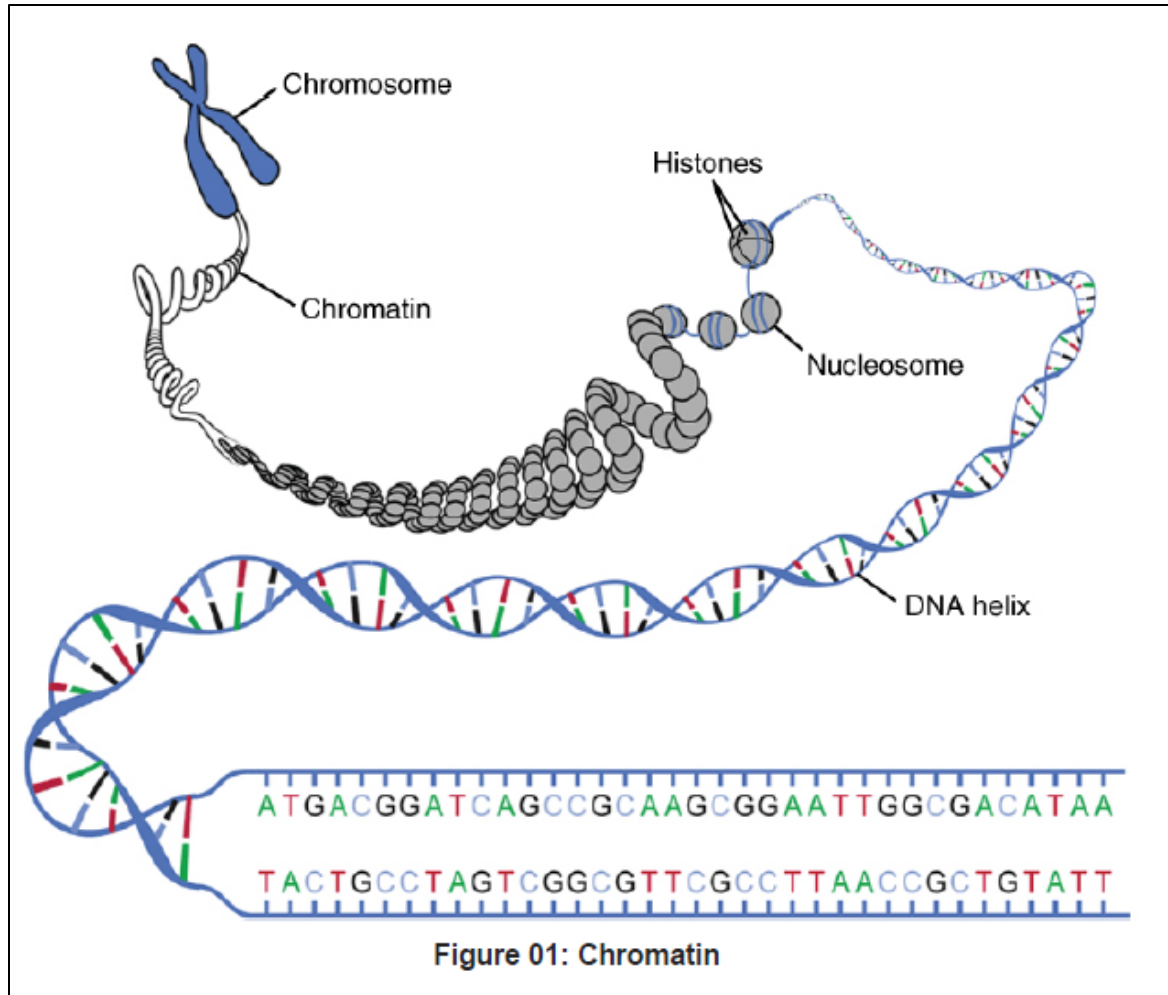
The '995, "Transposition of Native Chromatin for Personal Epigenomics," claims priority to a May 23, 2013 provisional application. EX1001, 1; Pet.12. The Challenged Claims are directed to innovative methods of analyzing chromatin of a sample of cells. EX1001, 43:24-44:57. The inventors of this patent coined the term "ATAC-seq" as the name of their method. EX1001, 24:35-36. ATAC-seq stands for Assay for Transposase-Accessible Chromatin using sequencing. EX1001, 24:35-36. ATAC-seq is now the industry-standard term for their method due to its elegant simplicity. EX2004, 1, 6 (Fig.3); EX2005, 1, 4. Indeed, Parse itself refers to its planned competing product as an "ATAC-seq" product, and to this method as "ATAC-seq." EX2006, 1-2.

“Eukaryotic genomes are hierarchically *packaged into chromatin*, and the nature of *this packaging* plays a central role in gene regulation.” EX1001, 1:24-26. And the ’981 underscores the critical importance—for epigenetic analysis—of the information conveyed by chromatin’s structural packaging, discussing the “[m]ajor insights into *the epigenetic information encoded within the nucleoprotein structure of chromatin* [that] have come from high-throughput, genome-wide methods for separately assaying the chromatin accessibility (‘open chromatin’), nucleosome positioning, and transcription factor (TF) occupancy.” *Id.*, 1:26-31.

As Petitioner’s own references explain, chromatin is found in (and only in) the cell nuclei of eukaryotes, and portions of the DNA in chromatin is organized by being condensed and tightly wrapped around proteins called “histones.” EX1036, 3; EX1041, 1. As the ’995 states, chromatin is:

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

EX1001, 12:54-60; *see also id.* 17:15-17 (distinguishing genomic DNA from chromatin: “The polynucleotide can be genomic DNA. The polynucleotide can be further bound to proteins, such as histones, and may be *optionally packaged in the form of chromatin*”). Chromatin exists in a variety of forms that can be present at any given time, including heterochromatin and euchromatin. EX1041, 2; EX1036, 3; EX1001, 18:12-19, 24:42-47. Heterochromatin regions are tightly packed and condensed; euchromatin regions, often referred to as “open chromatin,” are relatively less condensed, which exposes particular genes for transcription into mRNA. EX1041, 2; EX1036, 3; EX1001, 4:52-55 (“Transposase... inserts only in regions of open chromatin”). The collection of chromatin forms a chromosome. EX1041, 1; EX1036, 4. The structure of chromatin is illustrated in the image below.



EX1041, 4 (Figure 1). In sum, only certain DNA is packaged with proteins in this fashion, and only eukaryotes have chromatin—and only in their cell nuclei.

EX1041, 2; EX1036, 3.

“[E]pigenetic information [is] encoded within the nucleoprotein structure of chromatin.” EX1001, 1:26-28. Epigenetics relates to modifications to a chromosome that impact what genes are transcribed to mRNA (which can then be expressed as proteins) *without* changing the chromosome’s DNA sequence—*e.g.*,

which portions of chromatin are “open” or not in a cell at any given time based on cellular signals and gene activity. EX1004, ¶¶3-4; EX1002, ¶¶77-80.

The Challenged Claims are directed to innovative two-step methods of analyzing chromatin of a sample of cells to assess an individual’s epigenome by (1) *contacting chromatin of a genome region with an insertional enzyme complex to tag nucleic acids*, and then (2) *assaying the tagged nucleic acids to provide sequence information*. EX1001, 43:24-44:57.

The ’995 is a continuation of App. No. 14/784,250—the first non-provisional application filed in ’995’s family, which issued as U.S. Patent 10,059,989 (“’989 Patent”/“’989”). During prosecution of the parent ’989’s application, the Examiner (the same as ’995’s) rejected certain claims as anticipated by U.S. Patent Publication 2015/0111788 to Fernandez *et al.* (“Fernandez”) (EX2002), and others as obvious based on Fernandez combined with additional references. EX2001, 380-385.

The Examiner argued that “Fernandez et al teach[es] wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said cell.” EX2001, 381. In an interview following this rejection, the applicant proposed an amendment to require that “the insertional enzyme complex *does not comprise an antibody specific to a protein that is part of said chromatin*,” and the Examiner indicated the Fernandez rejections would be withdrawn if the claims

were amended in this manner. EX2001, 409, 421. Following the interview, applicant submitted the amended claims and an IDS, which identified U.S. Patent 9,080,211 to Grunenwald (EX2003) (the patent Petitioner's EX1003 matured into) on its first page (EX2001, 401, 413)—after Grunenwald had *already* been referenced twice and incorporated by reference in the pending specification (EX1001, 13:19-26, 14:36) and identified in an earlier IDS (EX2001, 295). The Examiner then issued a Notice of Allowance, stating in the Reasons for Allowance that:

No prior art was found teaching or suggesting a method for analyzing chromatin comprising contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin... An updated search did not reveal any prior art against the claimed invention. In fact, the prior art teaches away from chromatin analysis as instantly claimed to obtain epigenetic information. Rather the art supports chromatin immunoprecipitation, which involves the use of an insertional complex that comprises an antibody specific to a protein that is part of the chromatin, as a main tool for investigating epigenetic marks... Accordingly, the instant invention is deemed novel and non-obvious over the prior art.

EX2001, 437-438.

Following this substantive prosecution of its parent, the '995 issued without additional rejections.

Petitioner now asserts that “the primary inventor” “put to rest” “any suggestion that the claimed invention of the '995 Patent is novel or inventive” in a tweet. Pet.3. Not so. Instead, that tweet confirms the technical advancements in the Claims. Jason Buenrostro tweeted: “ATAC-seq is so easy to do that anyone can do it!” Pet.4. Prior to ATAC-seq, “[e]pigenomic studies of chromatin accessibility ha[d] yielded tremendous biological insights, but [were] limited in application by their *complex workflows* and *large cell number requirements*.” EX1001, 32:37-40. The innovative ATAC-seq method was a paradigm shifting technique that allowed researchers to quickly and simply analyze the epigenome of samples of any size. As an example, DNase-seq, is *44-steps*, requires *50 million cells* and *3 days* (two overnight incubations) to get results. EX1001, Fig.1B, 29:6-21. The methods of the Challenged Claims include the method referred to as “ATAC-seq,” a method of analyzing chromatin that, in comparison, can be practiced on as little as a *one-cell* sample in *two steps* in *less than a day*. *Id.* As Buenrostro confirmed, the novelty of the method is its simplicity and the possibilities it unlocked: “ATAC-seq is so easy... anyone can do it.” EX1029.

III. Petitioner's References

A. Grunenwald (EX1003)

Petitioner's central Grunenwald reference, U.S. Patent Application 2010/0120098, titled "Transposon End Compositions and Methods for Modifying Nucleic Acids," discloses methods, compositions, and kits for using a transposase and a transposon end to generate fragmented DNA for analysis. EX1003, 1 (Abstract). Grunenwald discloses a method for creating libraries of tagged DNA fragments for use in next-generation sequencing. EX1003, ¶¶11, 16.

As discussed above, Grunenwald was not only *cited to the Office* during the prosecution leading to '995, but was also *repeatedly cited* and, indeed, *incorporated by reference into the specification of '995*. See, e.g., EX1001, 13:19-26 ('995 citing and incorporating "US20100120098" by reference (along with another publication) as describing this prior art system that "fragment[s] and add[s] adaptors to the polynucleotides"), 14:31-36 (cited (along with other art) as disclosing "method[] for tagmenting *isolated* genomic DNA"). But, unlike '995—which, *inter alia*, requires *contacting chromatin* (not just DNA) and aims to avoid "perturbing *the in vivo context* and *modulating the epigenetic state* [of the cell] in unknown ways" (e.g., EX1001, cl.1; 1:38-41 (discussing one of "three major ways" existing protocols were "problematic"))—Grunenwald *does not mention chromatin at all*, and Grunenwald's disclosures of results, methods, and data, are

focused on *in vitro* transposition for fragmenting and acquiring the relevant *target DNA, which is not chromatin*. EX1003, ¶161; *see, e.g.*, EX1001, 6:28-29 (contrasting “chromatin” with “naked genomic DNA”), 17:15-17 (contrasting “optional[] packag[ing] in the form of chromatin” with “genomic DNA” more generally). Grunenwald states that “[a]n important step in embodiments of the method of the present invention is the use of an *in vitro* transposition reaction to fragment and tag the *target DNA* fragments. The *in vitro* transposition reaction requires a transposase...” EX1003, ¶92. Grunenwald further defines “transposase” to mean “an enzyme that is capable of forming a functional complex... and catalyzing insertion or transposition of the transposon end-containing composition into the double-stranded target DNA with which it is incubated in an *in vitro* transposition reaction.” EX1003, ¶93. Even to the extent Grunenwald briefly mentions *in vivo* transposition, it does not address any transposition of chromosomal DNA *of the nucleus of a eukaryotic cell* (the only cellular location where chromatin exists). EX1003, ¶157; EX1041, 1.

B. O’Geen (EX1005)

O’Geen is an excerpted chapter from a book, *Epigenetics Protocols*, and is titled “Using *ChIP-Seq Technology* to Generate High-Resolution Profiles of Histone Modifications.” EX1005, 4. Petitioner relies on O’Geen for disclosures allegedly related to claim 2 and generating a representation of epigenetic features.

Pet.46. As its title reflects, O’Geen employs a previously-existing protocol significantly different from ATAC-seq, termed “ChIP-Seq”—a prior art method distinguished in the ’995. *E.g.*, EX1001, 14:56-58. O’Geen states:

Currently, the method of choice to study the epigenome is the chromatin immunoprecipitation (ChIP) assay. To perform a ChIP assay, proteins such as histones or transcription factors are covalently crosslinked to their genomic DNA substrates in living cells. This provides an opportunity to take a snapshot of histone or other protein-DNA interactions in a given cell type, in cells taken at different developmental stages, or in cells altered by disease. After isolation and fragmentation of chromatin, the protein-DNA complexes are captured using *antibodies specific to the histone or transcription factor of interest*.

EX1005, 5. Unlike the ’995, O’Geen’s immunoprecipitation (as the Office found in the Notice of Allowance in the ’995’s parent application) “involves the use of an insertional complex that comprises an antibody specific to a protein that is part of the chromatin.” EX2001, 437-438; EX1005, 7 (“ChIP grade antibodies specific for the following six histone modifications”). And O’Geen states that its protocol is “based on sonication,” which is the use of ultrasound to fragment DNA, as opposed to the ’995’s use of tagmentation. EX1005, 21 (“Chromatin can be sheared by sonication... this method is based on sonication”); EX1001, 1:54-62.

C. Okino (EX1004)

Okino is an international patent publication, WO 2010/065266, titled “Chromatin Structure Detection.” Petitioner cites Okino as a secondary reference, relying on it for permeabilizing and lysing cells, and not for any disclosure of chromatin or an insertional enzyme complex or transposase. Pet.51-58, 64-65.

D. Pitt (EX1006)

Pitt is an article titled “Ultrasonic Drug Delivery – A General Review.” EX1006, 1. Petitioner relies on Pitt for disclosures allegedly related to claim 9 and permeabilizing a cell by ultrasonication. Pet.58. As its title reflects, Pitt provides a “General Review” of using ultrasound to deliver therapeutic agents (including DNA, proteins, and small chemicals) into cells—but not into cell nuclei. EX1006, 6, 10, 12. Pitt states that the delivery of proteins is “usually much more complex” than small molecule drugs. EX1006, 10. The problem Pitt purports to address in connection with protein delivery is the “slow diffusion of proteins *through skin and polymeric depots*.” EX1006, 12. Pitt does not disclose permeabilizing a cell nucleus for protein delivery. EX1006, 10-11.

E. Adey (EX1009)

Adey is an article titled “Rapid, low-input, low-bias construction of shotgun fragment libraries by high-density *in vitro* transposition.” EX1009, 1. Petitioner relies on Adey for disclosures allegedly related to certain dependent claims requiring a second nucleic acid insert element. Pet.60-61. Unlike ’995, Adey

discloses an *in vitro* method of fragmenting isolated target DNA (as opposed to chromatin of a genome region). EX1009, 11-12 (“DNA was then isolated...”).

IV. Claim Construction

No terms require construction for considering institution. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). If a proceeding is instituted, 10x reserves the right to address the construction of certain terms in view of the specification and the embodiments described therein. For the purpose of this POPR, 10x has assumed the constructions explicitly set forth in the Petition. Pet.22-25.

V. Ground 1: Petitioner’s Anticipation Analysis Is Legally Deficient

Petitioner’s Ground 1 asserts anticipation of Claims 1, 3, 5-6, and 10-23 by Grunenwald. Pet.25.

Anticipation requires that a single reference disclose all elements of the asserted claims—*arranged as in the claims*—“without the need to pick and choose elements from different disclosures” within the same reference. *See Captioncall, LLC v. Ultratec, Inc.*, IPR2020-01215, Pap.6, 16-17 (Jan. 27, 2021); *BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391, 1400-01 (Fed. Cir. 2022); *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369, 1371 (Fed. Cir. 2008). But Petitioner has failed to show that Grunenwald discloses each and every limitation as arranged in

the claims, including, *e.g.*, “contacting chromatin of a genome region,” and thus cannot meet its burden as to *any* claim in Ground 1.

A. Petitioner Fails To Clearly Identify The “Biological Sample” In Grunenwald

To begin with, it is unclear what aspect of Grunenwald Petitioner maps to the claimed “biological sample.” Pet.25-26. It is unclear if Petitioner intended to map DNA, a cell, a cell nucleus, or something else to the “biological sample” limitation. Petitioner argues “Grunenwald discloses methods for analyzing a biological sample—specifically, by analyzing its DNA.” Pet.25. From this language, one might guess that Petitioner is equating the claimed “biological sample” to DNA in Grunenwald. However, Petitioner then asserts “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....’” Pet.26. Petitioner later relies specifically on “chromosomal DNA,” but nowhere identifies what the corresponding “biological sample” containing chromosomal DNA would be in Grunenwald. Pet.25-26, 30-33.

Petitioner asserts in connection with claim 3 (Pet.36) that its analysis of the preamble of claim 1 (Pet.25-26) establishes Grunenwald’s sample “is a cell or nucleus.” But Petitioner fails to identify any disclosure of Grunenwald indicating that any chromosomal DNA is *still in a cell* (as opposed to, *e.g.*, having already

been isolated from a cell) when Grunenwald's transposome composition allegedly contacts chromosomal DNA. Pet.30.⁴

Further, Petitioner elsewhere mixes and matches *in vitro* and *in vivo* embodiments in Grunenwald (*see infra*, §V.B.2.c), and Petitioner's quote referring to an "*in vivo* or *in vitro* source" (Pet.26) only compounds the issue. It also does not establish whether the "chromosomal DNA" Petitioner later relies on (Pet.30) comes from an *in vivo* or *in vitro* source, and Petitioner entirely fails to explain how "chromosomal DNA" referred to in Grunenwald could be "*isolated*" (Pet.30 (citing EX1003, ¶146)) yet *still in a cell*.

B. Petitioner Fails To Show Grunenwald Discloses "Contacting Chromatin Of A Genome Region"

The Petition's arguments regarding the "contacting chromatin of a genome region" limitation also lack sufficient clarity for institution. Pet.29-31.

Petitioner's citation to certain paragraphs of its expert's declaration only adds to the confusion, as those paragraphs do not consistently correspond to Petitioner's

⁴ Petitioner's claim 4 analysis (found in Ground 3) relies on its Ground 1 claim 3 analysis, and asserts the cell lysis of claim 4 would happen after the first step of claim 1. Pet.53. Petitioner's analysis of these dependent claims indicates its own belief that the chromatin would be inside an intact cell such that the cell would exist to be lysed after step 1 of Claim 1.

arguments. And even to the extent, *arguendo*, it is assumed Petitioner’s arguments might be understood, Petitioner’s conclusory assertions fail to establish either: (1) that Grunenwald ***expressly*** discloses contacting “chromatin of a genome region” (Pet.30), or (2) that this limitation is ***inherently*** disclosed (Pet.31-33). The cited paragraphs of Petitioner’s expert declaration (as well as its *mis*-cited and *un*-cited paragraphs, which might better correspond to Petitioner’s arguments) are similarly conclusory and entitled to no evidentiary weight, as Petitioner’s expert also fails to identify the factual underpinnings of his opinions. *See, e.g.*, EX1003, ¶¶137-146.

1. Petitioner’s *Express* Disclosure Theory Fails

(a) Contacting Chromatin

Petitioner begins by asserting “Grunenwald discloses that the insertional enzyme complex contacts ***nucleic acid...***” Pet.29.⁵ Petitioner then points to a

⁵ Petitioner identifies as support Figure 2, which shows a transposase inserting transposon ends into double stranded DNA “*In Vitro*,” but ***shows no chromatin or histones***. Pet.29; *cf.* EX1001, 12:54-60 (“The term ‘chromatin’ as used herein[] refers to a complex of molecules including proteins and polynucleotides (e.g., DNA, RNA), ***as found in a nucleus of a eukaryotic cell. Chromatin is composed in part of histone proteins*** that form nucleosomes, genomic DNA, and other DNA

single out-of-context recitation of “chromosomal DNA” in Grunenwald, but extracts and then contorts that single quote with ellipses to argue “Grunenwald expressly discloses that the target DNA contacted by the insertional enzyme complex may ‘comprise[] or consist[] of genomic DNA, subgenomic DNA, [or] ***chromosomal DNA***....’” Pet.30 (emphasis original) (citing EX1003, ¶146). After attempting to twist the *definition* of “target DNA” into an express disclosure of Grunenwald performing its method on chromatin, Petitioner then tries to bridge the gap between its evidence and the ’995 claim language, offering the conclusory (and ***mistaken***) assertion that “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.” Pet.30 (citing EX1002, ¶146).⁶ But Petitioner fails to support its string of

binding proteins (e.g., transcription factors) that are generally bound to the genomic DNA.”), 6:28-29 (contrasting “chromatin” with “naked genomic DNA”).

⁶ Petitioner relies only on Grunenwald’s reference to “chromosomal DNA” and not to references to “genomic DNA” or “subgenomic DNA” in arguing that Grunenwald somehow discloses contacting chromatin. Pet.30.

arguments—including the leap at the end—with supporting evidence,⁷ and cannot meet its burden for institution.

First, Petitioner’s quotation from Grunenwald about “chromosomal DNA” is heavily doctored. Pet.30. In the sentence just *before* the language Petitioner quotes, Grunenwald states “[i]n some embodiments, the ***target DNA comprises or consists of*** eukaryotic ***and/or prokaryotic*** dsDNA...” (EX1003, ¶146)—but, as Petitioner’s own references confirm, ***chromatin is not found in prokaryotes***. See EX2007, 4 (“**chromatin**”: “the complex of DNA and histone proteins that makes up the basic material of eukaryotic chromosomes.”) (underscore added, other emph. original); EX1041, 1 (describing the packaging of DNA in eukaryotic organisms “known as chromatin”); EX1036, 2-3 (contrasting the chromosome found in the nucleoid of prokaryotes with the chromatin found in a eukaryote’s nucleus).⁸ And even the sentence Petitioner *does* include in its quote does not

⁷ Mere assertions of a conclusion—whether or not from any expert—are not evidence, and cannot carry Petitioner’s burden. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15-16 (Aug. 24, 2022) (precedential).

⁸ See also EX2007, 5 (“**prokaryotes**”: “the Bacteria and the Archae collectively, unicellular microorganisms whose small simple cells lack a membrane-bounded nucleus, mitochondria, chloroplasts and other membrane-bounded organelles

make the specific connection Petitioner requires, starting with “***For example***....”

EX1003, ¶146. Petitioner never matches up the disclosure of “***chromosomal DNA***” to any particular Grunenwald embodiment on which it might rely—and certainly not ***to chromatin***. Pet.30. And Petitioner’s ellipsis in this “For example” sentence hides that Grunenwald explained “***chromosomal DNA***” comes, *e.g.*, “***from an isolated chromosome or a portion of a chromosome, e.g., from one or more genes or loci from a chromosome***....” EX1003, ¶146; *see also* EX1001, 6:28-29. Petitioner simply discards these words of Grunenwald entirely: Petitioner ***never addresses this language in the only Grunenwald sentence that even mentions “chromosomal DNA.”*** Pet.30. Not surprisingly, ***Grunenwald nowhere mentions “chromatin”*** (which, as defined by the ’995, is the complex of molecules including proteins and polynucleotides “as found in a nucleus of a eukaryotic cell” (EX1001, 12:54-60)) ***or “histones”*** (which, *e.g.*, the ’995 and Petitioner’s own cited dictionary confirm are a key part of chromatin (EX1001, 12:54-60 (“Chromatin is composed in part of histone proteins”); EX2007, 4); *supra*, n.5.

typical of plant, animal, fungal, protozoan or algal cells. Their DNA is usually in the form of a single circular molecule and is not complexed with histones.... *a. prokaryotic. cf. eukaryotes.*”) (underscore added, other emph. original).

Petitioner’s only cited support to make the leap critical to its argument—that “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*”—is Paragraph 146 of its declaration from Dr. Cooper. Pet.30 (citing EX1002, ¶146). But this cited Paragraph 146 does not explain why POSITA would have understood Grunenwald’s “chromosomal DNA” to mean chromatin in a eukaryote—it states only that “POSA would recognize that contacting chromosomal DNA or contacting DNA *in vivo* in a cell would require contacting a genome region.” EX1002, ¶146. Dr. Cooper’s conclusory assertion purports to be about a *different* limitation—the “genom[ic] region” limitation. It is unrelated to (and therefore *does not* provide support for) Petitioner’s assertion that “chromosomal DNA” “is chromatin” or that Grunenwald’s embodiments are contacting chromatin if the contacted nucleic acid is “chromosomal DNA.” Pet.30. Nor can Petitioner’s assertion that “Grunenwald’s methods were *applicable to* chromatin” (Pet.18), even if substantiated, establish anticipation.

To the extent, *arguendo*, Petitioner intended to cite Paragraph 139 of Dr. Cooper’s declaration rather than 146 (and to the extent, *arguendo*, ***uncited*** Paragraph 139 is even considered by the Board (the Petition provides no basis for doing so)), Petitioner still fails to meet its burden. *U.S. Well Servs., LLC v.*

Haliburton Energy Servs., Inc., IPR2022-01163, Pap.9, 12-17 (Dec. 20, 2022)

(denying institution where petitioner “improperly shift[ed] the burden of deciphering Petitioner’s arguments,” including by “fail[ing] to articulate with sufficient clarity how th[e] disclosures anticipate”); *U.S. v. Dunkel*, 927 F.2d 955, 956 (7th Cir. 1991) (“Judges are not like pigs, hunting for truffles buried in briefs.”). Paragraph 139 asserts “chromosomal DNA exists in the form of chromatin, and whether in a cell or isolated if... Grunenwald is being performed on chromosomal DNA it is being performed on chromatin.” EX1002, ¶139.

First, Dr. Cooper’s conclusory assertion *never says* the disclosure of “chromosomal DNA” in Grunenwald would be understood to mean *chromatin* (which is a “highly condensed form of DNA *with histone proteins*” (EX1041, 2)), and thus adds nothing to Petitioner’s conclusory assertion and is insufficient support for Petitioner’s assertion that “chromosomal DNA *is* chromatin, and so in embodiments wherein the contacted nucleic acid is chromosomal DNA, chromatin is contacted with the insertional enzyme complex.” Pet.30; *Xerox*, IPR2022-00624, Pap.9, 15-16; §42.65(a). Indeed, Petitioner’s expert ignores that chromosomal DNA includes, for example, prokaryotic chromosomal DNA, and that DNA in prokaryotes is *not* packed with proteins and other polynucleotides into chromatin. EX1036, 2; EX2007, 4-5.

Second, even if, *arguendo*, Dr. Cooper’s assertion supported Petitioner’s contention that “chromosomal DNA is chromatin” (it doesn’t), it should be given no weight: it is conclusory and lacks the required disclosure of underlying factual support for the opinions. *Xerox*, IPR2022-00624, Pap.9, 15-16 (denying institution and according petitioner’s expert “little weight” where the expert’s declaration was conclusory and failed to “cite to any additional supporting evidence or provide any technical reasoning to support his statement”); *Motorola Mobility LLC v. Maxell, Ltd.*, IPR2023-00110, Pap.7, 34-35 (June 15, 2023) (finding cited declaration testimony was “conclusory, unsupported, and entitled to little or no weight” where it did not provide “any additional supporting evidence or technical reasoning”).

Third, Dr. Cooper refers to chromatin “*in a cell*” (EX1002, ¶139), but cites *no disclosure of* any method of Grunenwald being used on “chromosomal DNA” “in a cell”—let alone in a *eukaryotic* cell (which is the only kind of cell that would have chromatin (EX1036, 2; EX2007, 4-5; EX1041, 1)). In fact, as discussed above, the only disclosure of “chromosomal DNA” in Grunenwald is a single disclosure that refers to it being “*isolated*.” EX1003, ¶146.

Fourth, with respect to Dr. Cooper’s reference to “isolated” “chromosomal DNA,” Petitioner’s expert fails to explain (or provide support for) why or how (particularly in the absence of any discussion in Grunenwald of histones or chromatin) POSITA would have understood the disclosure of isolated

“chromosomal DNA” to instead mean *chromatin* as opposed to naked DNA.

Pet.30; EX1002, ¶139. Dr. Cooper also never explains how his reliance on “isolated” chromosomal DNA (*i.e.*, DNA *not* in a cell (EX1002, ¶139 (“whether in a cell *or isolated*”))) is consistent with Petitioner’s argument elsewhere that the claimed “biological sample” in Grunenwald *is a cell* (Pet.36 (claim 3); 51 (claim 4); *see also supra*, §V.A; *infra*, pp.40-42)).

To the extent Petitioner assumes that any *in vitro* chromosomal DNA is still *inside an intact cell (and an intact cell nucleus)*, Petitioner has failed to establish that is what Grunenwald discloses or that POSITA would have understood “*in vitro*” in Grunenwald to mean anything other than isolated components of a cell (*e.g.*, a cell-free extract). At best, Petitioner points to a generic disclosure of DNA in Grunenwald and a comment that the DNA “may be *derived*” from an *in vivo* or *in vitro* source (Pet.26), **not** that Grunenwald’s “transposome composition” contacts chromosomal DNA *while the DNA is in a cell*, let alone that it contacts chromatin inside a cell nucleus. Nor does Petitioner address how chromosomal DNA could be “isolated” and yet still be inside a cell nucleus. EX1003, ¶146; Pet.30. Curiously, while Petitioner asserts DNA would be extracted from a cell and isolated prior to sequencing (Pet.53), Petitioner does not identify any reference in Grunenwald to lysing the cell after the transposome composition contacts DNA and before DNA sequencing. Pet.53. And, as addressed above (*supra*, p.22),

Petitioner ignores Grunenwald’s reference to “chromosomal DNA” being “isolated.” EX1003, ¶146.

(b) “Of a Genome Region”

Petitioner does not even attempt to identify any disclosure *in Grunenwald* that Petitioner alleges teaches this limitation. Pet.30. Indeed, in asserting Grunenwald discloses “contacting chromatin of a genome region,” Petitioner’s only mention of a “genome region” in arguing express disclosure is simply a quote *from the claim language itself*. Pet.30. Petitioner asserts (erroneously) that “chromosomal DNA” is chromatin, but does not even assert, let alone establish, that “chromosomal DNA” is chromatin *of a genome region*.

To the extent Petitioner seeks to rely on Paragraph 146 of Dr. Cooper’s declaration, that paragraph—which would be improperly incorporated by reference (given Petitioner’s failure to provide any analysis in the Petition about express disclosure of “genomic region”)—fails to cite any support from Grunenwald for its assertions, and, *at best*, it provides an inadequate and conclusory *inherency* opinion (which also fails, as discussed below). *Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Pap.12, 9-10 (Aug. 29, 2014) (informative) (denying institution and refusing to consider improperly incorporated expert arguments where the “Petition includes citations to the Declaration to support conclusory statements for

which the Petition does not otherwise provide an argument or explanation”);

Xerox, IPR2022-00624, Pap.9, 15-16.

Dr. Cooper’s Paragraph 146 also refers to an (uncited and alleged) *in vivo* disclosure in Grunenwald, but Petitioner’s express disclosure theory elsewhere relies on *in vitro* disclosures. For example, the Petition asserts that “Grunenwald discloses that the insertional enzyme complex contacts nucleic acid ‘to produce tagged nucleic acid molecules.’” Pet.29. Petitioner points to Figure 2 as “showcas[ing] the disclosure of the limitation.” Pet.29. But Figure 2 makes no mention of “a genome region” and is explicitly about *in vitro* transposition, as it is titled “Fragmenting by *In Vitro* Transposition.” Pet.30 (citing EX1003, Fig.2). Petitioner cannot meet its burden for anticipation by improperly mixing and matching across different embodiments within Grunenwald. *See infra*, V.B.2.c; *Captioncall*, IPR2020-01215, Pap.6, 16-17; *Net MoneyIN*, 545 F.3d at 1369, 1371.

2. Petitioner Has Not Established Inherency

(a) Contacting Chromatin

Petitioner’s inherency theory also fails because it does not present “persuasive technical reasoning to explain” that a limitation would *necessarily* be met. *See, e.g., Albaad Massuot Yitzhak, Ltd. v. Edgewell Pers. Care Brands, LLC*, IPR2017-00693, Pap.11, 9-10 (July 17, 2017). A conclusory assertion of inherency is not entitled to any weight. *Id.* Further, inherency may not be

established by “*probabilities or possibilities.*” *See, e.g., Crown Operations Int’l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377 (Fed. Cir. 2002) (citing *Cont’l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991)); *see also Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Pap.91, 35-41 (May 7, 2021) (finding no inherency where the necessary salt “does not form ‘*every time*’” and explaining the “inherent result must inevitably result from the disclosed steps”); *ESET, LLC v. Finjan, Inc.*, IPR2017-01738, Pap.57, 37-39 (Jan. 24, 2019) (finding no inherency where evidence was that limitation “*might*” have been present); *Pungkuk Wire Mfg. Co. v. Seong, Ki Chul*, IPR2016-00763, Pap.70, 8-10 (Aug. 16, 2017) (finding no inherency where evidence only established “it is *nearly* impossible” to practice claim without causing the necessary result); *Galderma Lab’ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App’x 838, 845-46 (Fed. Cir. 2020) (nonprecedential) (reversing anticipation where efficacy limitations were not inherent because art did not disclose the specific formulation and varying the factors in the disclosed formulations would lead to some formulations lacking the claimed efficacy limitations). “The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *Crown Operations*, 289 F.3d at 1377. Here, Petitioner’s conclusory assertions of inherency cannot meet its burden.

As an initial matter, the foundation of Petitioner’s inherency argument for “contacting chromatin” is based on its assertion that Grunenwald’s methods “*can be applied to chromosomal DNA in vivo....*” Pet.31.⁹ But, Petitioner points to ***no disclosure*** in Grunenwald’s various embodiments ***of actually applying*** any of Grunenwald’s methods to chromosomal DNA *in vivo*. See Pet.31-33. And, an assertion that a method described in a reference “***can***” be applied in a certain context is different from the reference disclosing the method ***actually being applied*** to a certain context in that reference. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 960 (Fed. Cir. 2014) (affirming finding of no anticipation for failing to show application of bimatoprost to skin was inherently present in reference where the evidence only showed that “application of eyedrops containing bimatoprost ***can*** result in the promotion of eyelash hair” and that application of the eyedrops “***may*** contact skin”) (emphases original); *Crown Operations*, 289 F.3d at 1377 (“The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient.”). Without establishing that Grunenwald actually teaches applying its methods to chromosomal DNA *in vivo*, the foundation for Petitioner’s argument about the inherency of chromatin fails. *Albaad Massuot*, IPR2017-00693, Pap.11,

⁹ Petitioner does not assert inherency based on any disclosure in Grunenwald applied to chromosomal DNA *in vitro*. See Pet.30-33.

9-10 (denying institution, noting petitioner must present “persuasive technical reasoning to explain” that a limitation must “necessarily” be present).

Further, even if, *arguendo*, Petitioner *had* established Grunenwald discloses its transposome composition (which Petitioner maps to the claimed insertional enzyme complex) contacting chromosomal DNA *in vivo*, Petitioner fails to even argue, let alone establish, that Grunenwald discloses its transposome composition contacting *eukaryotic* chromosomal DNA *in vivo* (as opposed to, *e.g.*, *prokaryotic* chromosomal DNA, as discussed above). As Petitioner’s own exhibit admits, *there is no chromatin in prokaryotes* (EX1041, 1; EX2007, 4-5)—thus, Petitioner cannot show Grunenwald *necessarily* discloses contacting *chromatin*, and its inherency argument fails.

Petitioner’s block quote referring to “some embodiments” and “target DNA” (Pet.31) only confirms that it cannot meet the high bar for inherency. Petitioner’s quote starts by suggesting the invention can be carried out *in vivo* “[i]n *some* embodiments.” Pet.31 (citing EX1003, ¶157). Grunenwald’s only mention of *chromosomal* DNA is not in the “*in vivo*” paragraph, but in an earlier paragraph of Grunenwald that defines “target DNA” broadly, and mentions many different kinds of DNA, including chromosomal DNA in the context of *isolated* chromosomal DNA, not *in vivo* chromosomal DNA, and not DNA specific to, let alone limited to, eukaryotes. EX1003, ¶146; *see also* EX1001, 6:28-29. Thus, Petitioner has not

established, and cannot establish, that “some embodiments” in Grunenwald’s Paragraph 157 necessarily includes *in vivo eukaryotic chromosomal DNA*. Pet.31-32. Petitioner also tellingly ignores that the patent referenced at the end of its block quote from Grunenwald is focused on *prokaryotes* (with *no chromatin*). *E.g.*, EX1045, 3:50-55; EX1036, 3-4; *Gilead Scis., Inc. v. Regents of the Univ. of Minn.*, IPR2017-01753, Pap.42, 25 (Apr. 22, 2020); *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965) (explaining it is “impermissible within... [the] 103 [framework] to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to [POSITA].”); *CSL Behring LLC v. Bioverative Therapeutics Inc.*, IPR2018-01313, Pap.10, 25-27 (Jan. 9, 2019) (“*CSL*”); *Bioeq IP AG v. Genentech, Inc.*, IPR2016-01608, Pap.11, 12-14 (Feb. 22, 2017) (denying institution where petitioner failed to address competing effect in reference).

And finally, Petitioner points to a Grunenwald disclosure about inserting the “transposon end” by electroporating a complex “into the host cell.” Pet.31 (citing EX1003, ¶157). But chromatin, while found only in eukaryotic cells, is not simply found “in the host cell” (Pet.31), but *in the cell’s nucleus specifically*. EX1036, 2. And the nucleus is separated from the other components by the “nuclear envelope, which consists of a double layer of membrane” and keeps enzymes in the nucleus

and cytoplasm separate. EX2008, 10, 34-35. Petitioner does not assert, let alone establish, that Grunenwald necessarily electroporates the *cell nucleus*. Pet.31-33. Thus, even if a complex were electroporated into the *cell*, it would not necessarily enter the *nucleus*. EX2008, 10, 34-35. (Other types of target DNA *are* found in the host cell, but outside the nucleus. For example, Grunenwald includes “mitochondrial DNA” and “chloroplast DNA” as examples of “target DNA.” EX1003, ¶146. Both are found in eukaryotic cells, and *both are located outside the nucleus—but neither of these is chromatin*. EX1003, ¶146; EX1036, 3; EX1041, 1; EX2008, 21-23, 27, 29; *See also* EX2007, 5 (“**prokaryotes**”: “the Bacteria and the Archae collectively, unicellular microorganisms whose small simple cells lack a membrane-bounded nucleus, mitochondria, chloroplasts and other membrane-bounded organelles typical of plant, animal, fungal, protozoan or algal cells. Their DNA is usually in the form of a single circular molecule and is not complexed with histones.... a. **prokaryotic. cf. eukaryotes.**”) (underscore added, other emph. original).

Petitioner also does not address whether the transposase that contacts the chromatin is necessarily one that does not “comprise an antibody specific to a protein that is part of said chromatin”; instead, Petitioner addresses that limitation separately, without connecting it to the context of the rest of the claim. Pet.33-35. But the claim plainly requires that the transposase that contacts the chromatin be a

transposase with particular characteristics, and Petitioner fails to show the argued transposase used in Grunenwald's alleged *in vivo* embodiment is necessarily one that is not "specific to a protein that is part of said chromatin." Pet.30-33; EX1001, claim 1 (43:25-40). Indeed, Grunenwald defines "transposase" to include **any** transposase, thus including those that comprise antibodies that **are** specific to a protein that is part of said chromatin. EX1003, ¶93. Petitioner fails to address any of these issues and cannot establish inherency.

(b) "Of a Genome Region"

Petitioner's only mentions of a "genome region" in the inherent disclosure portion of its Petition are unexplained afterthoughts. Pet.31, 33. Petitioner asserts that, "[b]ecause 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...." Pet.31 (citing EX1002, ¶¶147-149). To the extent Petitioner's theory can be understood at all, Petitioner makes a **double** inherency argument, jumping from arguing the inherency of chromatin (which fails, as discussed above, (*supra* §V.B.2.a)) to arguing the inherency of genomic DNA (which it says "is necessarily part of the chromatin"). Pet.31. But Petitioner does not assert, let alone establish, that Grunenwald's transposome composition, which it elsewhere maps to the claim's "insertional enzyme complex," would *necessarily* contact the "genomic

DNA”; nor does Petitioner assert, let alone explain how, disclosure of “genomic DNA” would disclose “chromatin *of a genome region*.” The cited paragraphs of Petitioner’s expert report (Pet.31 (citing EX1002, ¶¶147-149)) do not provide any further explanation, and are, in fact, directed to a different limitation (“to produce tagged nucleic molecules”). Further, Petitioner elsewhere asserts it is Grunenwald’s “***chromosomal*** DNA” that is the DNA of interest and that somehow discloses “chromatin,” but here, without explanation, jumps to some sort of “***genomic*** DNA” inherency argument in attempt to cover “genome region.” Compare Pet.31 (“genomic DNA”) with Pet.30 (“chromosomal DNA is chromatin”). Petitioner cannot mix and match embodiments in arguing anticipation. See *infra*, §V.B.2.c.

To the extent Petitioner seeks to rely on Paragraph 146 of Dr. Cooper’s declaration, that paragraph is not cited in support of any inherency argument for “genome region” in the Petition (Pet.31-33), and any intended reliance on that paragraph by Petitioner is certainly not clear from its exceedingly confusing argument regarding the “contacting chromatin of a genome region” limitation. In any case, the single conclusory sentence from Dr. Cooper in that paragraph is devoid of any identification of underlying factual support and cannot meet the high burden for inherency. EX1002, ¶146 (merely asserting, without evidence, the conclusion that “A POSA would recognize that contacting chromosomal DNA or

contacting DNA *in vivo* in a cell would require contacting a genome region.”); *Xerox*, IPR2022-00624, Pap.9, 15-16. Indeed, Petitioner’s expert provides no explanation as to why contacting chromosomal DNA would *necessarily* mean contacting a genome region. And, it is not clear what kind of DNA is meant by Dr. Cooper’s generic reference to “contacting DNA *in vivo*,” nor how it would be relevant to the analysis.

(c) Mixing and Matching Embodiments

Despite Petitioner’s reliance on “*in vivo*” transposition in attempting to establish that Grunenwald’s transposome complex inherently contacts chromosomal DNA (Pet.31-33), Petitioner relies on separate *in vitro* disclosures throughout its mapping (and therefore improperly mixes and matches embodiments). *E.g.*, Pet.27 (citing EX1003, ¶161 (“All of the embodiments... herein use an *in vitro* transposition reaction...”)); Pet.29 (citing EX1003, Figure 2 (titled “Fragmenting by *In Vitro* Transposition”)). This cannot demonstrate anticipation, which requires that a single reference disclose all elements of the asserted claims arranged as in the claims “without the need to pick and choose elements from different disclosures” within that same reference. *See Captioncall*, IPR2020-01215, Pap.6, 16-17; *BlephEx*, 24 F.4th at 1400-01. For this additional reason, Petitioner’s Ground 1 fails.

Petitioner’s inherency argument for “contacting chromatin” is premised on Grunenwald “disclos[ing] that its methods of using an insertional enzyme complex to tag and fragment DNA can be applied to chromosomal DNA *in vivo*....” Pet.31. But Petitioner’s arguments about Grunenwald disclosing, *e.g.*, the “insertional enzyme complex” rely on *in vitro* disclosures. *See* Pet.27 (citing EX1003, ¶161 (“All of the embodiments... herein use an *in vitro* transposition reaction...”)); Pet.29 (citing EX1003, Figure 2 (titled “Fragmenting by *In Vitro* Transposition”)). Petitioner’s mixing and matching of alleged disclosures about *in vivo* and *in vitro* transposition is improper and cannot satisfy its burden. *Net MoneyIN*, 545 F.3d at 1369-71 (“it is not enough that the prior art reference... includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention”); *Apple Inc. v. Argina Tech. Ltd.*, IPR2023-00453, Pap.7, 41 (June 14, 2023) (denying institution where petitioner “attempt[ed] to demonstrate anticipation by combining parts of separate embodiments”); *Fujian Sanan Grp. Co. v. Epistar Corp.*, IPR2018-00971, Pap.9, 8-11 (Nov. 20, 2018) (denying institution where petitioner “relies on distinct teachings from different embodiments in [the reference] and does not direct us to disclosure in [the reference] of arranging these distinct teachings from different embodiments in the same way [the] claims... require.”); *CaptionCall*, IPR2020-01215, Pap.6, 16-17

(“[a]nticipation requires all elements arranged as in the claim *without the need to pick and choose elements from different disclosures...*”) (citations omitted).

VI. Grounds 2-8: Petitioner’s Obviousness Analyses Are Flawed And Cannot Support A Finding Of Obviousness

Grounds 2-8 depend entirely on Grunenwald disclosing “an insertional enzyme complex [that] does not comprise an antibody specific to a protein that is part of said chromatin,” and that contacts “chromatin of a genome region.”¹⁰ Pet.46-65. Petitioner cannot meet its burden as to Grounds 2-8 for the same reasons Petitioner cannot meet its burden for Ground 1 in addition to the issues identified below. *Supra*, §V.¹¹

¹⁰ Petitioner asserts that Grounds 6-8 are necessary “[t]o the extent Patent Owner contends that... Grunenwald’s disclosure of electroporation fails to inherently lead to permeabilization of cells so as to contact chromatin and produce tagged nucleic acid molecules...” Pet.65. Even if, *arguendo*, Okino’s permeabilization technique was used, Petitioner has not addressed Grunenwald’s other deficiencies (*supra*, §V), and thus these Grounds fail.

¹¹ While Ground 6 purports to address a gap in Ground 1, Petitioner fails to explain how Grunenwald would be modified or why, and fails to provide any arguments regarding reasonable expectation of success. Pet.65.

A. Petitioner Fails to Assert—Let Alone Prove—Its References are Analogous Art to the '995

Nowhere does Petitioner assert—let alone attempt to provide analysis to establish—that any of its references named in its grounds (Grunenwald, O’Geen, Okino, Pitt, and Adey) are analogous art *to the '995*; instead, Petitioner simply suggests they are analogous *to its cited Grunenwald reference*. Pet.49, 53, 55, 59, 63, 64-65. But a petitioner *cannot meet its burden* when it “argue[s] that [the prior art reference] is analogous to another prior art reference *and not the challenged patent*.” *Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373, 1374 (Fed. Cir. 2023). “[A] patent challenger *must compare the reference to the challenged patent*.” *Id.* Petitioner failed to perform this required analogous art analysis by failing to address whether its relied-upon art is analogous *to the challenged '995*; Petitioner only asserts that O’Geen, Okino, Pitt, and Adey (Petitioner’s secondary obviousness references), are analogous *to Grunenwald* (its primary obviousness reference). Pet.49, 53, 55, 59, 63, 64-65. Thus, because Petitioner’s Grounds 2-8 rely entirely on obviousness, and Petitioner was therefore *required* but *failed* to establish that its obviousness art is analogous to the challenged '995 as a threshold issue, Grounds 2-8 must each be rejected as Petitioner cannot meet its burden to establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.4th at 1380.

B. Petitioner’s Motivation To Combine And Reasonable Expectation Of Success Analyses Are Conclusory

Petitioner’s “arguments” that POSITA would be motivated to combine its various references, and have a reasonable expectation success in doing so, are entirely conclusory for each of its Grounds 2-8, and therefore fail. *Salpeter v. ARP Wave, LLC*, IPR2019-01384, Pap.12, 16-17 (Jan. 27, 2020) (denying institution and stating “[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements”) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)); *Health Care Logistics, Inc. v. Kit Check, Inc.*, IPR2019-00385, Pap.7, 14-15 (June 3, 2019) (denying institution and noting “[i]n the absence of a persuasive rationale supporting the asserted combination of prior art, it is insufficient for Petitioner to merely use [the claims] as templates to piece together the teachings of the prior art so that the claims are rendered obvious.”); *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning based on evidence of record, to support the legal conclusion of obviousness.”).

For example, Petitioner’s **Ground 3**, motivation to combine argument for Claim 4 (a claim which depends from claim 3 and requires lysing the cell or cell nucleus) appears to be that POSITA “would be aware of the need to extract and isolate that [tagmented] DNA prior to sequencing.” Pet.53. Petitioner asserts

POSITA therefore would have found it obvious to lyse the cells after the transposome composition allegedly contacts chromosomal DNA and before sequencing the DNA because it “was one well-known, routine and commonly-used method.” Pet.53. But this two-sentence explanation is too conclusory to meet Petitioner’s burden. Petitioner does not address, for example, how Petitioner’s citations to Grunenwald’s alleged *in vitro* methods for the transposome composition contacting chromosomal DNA could be combined with post-tagmentation cell lysis. Indeed, Petitioner fails to establish (including for Claim 3 of Ground 1 (Pet.36 (citing Section IX.A.1.a)), from which this theory depends) that the alleged contacting of the chromosomal DNA even happens *inside a cell*. Thus, Petitioner failed to establish that there is a cell (let alone a eukaryotic cell with chromatin in the nucleus) *that can subsequently be lysed*. See *supra*, §V.A, V.B. To the extent Petitioner intended to advance only an *in vivo* theory for Grunenwald and claim 1, Petitioner failed to say so, and 10x should not be forced to guess as to Petitioner’s theory. *U.S. Well Servs.*, IPR2022-01163, Pap.9, 12-17.¹²

¹² In Ground 4, unlike Ground 3 (and Grounds 2 and 5-8), Petitioner specifies the ground relates only to “Grunenwald’s *in vivo* embodiment” (whatever that is). Pet.59.

Ground 3's sparse analysis is also the entirety of the evidence Petitioner relied on for its **Grounds 6-8** (Pet.64-65), which thus fails for at least the same reasons. Even more significantly, the Ground 3 analysis Petitioner cites is directed to lysing a cell *after* tagmentation and before sequencing. Pet.65 (citing Pet. Part IX.C.1.a-b (addressing Ground 3 claim 4)). **Grounds 6-8** purport to differ from Grounds 1, 2, and 5 only with respect to Okino's alleged disclosure of permeabilization. But Petitioner does not explain how its Ground 6-8 arguments, which assert the obviousness of permeabilizing the cell *before* tagmentation, can be supported simply by pointing to Ground 3 arguments about motivation to combine and reasonable expectation of success regarding *lysing cells after* tagmentation. Pet.65 (citing Pet. Part IX.C.1.a-b). Additionally, Petitioner does not address why POSITA would have modified Grunenwald to add permeabilization of cells. Furthermore, Petitioner's **Grounds 6-8** refer only to "permeabilization of cells" generally, and not permeabilizing the nucleus. Pet.64-65. Petitioner never addresses how Grunenwald's transposome composition (which is not mentioned in Okino) would enter the cell nucleus even assuming that the cell wall itself was permeabilized as in Okino, and that the transposome composition got past the cell membrane and into the cytoplasm (where chromatin *is not found*). Pet.65. Nor does Petitioner address how or why POSITA would have expected its unspecified "transposome composition" would *work* on

chromatin in the nucleus (even if it somehow got into the nucleus, which would be required in order for the transposome composition to contact any chromatin).

Pet.64-65 (citing Pet. Part IX.C.1.a-b); EX1001, 43:27-32.

Similar to Grounds 6-8, **Ground 4** (addressing claim 9) adds a limitation related to permeabilizing, but Petitioner again does not address how Grunenwald's transposome composition (which is not mentioned in Okino) would be able to enter the cell *nucleus* (where the chromatin is located) when the cell is permeabilized in the manner Petitioner argues. Pet.58-59. Further, while Petitioner seems to argue that the claimed permeabilization would be used to transport the transposome composition into the cell (Pet.58), Petitioner then argues, as part of what may be its motivation to combine argument, about the need to "extract and isolate that DNA" and then refers to transporting proteins across cell membranes. Pet.59. It is unclear from the Petition how Petitioner proposes modifying Grunenwald with Pitt, and whether Petitioner contends the permeabilization would be used to transport the transposome composition into the cell body, *or* whether Petitioner is somehow asserting (without saying so) that permeabilization relates to extracting and isolating DNA, *or* whether Petitioner is arguing both. Pet.59.

Ground 2 is also deficient. Petitioner purportedly relies on O'Geen to address claim 2's requirement of "generating a representation of epigenetic

features of said genome region at least in part by mapping said sequence information to said genome region.” Pet.46. Petitioner asserts that, “[r]ather than using immunoprecipitation and sonication as taught by O’Geen to fragment and tag chromatin, Grunenwald uses the method of tagmentation described above.”

Pet.49. But Petitioner does not explain how Grunenwald would modify O’Geen (or vice versa, depending on which reference is the base. For example, Petitioner does not explain what steps of Grunenwald would replace which steps of O’Geen’s method to end up with the invention of claim 2, or why a simple swap of certain steps would be compatible. Pet.46-51. Furthermore, **Ground 7**, which purports to modify Ground 2 (Pet.64-65), seemingly identifies Grunenwald as Ground 7’s base (not O’Geen) (Pet.6, 46) (*infra*, §VI.C).

And, for **Ground 5**, Petitioner merely argues that “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.” Pet.64. But Petitioner does not address what benefit the Nextera™ kit would provide, or any other reason POSITA would have been motivated to implement Adey’s tagmentation method with Grunenwald.

Pet.64. Petitioner’s argument is no more than POSITA *could* have used Adey’s Nextera™ kit with Grunenwald, but that does not establish POSITA *would* have been motivated to do so. *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir.

2020) (“The obviousness inquiry does not merely ask whether a skilled artisan *could* combine the references, but instead asks whether ‘they *would have been motivated* to do so.’”). Further, Adey purports to be about “*in vitro* transposition” (EX1009, 1). Petitioner has not addressed why or how POSITA would combine the alleged *in vivo* disclosures of Grunenwald with an *in vitro* reference like Adey.

In sum, Petitioner cannot meet its burden with respect to motivation to combine and reasonable expectation of success for the obviousness grounds.

C. Ground 2: Petitioner’s Obviousness Analyses Lacks The Requisite Particularity For Additional Reasons

Petitions must identify “with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim.” §312(a)(3). Ground 2 fails to meet this requirement, as Petitioner identifies **Grunenwald** as the primary reference when listing its “identification of challenge” listing (Pet.5-6), but in the body of the Petition Petitioner describes Ground 2 as “**O’Geen** in view of Grunenwald” (Pet.iv, 46) and argues POSITA “would have had a reason to modify **O’Geen**” (Pet. 50). *Scanstrut, Inc. v. Nat’l Prods., Inc.*, IPR2020-01542, Pap.7, 10-12 (Mar. 16, 2021) (denying institution for lack of particularity where petitioner’s “Identification of Challenges” listed two grounds, but the petition included a heading with a third ground). The Ground 2 argument proceeds with listing O’Geen first and Grunenwald second (Pet.46), but later lists Grunenwald

first (Pet.48) (“Grunenwald and O’Geen”). To add to this confusion, Ground 7, which purports to modify Ground 2, identifies **Grunenwald** as the base reference. Pet.6.

Petitioner’s analysis of the obviousness grounds does not provide sufficient clarification to remedy this failure. For example, Petitioner argues it would have been obvious “to *combine* O’Geen’s methods... with Grunenwald,” but it is not clear from Petitioner’s analysis whether it proposes to modify O’Geen’s method or Grunenwald’s. Pet.49; *Elk Engineering SDN. BHD. v. Wilco Marsh Buggies & Draglines, Inc.*, IPR2020-00344, Pap.7, 12-16 (June 23, 2020) (rehearing denied) (denying institution for lack of particularity where petitioner’s grounds included three references without showing how two of the references would be combined with the third). Petitioner’s motivation to combine arguments also lack particularity regarding what aspects of the base reference would be modified by what teachings of the secondary reference, and its reasonable expectation of success arguments are, at best, conclusory. Pet.46-50; *supra*, §VI.B. Thus, Petitioner has failed to carry its burden by failing to be clear about what its obviousness argument actually *is*. *ADT LLC v. Vivint, Inc.*, IPR2022-00634, Pap.7, 13-15 (Oct. 4, 2022) (denying institution where one of petitioner’s grounds lacked particularity and petitioner failed to explain the interplay between its two

references noting, if IPR were instituted, lack of particularity would prejudice owner); §312(a)(3).

Further, in these circumstances instituting trial would impose an improper burden and a clear denial of due process on 10x, which would be forced to defend against a “nose of wax” Petitioner might attempt to bend one way or the other as trial proceeds: as 10x defeats one argument, Petitioner will certainly claim to have made the other. *ADT*, IPR2022-00634, Pap.7, 13-15; *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 296 (2016) (Alito J., concurring in part) (If a petition fails to state its challenge with particularity... the patent owner is forced to shoot into the dark. The potential for unfairness is obvious.”).

VII. Institution Should Be Denied Under 35 U.S.C. §325(d)

This Petition, which simply rehashes art that was before the Examiner, along with secondary references merely cumulative of that art, without showing Examiner error is precisely the sort of wasteful do-over the *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH* (IPR2019-01469, Pap.6, 8-9 (Feb. 13, 2020) (precedential) (“*AB*”)) framework was intended to prevent. Both parts of the *AB* framework point to denial.

As to *AB* part one, Petitioner’s central reference, **Grunenwald**—the sole reference for Ground 1, and on which all of Petitioner’s other Grounds depend (*see supra*, n.3)—was not only *cited to the Examiner* during ’995’s prosecution (it is

listed on the face of '995) (EX1001, 1; EX1007, 97 (IDS); Pet.66), but was also *explicitly cited twice in the as-filed specification that the Office examined*—including in a passage affirmatively *incorporating Grunenwald by reference* for its teachings of a prior art system that, *inter alia*, “fragment[s] and add[s] adaptors to the polynucleotides.” EX1001, 13:19-26, 14:31-36; EX1007, 24 (17:16-20), 25-26 (18:33-19:2). Additionally, Grunenwald was introduced by applicant in the first IDS filed in '995's parent application (before the same Examiner as '995) (EX2001, 295); and the patent into which Grunenwald matured, U.S. Patent 9,080,211, was *also* of record in both '995's and its parent's prosecution. EX1001, 1; EX1007, 97; EX2001, 401; EX2003; *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Pap.8, 22-23 (Dec. 15, 2017) (precedential as to §III.C.5, first paragraph) (“*Becton*”); *see Motorola Mobility LLC v. Maxell, Ltd.*, IPR2022-01287, Pap.11, 16 n.8 (Feb. 2, 2023). Of Petitioner's four other secondary¹³ references, Petitioner acknowledges two were similarly before the Examiner (Pet.66)—and Petitioner fails to show that the last two are anything other than cumulative of art that was. Indeed, Petitioner's failure to conduct *any* analysis of whether its art was cumulative is, by itself, fatal under *AB* part one.

¹³ *See supra*, §VI.C.

And as to *AB* part two, Petitioner further fails to show *any* Examiner error, let alone a material one. Petitioner’s only allegation is that the Examiner erred “by not considering the relevant teachings in Grunenwald, Okino, and Adey,” arguing the Examiner “did not discuss or cite any passage or disclosure” from these three references. Pet.67. But this is essentially a complaint that the Examiner failed to make rejections after considering this art, and such “silence” by the Examiner does not constitute the required material “error” under *AB* part two. *Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01533, Pap.14, 19 (Mar. 27, 2023); *Microsoft Corp. v. AlmondNet, Inc.*, IPR2022-01319, Pap.9, 11 (Jan. 30, 2023) (exercising §325(d) discretion where the art was before the Examiner, there was no evidence it was concealed, and the petitioner’s only argument of error was “the prior art references in the Petition ‘were not substantively considered during [prosecution]’”). And Petitioner fails to assert, let alone explain, why the Examiner’s conclusion as to patentability would have differed based on these additional cumulative references. Pet.67-68; *Becton*, 22-23; *see Motorola*, IPR2022-01287, Pap.11, 16 n.8.

Revisiting the same or substantially the same previously-considered art and arguments already overcome during prosecution without any showing of material error—simply because Petitioner wishes for a different outcome—is a waste of the Board’s limited resources and unfairly burdens 10x.

A. Advanced Bionics Part One Favors Denial

AB part one considers whether the same or “substantially the same” art or arguments “previously were presented to the Office.” *AB*, 8. The *Becton* Factors relevant to *AB*’s part one inquiry include: “(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination;” and “(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art.” *AB*, 9 n.10, 10; *see also Becton*, 17-18.

First, Petitioner’s Ground 1 is anticipation by **Grunenwald**, and Grunenwald is also central to every *other* Ground urged by Petitioner. Pet.25. But Petitioner concedes that “Applicant identified Grunenwald,” that “Grunenwald [is] mentioned in the specification of the ’995 Patent,” and that “the Examiner indicated that the IDS, which identified Grunenwald, was acknowledged and considered.” Pet.66, 15. But as noted above, while this is enough to confirm Grunenwald is “previously presented art” for purposes of *AB* part one, Petitioner’s description is a significant understatement: Grunenwald was affirmatively ***incorporated by reference*** into the ’995’s specification for its teachings of a system employing an “insertional enzyme complex,” including, *e.g.*, “an insertional enzyme and two adaptor molecules (the ‘transposon tags’) that are

combined with polynucleotides to fragment and add adaptors to the polynucleotides.” EX1001, 13:19-26 (“Such a system is described in a variety of publications, including... US20100120098 [Grunenwald]... which [is] incorporated by reference herein”). Moreover, Grunenwald was before the same Examiner during the entire prosecution of ’995’s parent application. EX2001, 295. Additionally, Petitioner’s Grunenwald reference matured into U.S. Patent No. 9,080,211 (EX2003), which was also of record in both prosecutions. EX1007, 97 (“9080211... Grunenwald”); EX2001, 401.

Nothing more is required under *AB* part one for Grunenwald—or for **Okino** and **Adey**, which Petitioner concedes were also before the Examiner in ’995’s prosecution. Pet.66 (“Applicant identified...Okino”; “Adey [is] mentioned in the specification”); EX2001, 388 (Adey also cited in IDS in ’995’s parent); *Agrinomix, LLC v. Mitchell Ellis Prods., Inc.*, IPR2017-00525, Pap.8, 10-11 (June 14, 2017) (denying institution under §325(d) where prior art reference was “discussed in the Specification” of challenged patent); *Keysight Techs., Inc. v. Centripetal Networks, Inc.*, IPR2022-01421, Pap.9, 9-10 (Mar. 22, 2023) (“*Advanced Bionics* makes clear that previously presented art includes art that was provided via an [IDS].”); *Ivantis*, IPR2022-01533, Pap.14, 13-14 (*AB* part one satisfied where an asserted reference was cumulative of a reference considered but

not discussed during prosecution); *Becton*, 22-23; *Motorola*, IPR2022-01287, Pap. 11, 16 n.8.

Not surprisingly, the *pre-AB* cases that Petitioner relies on to argue *AB* part one (Pet.66-67) change nothing—and have been *superseded by AB*, which is precedential and makes clear that references presented to the examiner in an IDS or the specification have been “considered” for purposes of §325(d). *AB*, 7-8; *see also Monolithic Power Sys., Inc. v. Volterra Semiconductor LLC*, IPR2020-01348, Pap.19, 11-13 (Mar. 4, 2021) (exercising §325(d) discretion where reference was incorporated by reference, noting that “the nature of incorporation by reference connotes that all of [the reference] would have been considered to be part of the [challenged patent’s] specification and would have been considered by the Examiner.”). While *pre-AB* panels in *3Shape*, *Limelight*, *Weber*, and *Microsoft* focused on whether references were the *basis of a specific rejection*, *AB* part one is satisfied if the references *were of record*. *AB*, 7-8. And this is not disputed for *Grunenwald*, *Okino*, and *Adey*.

Petitioner’s only remaining argument for *AB* part one is that two of its secondary references, **O’Geen** and **Pitt**, each cited for a single dependent claim, “were not in front of the Examiner during prosecution.” Pet.66. To begin with, O’Geen and Pitt are relied on as secondary references for Grounds 2, 4 and 7 (which together cover just two claims—2 and 9), and this is insufficient to stave

off §325(d) denial. *Miltenyi Biomedicine GmbH v. The Trustees of the Univ. of Pa.*, IPR2022-00853, Pap.11, 45 (Oct. 11, 2022) (citing *Kayak Software Corp. v. IBM*, CBM2016-00075, Pap.16, 10 (Dec. 15, 2016) (informative) (finding reliance on new reference solely for “additional subject matter of certain dependent claims[] is insufficient to persuade us that exercising our discretion under U.S.C. §325(d) is inappropriate.”)). But Petitioner’s argument is also flawed: both O’Geen and Pitt are at best ***cumulative*** of art that *was* before the Examiner. *See* §325(d) (encompassing “substantially the same” art).

Petitioner tellingly *makes no argument* that these two references, O’Geen and Pitt, are *not* cumulative of the art that was before the Examiner (Pet.66-67)—indeed, the Petition never uses the word “cumulative.” But this is a mandatory part of any §325(d) analysis, and Petitioner’s failure to include it is fatal to its *AB* part one argument. *See, e.g., Autel Intelligent Tech. Corp. v. Orange Elec. Co.*, IPR2021-01545, Pap.8, 17, 20-23, 27 (Apr. 8, 2022) (denying institution under §325(d) where Petitioner failed to “persuasively identify any specific, substantial difference between [petitioner’s reference] and the Third Reexamination’s prior art”); *see also Darfon Elecs. Corp. v. Shipman*, IPR2022-01008, Pap.11, 14 (Dec. 2, 2022) (denying institution under §325(d), noting “Petitioner does not address whether the proffered art is cumulative to or substantially the same as the art considered during prosecution.”); *Alarm.com, Inc. v. Vivint, Inc.*, IPR2022-00728,

Pap.6, 20-22 (Nov. 1, 2022) (concluding art was cumulative, noting “Petitioner does not address the similarities between [references] applied during prosecution... and [the reference] relied upon in each of the asserted grounds”).

Moreover, had Petitioner bothered to provide this mandatory analysis, it would simply have confirmed these two references *are* cumulative of art affirmatively argued in prior art rejections during prosecution of ’995 and its parent. For example,

- **O’Geen**: Petitioner argues O’Geen solely for purposes of Claim 2, to supply purported teachings of “generating a ***representation of epigenetic features*** of said genome region at least in part ***by mapping*** said sequence information to said genome region.” Pet.46-48. But in examining ’995’s parent, the same Examiner already found such epigenetic mapping was taught by, *e.g.*, the Fernandez reference (which, like O’Geen, related to “ChIP-Seq”). *See* EX2001,¹⁴ 380-381 (Examiner stating that “Fernandez

¹⁴ ’995’s parent was allowed after amendments unrelated to such mapping. *See* EX2001, 410 (applicant stating “Fernandez’s method relies on antibody-transposase conjugates that are ***specific*** for proteins in the chromatin Such conjugates are excluded from the present claims and, as such, Fernandez cannot anticipate”) (emphases original), 411 (same for obviousness), 437 (Notice of

teaches in the Examples 3 and Example 4 wherein software is used to extend the sequence read alignments and generate signal maps. Fernandez et al teach that peaks and signal maps are entered into gene annotation and sample comparison. These are used to compare the representation of genomic sequences in the DNA libraries...”); EX2002, Figure 1, [0017] (“One embodiment of the invention... is a novel, patentable method that significantly improves ChIP...”); EX1005 (O’Geen) (titled “*Using ChIP-Seq Technology to Generate High-Resolution Profiles of Histone Modifications*”); Pet.50 (acknowledging “the *ChIP-seq method taught by O’Geen*”).

- **Pitt**: Petitioner argues Pitt solely for purposes of claim 9, to supply purported teachings of “permeabiliz[ing] by... ultrasonication.” Pet.58. But the art before the ’995 Examiner already disclosed the use of physical permeabilization techniques (e.g., EX2009, ¶212 (“Cells may be disrupted, partially (e.g., *permeabilized*) to allow uptake of transposons or fully (e.g.,

Allowability) (finding amendments—including addition of “wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin” (*id.* 413)—“obviate the rejections” based on Fernandez).

lysed) to release interior components.”); *see also id.* ¶200 (“If transposition is carried out *in vivo*, transposition into the sample nucleic acids is preferably achieved by electroporating...”); EX2002, ¶27 (“The transposome is so stable that it can be introduced via electroporation into living organisms...”), and Petitioner’s own expert asserts that ultrasonication was already known to be an established form of physical permeabilization— “[s]imilar to electroporation, ***ultrasonication is also an established, physical method of permeabilization*** as early as 1998.” EX1002, ¶84.

Thus, for each of Petitioner’s cited references, the same or substantially the same ***art*** was already before the Office in connection with ’995’s prosecution.

Second, Petitioner does not even *assert* its ***arguments*** here are new. Pet.66-67. But, even if it had, this would be irrelevant and need not be reached by the Board: *AB* part one is met where ***art or*** arguments were previously presented. *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20 (Nov. 1, 2022).

Thus, *AB* part one is satisfied.

B. Advanced Bionics Part Two Favors Denial

AB part two considers whether a petitioner has demonstrated that the Office erred in a manner material to the challenged claims’ patentability. *AB*, 8-9. *Becton* factors relevant to the part two inquiry include: (c) the record developed by the

Office in previously reviewing the art or arguments; (e) whether petitioner sufficiently pointed out how examiner erred in evaluating the art; and (f) the extent to which petitioner's additional evidence and facts warrant reconsideration of the prior art or arguments. *AB*, 9-10. "If a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review." *Id.*, 8-9. "***If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability. At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.***" *Id.*, 9.

Petitioner asserts the Examiner "materially erred by not considering the relevant teachings of **Grunenwald**," including "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" (Pet.67-68)—but this ignores the Examiner's substantive rejection based on Fernandez.¹⁵ EX2001, 380-381. Far from showing error by the Examiner, this complaint that "the Examiner did not discuss or cite any passage or disclosure of Grunenwald"

¹⁵ It is also incorrect, as explained *supra*, §V.

(Pet. 67) is *Petitioner's* mistake: Petitioner erroneously “equates Examiner’s silence in discussing relevant prior art to a material error.” *Ivantis*, IPR2022-01533, Pap.14, 19; *AlmondNet*, IPR2022-01319, Pap.9, 11 (exercising §325(d) discretion to deny institution). It also ignores that ***Grunenwald, which Petitioner argues discloses these limitations (Pet.41-44), is incorporated by reference. See Monolithic***, IPR2020-01348, Pap.19, 11-13 (exercising §325(d) discretion and denying institution, noting it was “difficult to suggest that the Examiner merely ‘overlooked’” the reference that was incorporated by reference and discussed at multiple points in the challenged patent’s specification).

Petitioner makes similar complaints that the Examiner did not “acknowledge” the teachings of Okino and Adey that fail for the same reason, as Petitioner does not even assert, let alone explain, how “acknowledging” the teachings of “cell lysis” or “permeabilization by the use of nonionic detergents” were material to patentability. (Pet.68). And again, as with Grunenwald, Petitioner’s complaint that “the Examiner did not discuss or cite any passage or disclosure of... Okino, or Adey” (Pet.67) is nothing more than a complaint that the Examiner did not issue a rejection that Petitioner wishes she had. And as the caselaw confirms, Petitioner’s silence here is not “error.” *E.g., AlmondNet*, IPR2022-01319, Pap.9, 11.

The Examiner acknowledged that the prior art taught tagmentation in living cells. Among other things, Petitioner entirely ignores the prosecution history of the '995's parent application, which directly contradicts Petitioner's assertion of "error." Pet.67-68. Specifically, the Examiner found that the prior art, Fernandez, disclosed tagmentation inside living cells *in vivo* but that the claims as issued were not anticipated or obvious because prior methods used an antibody specific to a protein in chromatin for epigenetic analysis. EX2001, 380-381 ("Fernandez et al teach wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said cell"), 437-438. Thus, the alleged "teaching" the Examiner purportedly "failed to acknowledge" in Grunenwald was *clearly acknowledged by the Examiner in Fernandez*, but the Examiner concluded no reference disclosed performing the claimed method for the purposes of developing an epigenetic profile without using "an antibody that is specific to a protein that is part of said chromatin." EX2001, 437-438 ("the prior art teaches away from chromatin analysis as instantly [claimed] to obtain epigenetic information. Rather the art supports chromatin immunoprecipitation, which involves the use of an insertional complex that comprises an antibody specific to a protein that is part of the chromatin, as a main tool for investigating epigenetic marks"); *Miltenyi*, IPR2022-00853, Pap.11, 45-47 (exercising §325(d) discretion and finding no material error where "substantially the same" teaching petitioner

argued was overlooked in its reference was “discussed at length” during prosecution in another reference); *ADT LLC v. Vivint, Inc.*, IPR2022-00612, Pap.8, 24-25 (Aug. 22, 2022) (exercising §325(d) discretion and finding no material error where petitioner did not argue it was error for the claims to issue over the art applied by the examiner in rejections during prosecution, and petitioner’s additional reference disclosed a similar teaching to the art already applied in the rejection). Petitioner does not even *assert* the Examiner’s conclusion is error, let alone *prove* it was. Pet.67.

And the record makes quite clear that the teachings of Grunenwald were not “overlooked.” Indeed, in addition to Grunenwald itself having been *called to the same Examiner’s attention in both the ’995 and its parent* in the form Petitioner uses as a reference here (EX1007, 97 (IDS); EX2001, 295), the teachings were before the Examiner in the form of Grunenwald’s issued patent (EX1007, 97 (“9080211... Grunenwald”); EX2001, 401). And, Grunenwald is *discussed twice in ’995’s specification*—and in one of those passages is *incorporated by reference*. EX1001, 13:19-26, 14:36. Where a reference has been incorporated by reference and discussed multiple times in the specification, “it is difficult to suggest that the Examiner merely ‘overlooked it.’” *See Monolithic*, IPR2020-01348, Pap.19, 11-13. And, in fact, the Examiner was well aware of Grunenwald and *applied it in a rejection* during examination of the ’995’s grandchild, U.S.

Patent No. 10,738,357, with pending claims similar to the '995's. EX2010, 144-147, 152-157; *Live Nation Entertainment, Inc. v. Complete Entertainment Resources B.V.*, PGR2017-00038, Pap.11, 12 (Jan. 16, 2018) (finding arguments presented during prosecution of a continuation application with claims of "very similar scope" to the challenged claims were relevant for § 325(d) analysis). The Examiner argued that many of the same Paragraphs of Grunenwald that Petitioner relies on (*e.g.*, Paragraphs 17 (Pet.29), 18 (Pet.34), 146 (Pet.30-31)) invalidated the pending claims (EX2010, 152-157) and ***10x overcame that Grunenwald rejection*** (EX2010, 224-225). Petitioner is well aware of that prosecution history, and yet, here, pretends it does not exist. EX2011, 30 (Petitioner stating: "The Examiner cited the combination of Grunenwald in view of Jouvenot and further in view of Audit as a combination that rendered the claims obvious.").

Petitioner does not explain how failing to "acknowledge" the teachings related to limitations in *dependent claims* could be material to the patentability of Claim 1. While Petitioner argues that the Examiner "fail[ed] to acknowledge" the teachings of Okino and Adey, Petitioner does not support that assertion (Pet.68) or explain how it is plausible on this record. For example, while Petitioner argues the Examiner did not acknowledge that **Adey** discloses "tagmentation with two tags" (Pet.68), Petitioner ignores that the Examiner ***had Adey before her*** during prosecution of the '995 and its parent (EX2001, 388 (listing Adey first in

IDS acknowledged by Examiner with only 4 total references, with title “Ultra-low-input, *tagmentation-based* whole-genome bisulfite sequencing”)), and that Adey was *discussed twice in the specification of the ’995* (“Adey, A. et al. *Genome Biol* 2010 11:R119, loaded *in vitro* with adapters for high-throughput DNA sequencing, can simultaneously fragment and tag a genome with sequencing adapters” (EX1001, 28:57-62, 27:37-38)). Similarly, Petitioner argues the Examiner failed to acknowledge that **Okino** discloses “cell *lysis*, and *permeabilization* by the use of nonionic detergents” (Pet.68), but ignores that the Examiner *had Okino before her*, along with *another reference describing cell lysis* (EX2001, 340, 344; EX2012, ¶65 (“Cell lysis may be achieved in a variety of ways, including sonication, French press (or other shearing methods)...”).

Furthermore, Petitioner does not explain how, *arguendo*, “failing to acknowledge” the teachings of two references Petitioner uses primarily for backup Grounds (Okino) or for certain dependent claims (Adey) was an error “material to the patentability” of Claim 1. *AB*, 21; Pet.68. In other words, had the Examiner “acknowledged” Okino and Adey as Petitioner argues, *Claim 1 would have issued*, as would each of the dependent claims.

Petitioner’s allegation of “error” is insufficient. Even assuming, *arguendo*, the Examiner somehow “overlooked” the teachings of these references—an implausible assertion at best—Ppetitioner’s cursory argument under

AB part two asserts that “the Examiner materially erred by not considering the relevant teachings in Grunenwald, Okino, and Adey.” Pet.67. That bare conclusory assertion is insufficient to meet Petitioner’s burden. For example, in *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20-21 (Nov. 1, 2022) the Board rejected Petitioner’s argument that the Board erred by failing to issue ““substantive action showing its consideration of the art,’ other than the Notice of Allowance,” explaining that “the lack of a rejection itself is not dispositive of whether there was material error.” The Board further explained that the Notice of Allowance demonstrated the Examiner considered petitioner’s primary reference and that the petitioner “does not specifically identify any alleged mistakes made by the Examiner.” *Id.* at 22; *Ivantis*, IPR2022-01540, Pap.14, 19 (Mar. 22, 2023) (“To the extent Petitioner equates the examiner’s silence in discussing relevant prior art to a material error... we are not persuaded.”); *Motorola*, IPR2022-01287, Pap.11, 22-23; *Eyenovia, Inc. v. Sydnexis, Inc.*, IPR2022-00963, Pap.7, 19 (Nov. 8, 2022) (exercising §325(d) discretion and finding petitioner failed to show material error where there was no rejection issued over the IPR references but each reference was before the examiner or cumulative of references before the examiner); *Google LLC v. Valtrus Innovations Ltd.*, IPR2022-01197, Pap.9, 23 (Jan. 3, 2023) (exercising §325(d) discretion where

petitioner failed to discuss how the examiner erred with respect to the reference with specificity).

Petitioner, at most, improperly “equates Examiner’s silence in discussing relevant prior art to a material error,” which is not sufficient to meet Petitioner’s burden to demonstrate error. *Ivantis*, IPR2022-01533, Pap.14, 19 (exercising §325(d) discretion where “Petitioner does not sufficiently demonstrate or explain why a different conclusion should be reached based on the same disclosures in the same references that were cited during prosecution.”); *Microsoft Corp. v. AlmondNet, Inc.*, IPR2022-01319, Pap.9, 11 (Jan. 30, 2023) (exercising §325(d) discretion where the art was before the Examiner, there was no evidence it was concealed, and the petitioner’s only argument of error was “the prior art references in the Petition ‘were not substantively considered during [prosecution]’”).

Thus, both parts of the *AB* test confirm that the Board should exercise its § 325(d) discretion to deny the Petition.

VIII. Institution Should Be Denied Under 35 U.S.C. §314(a)

“Even when a petitioner demonstrates a reasonable likelihood of prevailing with respect to one or more claims, ...institution of review remains discretionary.” *Chevron Oronite Co. v. Infineum USA L.P.*, IPR2018-00923, Pap.9, 10 (Nov. 7, 2018) (informative). Indeed, “the Board may consider the *number of claims and grounds that meet the reasonable likelihood standard* when deciding whether to

institute *inter partes* review under” § 314(a). *Id.*, at 10-11 (denying institution where “Petitioner demonstrate[d] at most, a reasonable likelihood of prevailing with respect to two dependent claims out of a total of twenty challenged claims”). The same is true here, particularly in light of Petitioner’s flawed anticipation analysis and the significant §325(d) concerns with respect to Ground 1 and Grunenwald—which flow through all Challenged Claims—as well as the fundamental failures of Grounds 2-8, which make those grounds plainly insufficient to meet the threshold for institution. *See Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Pap.7, 42-43 (Jan. 24, 2019) (informative) (denying institution where “Petitioner demonstrate[d] a reasonable likelihood of prevailing with respect to only two claims on one asserted ground” explaining that “instituting a trial with respect to all twenty-three claims and on all four grounds... would not be an efficient use of the Board’s time and its resources.”).

Thus, even if, *arguendo*, the Board concludes Petitioner has met its burden for some claims or Grounds, the Board should nevertheless deny institution under §314(a).

IX. Conclusion

Petitioner has failed to show there is a reasonable likelihood they will prevail in proving the Challenged Claims unpatentable, and the Petition should be

denied in its entirety. In addition, or alternatively, the Board should exercise its discretion to deny the Petition under §§325(d) and/or 314.

Respectfully submitted by:

Dated: July 28, 2023

/J. Steven Baughman/

J. Steven Baughman (Reg. No. 47,414)

Megan Raymond (Reg. No. 72,997)

*Attorneys For Exclusive Licensee 10x
Genomics, Inc.*

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1). According to the word-processing system's word count, the brief contains 13,717 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

Dated: July 28, 2023

Respectfully Submitted,

By: /Megan Raymond/
Megan Raymond (Reg. No. 72,997)
GROOMBRIDGE, WU, BAUGHMAN &
STONE LLP
801 17th Street, NW, Suite 1050
Washington, DC, 20006
P: (202)-505-5878
megan.raymond@groombridgewu.com

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

Petitioner's Counsel of Record:

Lead Counsel:	Derek C. Walter Reg. No. 74,656 derek.walter@weil.com Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 Telephone: (650) 802-3934 By Electronic Mail
Backup Counsel:	Adrian C. Percer Registration No. 46,986 adrian.percer@weil.com Weil, Gotshal & Manges LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 Telephone: (650) 802-3124 William Sutton Ansley Registration No. 67,828 sutton.ansley@weil.com Weil, Gotshal & Manges LLP 2001 M Street NW, Suite 600 Washington, DC 20036 Telephone: (202) 682-7018 By Electronic Mail

Dated: July 28, 2023

Respectfully submitted,

By: /Sayem Osman
Sayem Osman