

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

10X GENOMICS, INC.,
Patent Owner

Case IPR2023-00876
Patent 10,155,981

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

LIST OF EXHIBITS

Exhibit	Description
EX2001	U.S. Patent Pub. No. 2007/0020640 A1
EX2002	File History of U.S. App. No. 13/859,450
EX2003	Dictionary of Microbiology and Molecular Biology (2d ed. 1987)
EX2004	File History of U.S. App. No. 14/792,094
EX2005	File History of U.S. App. No. 13/387,343
EX2006	U.S. Patent Pub. No. 2007/0238113
EX2007	Laird <i>et al.</i> , <i>Hairpin-bisulfite PCR: assessing epigenetic methylation patterns on complementary strands of individual DNA molecules</i> , 101 PNAS 204-09 (Dec. 12, 2003)
EX2008	Parse Biosciences, Inc. v. 10x, Genomics Inc., IPR2023-00958, Pap.1, (May 25, 2023)
EX2009	File History of U.S. App. No. 14/172,694
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I. Introduction

Patent Owner 10x Genomics, Inc. (“PO”) submits this §42.107¹ Preliminary Response to the above-captioned Petition (“Petition”/“Pet.”). Petitioner asserts the methods of Claims 1-6 (the “Challenged Claims”) of U.S. Pat. No. 10,155,981 (the “’981 Patent”/“’981”) are “described in the specification as nothing but mere prior art techniques” (Pet.1-2), but concedes they are *novel*: Petitioner advances no §102 ground, and instead argues only that ’981’s revolutionary method—which was invented by Nobel Laureate Sydney Brenner and his team and unlocked the ability to do high-resolution single-cell analysis—was somehow obvious. The Board should deny the Petition because Petitioner’s inadequate obviousness arguments are fatally deficient.

To begin with, *two threshold failures* compel denial without the need for any further analysis. *First*, the Petition presents the classic case for discretionary denial under §325(d). The Petition’s two grounds assert obviousness based on two recycled references (**Linnarsson** and **McCloskey**) whose substance was already thoroughly considered by the Office. **Linnarsson**, Petitioner’s primary reference (EX1003), was the explicit basis of rejection during prosecution, was distinguished

¹ 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.

and overcome, and featured prominently in the '981's initial Notice of Allowance. EX1005, 238. **McCloskey**, Petitioner's secondary reference (EX1004), is simply a less-detailed version of "US20070020640" to McCloskey *et al.* ("McCloskey '640") (EX2001). ***McCloskey '640 was asserted by the Office, substantively considered, and then overcome*** in the prosecution chain of applications leading to the '981. *See, e.g.*, EX2002, 335-336, 372-373.

And Petitioner identifies no cognizable error that would let it escape discretionary denial in this textbook §325(d) fact pattern. Instead, the only "error" Petitioner suggests—that the Examiner overlooked, and never acknowledged, the teachings of McCloskey '640—is palpably false, as it was ***substantively considered*** in '981's priority applications. Reconsidering the same references and arguments would waste both the Board's and PO's time and resources. This is exactly the case §325(d) was meant to prevent.

Second, Petitioner entirely fails to assert or analyze whether its references are analogous art to the '981 Patent (instead discussing only whether they are analogous to one another). This failure impacts both 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 setting aside these fatal threshold errors, Petitioner’s purported motivation to combine with a reasonable expectation of success fails. Linnarsson is focused on gene *expression* and tagging *all* of the mRNA transcribed from expressed genes. *See* EX1003, 1 (Abstract); Pet.6. In contrast, McCloskey is about stamping only copies of a *particular gene*. McCloskey’s disclosure of “Encoding PCR Products with Batch-stamps and Barcodes” uses a batch-stamp that identifies the sample from which cells originated in order to identify contamination (*i.e.*, to identify sequences originating from a *different* sample leftover from a prior analysis) and a barcode that distinguishes between *copies of a particular allele in the sample* (without identifying the cell of origin).

Petitioner’s motivation to combine and reasonable expectation of success arguments rest, *inter alia*, on the premise that McCloskey stamps “*each* sample polynucleotide.” Pet.54-55. But Petitioner fails to prove this premise is true (and from a simple reading of McCloskey it is not), and thus fails to support its motivation to combine and a reasonable expectation of success arguments. In addition, Petitioner argues motivation to combine based on its assertion that McCloskey addresses an amplification bias issue in Linnarsson, but ignores that Linnarsson *already addresses* amplification bias, and fails to explain how any amplification bias “solution” in McCloskey would actually improve Linnarsson’s process. And, with respect to reasonable expectation of success, Petitioner also

fails to explain how *each* sample nucleotide in Linnarsson would be tagged based on McCloskey's teachings.

Further, apparently hoping to mask the failures of its obviousness arguments, the Petition devotes substantial space to suggesting that the Challenged Claims lack written description or are somehow invalid because of arguments PO made in §101 arguments about unrelated patents in an unrelated proceeding (Pet.12-17). Petitioner is incorrect as to each, but, more importantly, its arguments are irrelevant in an *inter partes* review proceeding.

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

The '981, "Methods For Analyzing Nucleic Acids From Single Cells," claims priority to an August 20, 2009 provisional. EX1001, 1; Pet.14-15. '981's Challenged Claims are directed to innovative methods of analyzing polynucleotides from a plurality of single cells that allow the user *not only to differentiate among the different polynucleotides* in an overall sample, *but also to track from which particular cell* each polynucleotide originated. EX1001, 6:33-7:22, claim 1 (30:18-48). This is achieved by using a multiplex identifier ("MID") with *two tag sequences*: "a *first* tag sequence associated with the single cell from which the sample polynucleotide is derived" and "a *second* tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same cell." *Id.* In other words, the claimed method

simultaneously employs (1) *cell-specific tags* and (2) *polynucleotide-specific tags*.

Id. Indeed, the innovative methods claimed in the '981 Patent allowed users to do what had not previously been possible: to determine the quantity of *each polynucleotide present in a cell on a cell-by-cell basis*, which Linnarsson and McCloskey cannot. EX1001, 6:33-7:22, claim 1 (30:18-48). The specification explains that combinatorially tagging the same polynucleotide with this first and second tag sequence provides a “correlation between a polynucleotide and its source” so that researchers can know, for example, how many individual polynucleotides are in each single cell within a sample. EX1001, 6:38-51. As discussed below, the claims were allowed because of their novel tagging of nucleotides, with each nucleotide being tagged with a cell-specific and polynucleotide-specific tag.²

² The Challenged Claims are directed to the innovative MID and its use, but the '981 Patent, like many other patents, discloses multiple inventions. EX1001, 1:50-61. One of the other inventions disclosed in the '981 Patent is the “reflex method,” which, using the MID, allows a user to fragment polynucleotides to ensure they are short enough in length for the entire fragment to be sequenced while enabling the user to track the origin of each fragment. *Id.*, 1:25-61.

III. Petitioner's Recycled References

A. Linnarsson (EX1003)

Linnarsson, a patent publication identifying Sten Linnarsson as sole inventor (EX1003 (“Linnarsson”), 1), is cited on '981's face and was the basis of multiple rejections by the Office in the '957 application that matured into '981, as well as '981's parent ('094) application. EX1001, 2; EX1005, 154-156; EX2004, 1085-1087.

Linnarsson discloses a method of preparing a cDNA library for sequencing by reverse-transcribing cDNA from mRNA initially produced by transcription of genes being expressed in the analyzed cells. EX1003, 1 (Abstract), 3:25-4:2; *see also* Pet.24. As part of this process, “single cells are placed in separate wells of a 96-well plate and lysed....” EX1003, 4:8-13; Pet.38. Each of those cells “contain[s] a plurality of mRNA molecules.” EX1003, 3:26-30; Pet.39-40. Linnarsson then adds cDNA synthesis primers (“CDSs”) and/or template switching oligonucleotides (“TSOs”), which are then incorporated into cDNA during reverse transcription from mRNA. EX1003, 18:32-33; *see also* Pet.25. The CDSs and/or TSOs identify the cell from which the tagged polynucleotide originated. EX1003, 19:4-7; Pet.25-27.

According to Petitioner, “Linnarsson discloses a cDNA synthesis primer... that includes a sequence of thymines....” Pet.25-26. Because every mRNA

molecule has a poly-A tail, “a sequence of thymines... hybridize with a sequence of adenines making up a poly-A tail... of an mRNA molecule.” Pet.41, 25-26; EX1003, 24:13-20, Figure 2. Thus, such CDSs are able to anneal to every mRNA molecule in a well.

Similarly, TSOs have a poly-guanosine sequence. Pet.26-27; EX1003, 18:19-21. In the process of reverse-transcribing mRNA into cDNA, reverse transcriptase typically causes two to five cytosines to be added to one end of the cDNA. EX1003, 16:18-31; Pet.26-27. The poly-guanosine sequence in TSOs “‘anneals transiently’ to the series of cytosine nucleotides at the end of [a] newly-synthesized strand.” Pet.26-27; EX1003, 18:19-23. The TSO annealing to cDNA causes “the reverse transcriptase to switch template and continue to synthesis [sic] a strand complementary to the TSO.” EX1003, 18:23-24. After the tags are added as part of the reverse transcription process, the cDNA (which includes a CDS and/or TSO) from each well is pooled, and a cDNA library is created. EX1003, 18:27-19:11; Pet.28.

Linnarsson’s method results in all the mRNA extracted from a single cell tagged with the same barcode in the process of reverse transcribing it into DNA. Thus, after amplification and sequencing of the reverse-transcribed DNA, it is impossible to distinguish among the multiple copies of polynucleotides (*e.g.*, multiple copies of mRNA resulting from overexpression of a particular gene) and

determine how many instances of that particular polynucleotide existed *in a particular cell* before amplification. *See* EX1003, 22:22-28.

B. McCloskey (EX1004)

Petitioner's EX1004 is an article, "Encoding PCR Products with Batch-stamps and Barcodes," by Megan L. McCloskey, Reinhard Stöger, R. Scott Hansen, and Charles D. Laird. EX1004 ("McCloskey"), 1. McCloskey purports to address a "source-uncertainty" problem that arises when pooled DNA samples are PCR'd. EX1004, 1, 2. To address this problem, McCloskey adds an "encoding oligonucleotide" with a batch-stamp and barcode as part of the DNA amplification process. EX1004, 2-4; Pet.30. The batch-stamp identifies the batch sample from which the cells originated in order to identify contamination (*i.e.*, to identify sequences originating from a different patient or sample leftover from a prior analysis) and the barcode distinguishes between *copies of an allele for a particular gene in the sample (without identifying the particular cell of origin)*. EX1004, 2-4; Pet.30.³ McCloskey's oligonucleotide sequence includes, *inter alia*, (1) a batch-stamp; and (2) a random barcode that distinguishes alleles of the same gene with (3) a genomic target-binding site that targets the specific gene to be barcoded prior to amplification. EX1004, 2; Pet.30-31.

³ Alleles are different versions of the same gene. EX2003, 3.

McCloskey's method involves lysing the cells and combining the contents (including the DNA) of those cells before tagging the copies of a particular gene within this combined material to determine the presence of alleles. EX1004, 2, 5. Copies of a particular gene (including any alleles or mutations) are tagged by annealing the genomic target-binding site of the oligonucleotide to the complimentary DNA sequence found on one end of the target gene. EX1004, 5. Because the oligonucleotide has a sequence that anneals only to a specific sequence of the target gene (which is subsequently amplified via PCR), *it does not tag other genes* (which, in McCloskey's process, are not amplified via PCR). EX1004, 2, 4-5.

McCloskey discloses that the incorporation of its oligonucleotides into the PCR'd DNA for the particular gene of interest allows researchers to identify and remove contaminated sequences (from different batch samples) and redundant sequences (amplified copies containing the same random barcode) after the gene of interest is PCR'd. EX1004, 3 (Fig. 1), 7. However, McCloskey's method does not allow a user to determine, *e.g.*, whether or which copy of a particular allele (or mutation) is present in a given cell because *no copies of the target allele are tagged with a sequence that tracks an allele to its cell of origin*. EX1004, 3. Thus, unlike the Challenged Claims, McCloskey's approach to removing redundant copies simply permits a user to determine whether the target gene was present,

including whether there were any alleles or mutations present, *in the sample when it was tagged. Id.*

IV. Petitioner Ignores The Bulk Of The '981 Patent's Prosecution History

Clearly hoping to lead the Board *away* from the Office's extensive analysis during prosecution of the seven non-provisional applications in '981's direct family tree, Petitioner myopically focuses solely on the single application (15/677,957 ("957 application")) that matured directly into the '981 Patent. Pet.17-19 ("Prosecution History Overview" discussing only the '957 application); EX1005 (attaching only the '957 application's prosecution history). But ***the six other applications in '981's family*** contain exhaustive discussion confirming both that (1) the substantive teachings of Petitioner's two cited references—Linnarsson and McCloskey—were squarely before the Office (indeed, it was the Office that raised and substantively addressed both Linnarsson and the more detailed McCloskey '640 in prosecution), and (2) Petitioner's regurgitation of those references and related arguments here fails to render the '981's claims obvious.

A. The Examiner's "Second Tag" Art From Prosecution Included McCloskey '640

Petitioner now argues (Pet.37-59) that McCloskey should be used, in its sole obviousness combination, to provide disclosure of '981's "second tag" (the ***polynucleotide-specific*** tag that Petitioner urges "distinguish[es]... other sample polynucleotides"). Pet.50-51. But during prosecution of '981's family the Office

already expressly *declined* to apply an even-more-detailed version of McCloskey to disclose a molecule-specific tag—along with a raft of *other* references (such as Kanda and Miner) over which McCloskey is, at best, *cumulative*.

For example, during prosecution of App. No. 13/387,343 (“’343 application”)—the first non-provisional application in ’981’s family, which, like the ’981, claimed use of a MID “whose identity can be used to differentiate polynucleotides in the sample”—the Office initially asserted that U.S. Pub. 2007/0238113 (“Kanda”) (cited on ’981’s face) taught the “limitation of [a] broadly recited multiplex identifier because F2 *can be used as the tag to differentiate a polynucleotide* in the sample.” EX2005, 686, 728-729; EX2006. But the Office withdrew that rejection “in view of the persuasive arguments made by the Applicant regarding the teachings of Kanda” (EX2005, 805), including that Kanda failed to teach sequencing the primer sequences (as the pending claims required), which would allow the user to “distinguish[] said polynucleotide strand from other polynucleotide strands in said sample.” EX2005, 789, 793-798. The Office identified some dependent claims as allowable but issued new rejections of others, asserting they were anticipated by or rendered obvious with a publication—Laird *et al.*, *Hairpin-bisulfite PCR: assessing epigenetic methylation patterns on complementary strands of individual DNA molecules*, 101 PNAS 204-09 (Dec. 12, 2003) (“*Laird*”)—that is cited in Petitioner’s McCloskey reference (EX1004, 2, 7)

and whose lead author, Charles D. Laird, is also a co-author of McCloskey (EX1004, 1). EX2005, 807-817; EX2007. Specifically, the Office asserted Laird disclosed the claimed MID because its “sequence *can be used as the tag to differentiate the hairpin polynucleotide* in the sample.” EX2005, 809-812. But, after Applicant argued Laird failed to disclose sequencing the MID as required by the pending claims (and amended the claims to specify the length of the polynucleotide of interest (EX2005, 844-851)), the Office withdrew these rejections, as well, and allowed the remaining claims. EX2005, 865-867. The Office stated, in its “Reasons for Allowance,” that “Laird alone or in combination with the art of record *does not disclose or make it obvious* the claimed method steps ‘a’ to ‘c’, wherein the polynucleotide strand comprises... *a multiplex identifier (MID) comprising a unique nucleotide sequence that distinguishes said polynucleotide strand from other polynucleotide strands in said sample...*” EX2005, 868-869. The Office further noted that “[t]he instant method has *several advantages... as compared to other extraction methods... that only use a single oligonucleotide sequence*, [including that the instant method] *allows [users] to analyze* homologous genomic locations in *a multiplexed sample (i.e., a sample having polynucleotides from different genomic samples) in which the polynucleotides are tagged with the multiplex identifier domain.*” EX2005, 868-869. Thus, the Office concluded that Laird failed to render obvious, *inter alia*,

using a “(MID) comprising a unique nucleotide sequence that distinguishes said polynucleotide strand from other polynucleotide strands in said sample.” EX2005, 868-869.

During later prosecution of ’343’s grandchild application (No. 13/859,450 (“’450 application”)), which issued as U.S. Patent No. 8,563,274 (“’274 Patent”/“’274”), the Office expressly considered a “potential rejection” that would have addressed Laird’s deficiencies using McCloskey ’640. EX2002, 335-336, 372-373, 383. In particular, the Office raised a number of references and, in July 24, 2013 and July 26, 2013 interviews, “requested that the Applicants provide a brief summary of how the claims are distinguished from [them].” EX2002, 335-336. One of the references raised by the Office and successfully distinguished by Applicant was McCloskey ’640, which, as Applicant explained, “does not provide *segments* of a region, where each of the segments has the same MID sequence; [and] also *doesn’t provide [a] composition in which all of the segments have a multiplex identifier that uniquely identifies the individual molecule of said contiguous region from which said segments originate.*” *Id.* (italics on first use of “segments” original). As Applicant summarized, the Office agreed: the “Examiner indicated that [a proposed] amendment [(replacing “fragments” with “segments” as noted below)] would likely distinguish the claims from the [cited] references for the reason outlined in the Applicants’ brief comments.” *Id.*, 336, 383. Per that

discussion, Applicant submitted the amended language below for independent claim 21 (all emphases except italics are original):

(Currently amended) A composition comprising a mixture of:

- a) a first plurality of segments ~~fragments that have been amplified from different parts~~ of a single nucleic acid molecule of a contiguous region locus in genomic DNA, wherein *each of said first plurality of segments fragments is appended to a first multiplex identifier (MID) sequence; and*
- b) a second plurality of segments ~~fragments that have been amplified from different parts~~ of another nucleic acid molecule of said contiguous region locus, wherein each of said second plurality of segments ~~fragments~~ is appended to a second MID sequence and said first MID sequence and said second MID sequence are different,
wherein all of the segments in said composition have a multiplex identifier that uniquely identifies an individual nucleic acid molecule of said contiguous region from which said segments originate.

And in '274's Notice of Allowance—acknowledging that the Examiner and Applicant “[d]iscussed the amended claims” and that “specific claim languages were discussed to overcome the potential rejection of said amended claims over Laird... *in view of McCloskey [’640]* (cited in the previous interview)” (EX2002, 372-373)—the Office:

“also noted that *the bulk of the cited references in the said IDSs or in the field of molecular tagging prior to the filing date of the instant application discloses tagging of sample or a nucleic acid of interest with*

an identifier in the form of barcode, or multiplex identifier or zipcode or tagging sequences *to track it in further analysis*. However, ...in the Examiner's opinion *it would not have been obvious to [POSITA] to modify the references* of the [sic] record... to arrive at the claimed composition... wherein, in said composition, all of the segments of each of the nucleic acid molecules of the contiguous region ***comprises a unique MID sequence that uniquely identifies each of the nucleic acid molecules.***"

EX2002, 374-375.

In the '981's second Notice of Allowance, after Applicant overcame the Examiner's anticipation rejection using ***Linnarsson*** by arguing Linnarsson lacked the second tag, the Examiner concluded that none of the art of record, ***"including the prior art submitted in the newly filed IDS"*** reasonably suggested the claimed invention. EX1005, 306; *infra*, §IV.B. The "newly filed IDS" noted by the Examiner was *one page* and contained just 13 references (EX1005, 285), one of which was "MINER et al., 'Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR.'" EX1005, 285; EX1013, 1.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.†	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	TS
	B16	BRENNER, S. et al. "In vitro cloning of complex mixtures of DNA on microbeads: Physical separation of differentially expressed cDNAs" PNAS 2000 Feb. 15; 97(4):1665-70.	
	B17	HUG, H. et al. "Measurement of the number of molecules of a single mRNA species in a complex mRNA preparation" J Theor Biol. 2003 Apr 21; 221(4):615-24.	
	B18	MINER et al. "Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR" Nucleic Acids Res. 2004 Sep 30; 32(17):e135.	
	B19		

EX1005, 285. Miner, which is discussed in McCloskey as applying the same principles used in McCloskey to “hairpin-bisulfite PCR” (EX1004, 2), discloses:

“us[ing] *molecular barcoding to label each genomic DNA template with an individual sequence tag prior to PCR amplification*. In addition, *we include molecular ‘batch-stamps’ that effectively label each genomic template with a sample ID and analysis date*. This highly sensitive method identifies redundant and contaminant sequences and serves as a reliable method for positive identification of desired sequences...”

EX1013, 1 (Abstract). These are the same teachings from McCloskey that Petitioner asserts disclose the claimed “second tag.” Pet.50-56, 58-60; EX1013, 1; EX1004, 1; EX1001, claim 1 (30:18-48).

B. The Examiner’s Reliance On Linnarsson In Prosecution

Petitioner’s sole obviousness argument urges combining these recycled McCloskey teachings with Linnarsson as a base reference asserted to provide disclosure of ’981’s method of analyzing a plurality of cells and tagging polynucleotides within those cells with a “first” tag (the *cell-specific* tag) (Pet.37-59). But this merely repeats the Office’s previous consideration of Linnarsson, with these same purported (but failed) “second tag” teachings in hand (*see supra*, §IV.A). The Office raised and applied Linnarsson in rejections during prosecution of the ’981’s parent and the ’981 itself; but Applicant overcame Linnarsson and

obtained the Challenged Claims because Linnarsson alone *or in combination with the art of record* (see §IV.A) did not anticipate or render obvious the Challenged Claims.

During prosecution of '981's parent application (No. 14/792094 ("094 application")), the pending claims—like '981's—included both first and second tags ("first and second multiplex identifier (MID) sequences"). EX2004, 860. For example, an August 30, 2017 amendment added this independent claim:

56. (New) A method of analyzing nucleic acids, the method comprising:

(a) providing a plurality of nucleic acid samples, each made from single isolated cells;

(b) *tagging a plurality of segments of the nucleic acid molecules* in the samples of (a) *with first and second multiplex identifier (MID) sequences*, wherein:

(i) the *first MID sequences* associated with a segment of a nucleic acid molecule of (a) *uniquely identifies the single isolated cell from which the nucleic acid molecule is provided*; and

(ii) the *second MID sequences are all different from each other*;

(c) sequencing the tagged segments of (b) to obtain the nucleotide sequences of the plurality of nucleic acids and the attached first and second MID sequences.

EX2004, 860. In response, for the first time in prosecution of the '981 patent family, the Office identified and asserted Linnarsson, WO2010/117,620 (Petitioner's primary reference here (EX1003)), and rejected the pending claims as anticipated. EX2004, 1084-1087. In particular, the Office found Linnarsson disclosed the *first* tag:

The cell specific tag (e.g., see figure 3) in the nucleic acid sample from each of the single cell is the first Multiplex Identifier (first MID) sequences associated with a segment of a nucleic acid molecule of (a) uniquely identifies the single isolated cell from which the nucleic acid molecule is provided.

EX2004, 1086. And the Office additionally found Linnarsson disclosed the *second* tag. EX2004, 1086 ("Different tags associated with cDNA segment of Linnarsson meets the limitation of second MID sequences [that] are different from each other.").

Prosecution then moved forward in the child application (U.S. App. 15/677,957 ("957 application")) that would eventually mature into the '981. The '957 application's as-filed claims included this independent claim:

1. A method of analyzing nucleic acids from a plurality of single cells, the method comprising:
 - (a) providing a sample comprising a plurality of single cells, wherein each single cell of the plurality of single cells comprises a plurality of sample polynucleotides;

(b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides, wherein each tagged polynucleotide comprises:

- (i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and
- (ii) a multiplex identifier (MID) sequence comprising:

- I. a *first tag sequence associated with the single cell from which the sample polynucleotide is derived*; and
- II. *second tag sequence distinguishing the sample polynucleotide from other pluralities of sample polynucleotides derived from the same single cell*

(c) sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences;

(d) using the first tag sequence to correlate the identified polynucleotide sequence with the single cell from which the polynucleotide sequence is derived, and

(e) using the second tag sequence to correlate the identified polynucleotide sequence with the plurality of sample polynucleotides [sic] from which the polynucleotide sequence is derived.

EX1005, 64. During '981's prosecution, the Office rejected these then-pending claims as anticipated by Linnarsson (EX1005, 154), but later withdrew that rejection after further argument (EX1005, 181-182) (and an

amendment clarifying that “the first tag sequence is a different sequence for different single cells in the plurality of single cells” (EX1005, 178)). As the Office correctly concluded in its initial August 28, 2018 Notice of Allowance for the ’981 patent, “The closest prior art, *Linnarsson* (WO 2010/117620), ***does not teach or suggest generating a plurality of tagged polynucleotides comprising an identifier sequence*** of instant claim 1(ii). The claimed identifier sequence comprises a first tag sequence, which distinguishes each single cell in a sample of a plurality of cells, ***and a second tag sequence, which distinguishes a sample polynucleotide from other sample polynucleotides derived from a single cell, which is not taught by Linnarsson.***” EX1005, 238. The Examiner confirmed even more broadly in a second Notice of Allowance, after reviewing an additional IDS (EX1005, 283-284), that this gap in Linnarsson was not filled by the art the Office had considered: “[a] ***thorough search*** of the prior art, ***including the prior art submitted in the newly filed IDS***, filed after the Notice of Allowance mailed on 8/28/2018, ***shows no art that teaches or reasonably suggests the claimed invention.***” EX1005, 306.

As discussed above, the “newly filed IDS” noted by the Examiner was *one page* and contained just 13 references (EX1005, 285), one of which was Miner, which included McCloskey’s teachings. EX1005, 285; EX1013, 1;

supra, §IV.A. Thus, the Examiner reviewed Miner, a reference with the very same teachings as McCloskey, which Petitioner relies on here as disclosing the “second tag” and motivating the combination of Linnarsson and McCloskey (Pet.50-56)—***after Applicant distinguished Linnarsson for lacking the “second tag,”*** and allowed the claims—finding they were neither anticipated nor obvious. EX1005, 306.

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

This is the prototypical IPR that §325(d) and the Board’s two-part framework in *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH* (IPR2019-01469, Pap.6, 8-9 (Feb. 13, 2020) (precedential) (“AB”)) were meant to prevent. Petitioner fails to show any error in the Examiner’s application during prosecution of the prior art teachings Petitioner now purports to invoke from Linnarsson and McCloskey. Instead Petitioner offers just a conclusory assertion—without support—that the “Examiner materially erred *by not considering the relevant teachings in the [McCloskey] ’640 Publication.*” Pet.71. Not only is this factually incorrect, but it is also legally insufficient to show “error.” *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).

Petitioner's secondary reference, an article by McCloskey, is at best cumulative of the far more detailed McCloskey '640, which *was raised by the Office and substantively discussed as the basis for a potential rejection using its asserted disclosure of a polynucleotide-specific tag—the same purported teaching for which Petitioner relies on McCloskey here. Supra*, §IV.A. But that disclosure in McCloskey '640 was *successfully distinguished and overcome by Applicant* in the face of the Office's contemplated rejection. Petitioner never acknowledges that prosecution history, never provides a substantive comparison of the disclosures of McCloskey and McCloskey '640, and never demonstrates any error in the Office's prior substantive consideration of McCloskey '640. And Petitioner concedes its primary reference, Linnarsson, was expressly overcome during prosecution as lacking this teaching of a polynucleotide-specific tag, which the Office found (with Laird) McCloskey '640 was inadequate to supply. Pet.50; *see also* EX1005, 238; EX2002, 335-336, 372-373, 383. Revisiting the same art and arguments already overcome during prosecution is a waste of the Board's limited resources and would unfairly burden PO.

A. Advanced Bionics Part One

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. *AB* part one is satisfied here.

First, the Office has clearly considered “the same or substantially the same prior art” before. Both of Petitioner’s Grounds rely on two recycled references: ***Linnarsson*** and ***McCloskey***. ***Linnarsson*** was the basis of explicit rejections—both in the application that issued as the ’981 Patent and in its parent ’094 application—which Applicant ultimately overcame. EX1005, 193-196; EX2004, 1085-1087. Petitioner points now to the *same Linnarsson disclosures* previously cited by the Office, and advances the *same arguments* that the Office made in prosecution, to assert that the Challenged Claims are obvious. For example, Petitioner points to Linnarsson page 4 (Pet.38) as disclosing the preamble, Linnarsson’s Figure 3 as disclosing the (“first”) cell tag (Pet.43), and Linnarsson’s disclosure of a “cDNA sample [with] a combination of tags” (Pet.43). The Office similarly pointed to page 4 of Linnarsson as teaching a method where “identification of expressed genes and identification of cells from which they are originated” and its Figure 3 as disclosing a “cell-tag.” EX1005, 195; EX2004, 1086 (arguing Linnarsson disclosed “[t]he cell specific tag (e.g., see figure 3)”).

And the Office also asserted that Linnarsson discloses “a distinct tag or combination of tags” such that “each cDNA sample comprised 2 distinct tags.” EX1005, 196; EX2004, 1086 (arguing Linnarsson disclosed “[d]ifferent tags”); Pet.28. Petitioner is, thus, repeating the *same* Linnarsson *prior art disclosures* and *arguments* in the hopes the Office might now repeat this same analysis (needlessly burdening its own resources and those of PO) but reach a different result.

The same is true for Petitioner’s cited **McCloskey** article (EX1004), whose substantive teachings that Petitioner argues should be combined in Linnarsson’s were already (like Linnarsson) raised *by the Office*, argued, and overcome during prosecution leading to the ’981 patent in the form of the far-more-detailed McCloskey ’640 (EX2001). While Petitioner offers the Board a conclusory seven-word assertion, *without any analysis*, that McCloskey is somehow “different” from McCloskey ’640, which is cited on the face of the ’981 and was raised and argued by the Office in prosecuting the related ’450 application in ’981’s priority chain (Pet.70; EX1001, 1; EX1005, 1124; EX2002, 335-336, 372-373, 383), Petitioner ***makes no attempt to show any “substantial difference” between McCloskey and McCloskey ’640.*** Pet.70, 30 n.6 (no explanation (in these, the only two discussions of this topic in the Petition) for Petitioner’s conclusory assertion that “the ’640 Publication and McCloskey are different”). This alone is reason enough to find *AB* part one is met. *See, e.g., Autel Intelligent Tech. Corp. v. Orange Elec. Co.,*

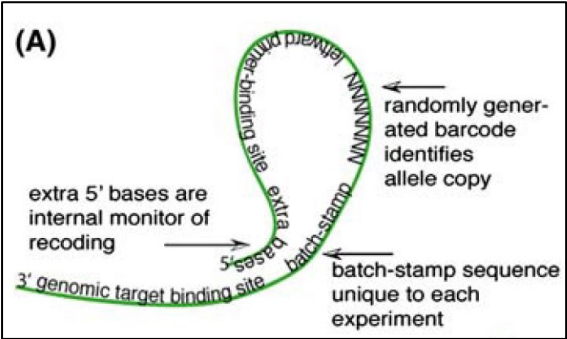
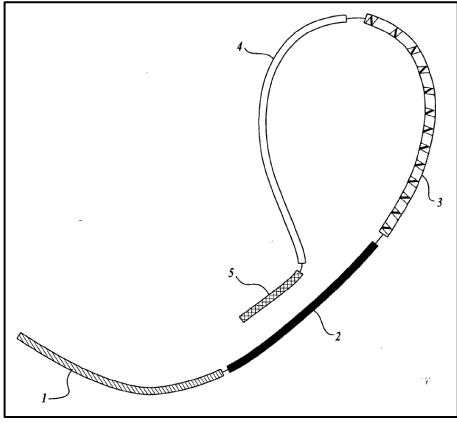
IPR2021-01545, Pap.8, 17, 20-23, 27 (Apr. 8, 2022) (denying institution under §325(d) where Petitioner failed to “persuasively identify any specific, substantial difference between [petitioner’s reference] and the Third Reexamination’s prior art”); *see also Darfon Elecs. Corp. v. Shipman*, IPR2022-01008, 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”). Petitioner’s conclusory assertion that the references are “different” is insufficient to show that they are.

Indeed, Petitioner has repeatedly conceded the parallels between its McCloskey exhibit and McCloskey ’640. Petitioner admits, in a Petition on a related patent, that:

McCloskey II [(the ’640 Publication)] is a *sister patent application that goes along with the McCloskey reference*. The subject matter of McCloskey II was invented by the authors of McCloskey. Thus, *similar to McCloskey, McCloskey II also discloses a method for tagging polynucleotides with ‘a molecular barcode and batch-stamp.’*

EX2008, 41. And in the current Petition, Petitioner essentially acknowledges that McCloskey '640 disclosed the information Petitioner now argues is relevant by complaining the Office erred by not “discuss[ing] or cit[ing] any passage or disclosure of” it. *See* Pet.71-72.

Moreover, an actual review of both references confirms the far-more-detailed McCloskey '640 raised and argued by the Office (and overcome by PO) during prosecution of '981's related '450 application ***already included the material on which Petitioner purports to rely***—and at minimum McCloskey is cumulative of the previously-considered McCloskey '640. Petitioner relies on McCloskey solely for its method of tagging nucleotides with an oligonucleotide that has a “batch-stamp” and “barcode” sequence, which Petitioner hopes to use to satisfy the '981's requirement of a “second” polynucleotide-specific tag. Pet.50-56, 58-59. But McCloskey '640 includes the very same teaching, as Petitioner now admits (EX2008, 41), and McCloskey '640 does so in far more detail. EX2001, 1 (Abstract) (“the present invention provides methods for authenticating a nucleic acid molecule and its sequence with a molecular barcode and batch-stamp”), Figs. 4A-G, ¶¶5, 20-27, 35, 46. Indeed, Petitioner's various cited McCloskey disclosures substantially overlap with McCloskey '640, *e.g.*:

McCloskey (EX1004)	McCloskey '640 (EX2001)
<u>“Batch-stamp” disclosures</u> Pet.50 (citing EX1004 at Fig. 1).  Pet.51 (quoting EX1004, 1-2 (“the batch-stamp, unique to each experiment, specifies the DNA source such as the patient or sample identification, and the date of reaction”))	Figure 1 and [0013], <i>see also</i> Figure 3 and ¶15  [0013] FIG. 1 shows an exemplary bar-coded oligonucleotide of the invention containing a sequence complementary to the target nucleic acid molecules (1), a batch-stamp sequence (2), random barcode (3), a leftward primer binding site (4), and a 5' tethering sequence (5), as described in EXAMPLES 1-5. The letter N represents a nucleotide randomly selected from A, T, C, or G. ¶27: “The term... ‘batch-stamp’ refers to information that uniquely identifies a specific experiment. For example, a batch-stamp may identify a sample, a patient, and/or an analysis date.”
<u>“Barcode” disclosures</u> Pet.55 (quoting EX1004, 2 (“Our method utilizes an encoding	¶21: “The bar-coded oligonucleotide further comprises a second sequence that provides a random barcode. The term

oligonucleotide with five distinct informational regions[:] the random barcode distinguishes among sequences arising from different cell or allele copies”))	‘random barcode’ refers to an arbitrary sequence than can uniquely identify a target nucleic acid in an experiment...” ¶¶54-63: (“EXAMPLE 2... This example describes an exemplary method of the invention for authenticating a PCR product from the FMR1 locus by using a bar-coded oligonucleotide with a 7-nucleotide random barcode.... 46 sequences were obtained from this experiment... 36 of the 46 were desirable and valid sequences, each of which had a unique barcode.”)
<u>Applications/Purpose</u> Pet.51 (quoting EX1004 1, 5 (“batch-stamps and barcodes [should] be used when amplifying irreplaceable DNAs and cDNAs for... single cell... analyses”))	¶3: “Problems with contamination and redundancy are particularly pronounced in PCR reactions with rare and irreplaceable DNA templates.” ¶6: “Examples of specific uses for the present invention include analysis of limited amounts of template DNA for

Pet.51 (quoting EX1004, 1, 5 (“to single-stranded cDNA templates”)) Pet.53 (quoting EX1004, Abstract (“The risks of...biased amplification...are especially high when limited amounts of template DNA are used.”))	biomedical, ancient DNA, and forensic purposes.” Abstract: “the present invention provides compositions for encoding both single-stranded and double-stranded target nucleic acids with coded oligonucleotides.” ¶5: “Barcoding permits, for example, quantification of the relative abundance of genomic methylation patterns or polymorphic sequences by correcting for skewing that can arise from PRC amplification or the cloning of the products.”
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Thus, the prior art substance of McCloskey that Petitioner now advances was already before the Office, and McCloskey (EX1004) is, at most, cumulative of McCloskey '640 (EX2001) and the other art that was already considered by the Office. Indeed, this would be the case even if McCloskey '640 had not been expressly discussed. *See, e.g., Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01533,

Pap.14, 13-14 (Mar. 27, 2023) (*AB* part one satisfied even where reference to which an asserted reference was cumulative was not discussed during prosecution); *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].”); *Becton*, 22-23; *Motorola*, 16 n.8; *cf.* Pet.72. But in fact, as detailed *supra* §IV.A, ***McCloskey ’640 was discussed and distinguished*** to avoid a potential rejection in the prosecution leading to ’981. *Becton*, 22-23; *see Motorola*, 16 n.8; *Eyenovia, Inc. v. Sydnexis*, IPR2022-00965, Pap.7, 13-14 (Nov. 7, 2022) (denying institution and considering arguments and rejections made during prosecution of related patents in §325(d) part one analysis); *see also 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 was relevant for §325(d) analysis). And, as detailed above (*supra*, §IV.A), the Office also expressly considered *other* references for potential disclosures of a polynucleotide-specific tag including, *e.g.*, Miner (EX1013) and Kanda (EX2006)—again confirming that Petitioner’s McCloskey (EX1004) is at best a cumulative stand-in.

Second, Petitioner’s mistaken assertion that the ***arguments*** here are new—even if, *arguendo*, it were credited—is 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).

But Petitioner's arguments are ***not*** new.

During prosecution, the Office initially argued the claims were anticipated by Linnarsson but then allowed the claims over those teachings and found no prior art of record taught or suggested the claimed invention. EX1003, 48; EX1004, 25. In the first Notice of Allowance the Examiner concluded Linnarsson did not disclose the "claimed identifier sequence," and in the second Notice of Allowance (following an additional IDS) the Office confirmed that "***[a] thorough search of the prior art, including the prior art submitted in the newly filed IDS***, filed after the Notice of Allowance mailed on 8/28/2018, ***shows no art that teaches or reasonably suggests the claimed invention.***" EX1005, 238, 306. This prior art already of record included McCloskey '640, and the "newly filed IDS" included Miner, which, ***using terminology identical to McCloskey***, disclosed using an oligonucleotide containing a batch-stamp and barcode to identify contamination and redundant sequences in PCR. EX1003, 2-3; EX1013, 1-2 ("we include molecular 'batch stamps' that effectively label each genomic template with a sample ID and analysis date. This highly sensitive method identifies redundant and contaminant sequences... In addition to adding the random barcode, we 'batch-stamped' molecules...").

The Examiner thus expressly considered whether the claims were obvious over the prior art of record—including **Linnarsson, McCloskey '640**, and **Miner**—and determined the Challenged Claims were not rendered obvious. In doing so, the Office specifically considered and rejected alleged prior art disclosure of the “second” polynucleotide-specific tag sequence, which Petitioner now reprises with McCloskey. *E.g.*, EX1005, 238, 306. And as detailed above (§IV.A), in the prosecution of '981's '450 parent application, McCloskey '640's oligonucleotide was specifically distinguished from the claimed MID to overcome a potential rejection: “US20070020640 [McCloskey '640]... does not provide *segments* of a region, where each of the segments has the same MID sequence; [and] also *doesn't provide [a] composition in which all of the segments have a multiplex identifier that uniquely identifies the individual molecule of said contiguous region from which said segments originate.*” EX2002, 335 (italics on first use of “segments” original). Petitioner here simply rehashes these same rejected teachings now from the less-detailed, summary McCloskey article (EX1004). Thus, Petitioner's assertion that “***no arguments*** were made during examination with respect to McCloskey or any similar reference disclosing an oligonucleotide with two tags” is wrong. Pet.70 (emphasis original).

Petitioner's outdated, pre-*AB* cases—*3Shape A/S v. Align Tech., Inc.*, IPR2019-00160, Pap.9, 39-42 (June 11, 2019) and *Microsoft Corp. v. Parallel*

Networks Licensing, LLC, IPR2015-00486, Pap.10, 15 (July 15, 2015)—do not yield a different outcome. First, while pre-*AB* panels in *3Shape* 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. Moreover, even in this respect Petitioner’s cases are not on point: Petitioner *ignores* that both Linnarsson and McCloskey ’640 (a more detailed version of McCloskey (EX1004)) *were* substantively considered during the prosecution of the ’981 and its related applications.

Petitioner’s argument that “the Examiner only considered an anticipation rejection based on Linnarsson, and did not consider any obviousness rejections”—and thus “the [obviousness] grounds in this Petition... involve different tests for validity and different elements of proof” (Pet.70-71)—is factually wrong. *First*, the Office *explicitly* considered obviousness combinations for both Linnarsson and McCloskey ’640. The Office asserted *Linnarsson* in an obviousness-type double patenting rejection in combination with PO’s ’149 patent (EX1005, 157), and considered *McCloskey* ’640 in a potential obviousness combination with Laird in a related application. EX2002, 372-373 (“specific claim languages were discussed to overcome the potential rejection of said amended claims over Laird... *in view of McCloskey [’640]* (cited in the previous interview)”). And the second ’981 Notice of Allowance expressly concluded the art of record (including Linnarsson,

McCloskey '640, and Miner) did not render the claims obvious: “A thorough search of the prior art, including the prior art submitted in the newly filed IDS..., shows no art that teaches *or reasonably suggests* the claimed invention.” EX1005, 306. Thus, although Petitioner wholly ignores these aspects of '981's prosecution history, Petitioner's third and fourth pre-*AB* cases, *Caterpillar* and *Delphi*,⁴ which Petitioner cites as support for this argument, are also inapposite, as both of Petitioner's references were considered in obviousness rejections here and therefore there are not “new” arguments. Pet.71 (citing *Caterpillar Inc. v. Wirtgen*

⁴ Additionally, the secondary references in *Delphi* were neither before the examiner nor cumulative of references that were—whereas here, McCloskey is clearly cumulative of references previously cited by the Office, including both McCloskey '640 and Kanda, which were both substantively considered in related prosecutions, as well as Miner, which was disclosed in prosecution of the '981. *See supra*, §IV.A; *Delphi Tech., Inc. v. Microchip Tech., Inc.*, IPR2017-00861, Pap.14, 17 (Aug. 29, 2017) (declining to exercise discretion where ground's primary reference was “in a combination with other art not previously before the Patent Examiner” and the secondary references were not “substantially similar” to the art that was).

Am., Inc., IPR2018-00155, Pap.8, 11-13 (May 23, 2018) and *Delphi*, IPR2017-00861, Pap.14, 15).

Thus, *AB* part one clearly points to denial.

B. Advanced Bionics Part Two

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's argument for error is simply that "the Examiner materially erred by not considering the relevant teachings in the [McCloskey] '640 Publication."

Pet.71. Petitioner is, to begin with, wrong on the facts: McCloskey '640 *was* raised by the Office and substantively considered during prosecution of applications leading to the '981 Patent, and was distinguished by Applicant. And Petitioner is also wrong on the law: Petitioner's threadbare assertion fails to show any actual "error" by the Examiner.

Petitioner is factually incorrect, ignoring the prosecution history of '981's parent applications where the Office raised and expressly considered (and Applicant expressly distinguished) McCloskey '640. Petitioner completely fails to address the prosecution history of '981's parent applications, but this history is considered under the *AB* analysis. *Becton*, 22-23; *see Motorola*, 16 n.8 ("In determining whether the same or substantially the same prior art previously was presented to the Office, the Board considers *applications directly related to the challenged patent*, such as a parent application."). In applications directly related to the '981 Patent, (1) the Applicant expressly distinguished McCloskey '640 from the claimed MID and overcame a potential rejection based on McCloskey '640 (EX2002, 335-336, 372-373, 383), (2) the Examiner made other rejections regarding the MID that were overcome (*supra*, §IV.A), and (3) the Examiner expressly acknowledged the IDS that listed McCloskey '640 (EX2009, 76 (April 2, 2014 IDS), 130 ("The method steps... are non-obvious improvements over the arts of the record and the ones cited in the IDS of April 2, 2014)).

Petitioner fails to explain how the teachings of McCloskey '640, summarized in McCloskey, were purportedly “overlook[ed]” in light of this prosecution history. *E.g.*, Pet.71-72. Petitioner also fails to explain why *Becton* factor “(c)” weighs against exercising the Board’s discretion to deny institution where McCloskey '640 was discussed as the basis of contemplated rejections by the Office. Pet.72; EX2002, 335-336, 372-373, 383.

In the '450 application, the Examiner and Applicant held an interview in which the Examiner “requested that the Applicants provide a brief summary of how the claims are distinguished from [a set of] references.” EX2002, 335. One of these references explicitly raised by the Office and distinguished by Applicant was McCloskey '640. *Id.* Applicant explained that McCloskey '640 “does not provide *segments* of a region, where each of the segments has the same MID sequence; [and] also doesn’t provide [a] composition in which all of the segments have a multiplex identifier that *uniquely identifies the individual molecule* of said contiguous region from which said segments originate.” *Id.* (italics on first use of “segments” original). As Applicant’s submissions reflect, the “Examiner indicated that the [discussed] amendment [*see supra*, 14] would likely distinguish the claims....” EX2002, 336. Further, the Office’s Notice of Allowance in the '450 application acknowledged that “specific claim languages were discussed *to overcome the potential rejection* of said amended claims over Laird... *in view of*

McCloskey et al (cited in the previous interview).” EX2002, 372-373. The Notice continued:

It is also noted that *the bulk of the cited references in the said IDSs or in the field of molecular tagging prior to the filing date of the instant application discloses tagging of sample or a nucleic acid of interest with an identifier in the form of barcode, or multiplex identifier or zipcode or tagging sequences to track it in further analysis.* However, it is [sic] *in the Examiner’s opinion it would not have been obvious to [POSITA] to modify the references of the record... to arrive at the claimed composition... wherein, in said composition, all of the segments of each of the nucleic acid molecules of the contiguous region comprises a unique MID sequence that uniquely identifies each of the nucleic acid molecules.*”

EX2002, 375. Thus, contrary to Petitioner’s assertions, the Office certainly did not “overlook[]” McCloskey ’640 during the prosecution leading to the ’981 (Pet.72)—to the contrary, McCloskey ’640 was raised by the Office, explicitly discussed, and overcome by Applicant.

Nor did the Office overlook the numerous other references asserted to disclose a polynucleotide-distinguishing tag in the applications to which the ’981 claims priority, and over which McCloskey is cumulative. *See supra*, §IV.A; Pet.73. And, as noted above, the Examiner expressly considered still more

references and arguments in this same vein that Petitioner ignores. For example, in '343 application, the Examiner argued U.S. Patent Pub. No. 2007/0238113 to Kanda, cited on '981's face, taught the "limitation of broadly recited multiplex identified because F2 can be used as the tag to differentiate a polynucleotide in the sample." EX2005, 728-729. The Examiner also argued that Laird disclosed the same. EX2005, 807-817. Applicant overcame both rejections, and the Examiner stated in its "Reasons for Allowance" that "Laird alone or in combination with the art of record does not disclose or make it obvious the claimed method steps 'a' to 'c', wherein the polynucleotide strand comprises... *a multiplex identifier (MID) comprising a unique nucleotide sequence that distinguishes said polynucleotide strand from other polynucleotide strands in said sample*..." EX2005, 868. The Examiner continued, noting "The instant method has several advantages... as compared to other extraction methods... that only use a single oligonucleotide sequence, allows to analyze homologous genomic locations in a multiplexed sample (i.e., a sample having polynucleotides from different genomic samples) in which the polynucleotides are tagged with the multiplex identifier domain." EX2005, 868-869. Thus, these same arguments were explicitly considered in the prosecution of the parent applications and were overcome, and there was no "error" in the Examiner determining that McCloskey '640 and similar art did not

disclose or render obvious the Challenged Claims’ polynucleotide-distinguishing tag.⁵

Petitioner also mischaracterizes ’981’s immediate prosecution history, implying the Examiner made just one “cursory statement that ‘the instant claims are neither obvious nor anticipated by the prior art.’” Pet.71-72 (arguing Examiner made this assertion in connection with double patenting “without expressly identifying any reference”). But Petitioner wholly ignores (in addition to the express discussions in prosecution of McCloskey ’640’s teachings) the Examiner’s further statements in the second Notice of Allowance:

A thorough search of the prior art, including the prior art submitted in the newly filed IDS, filed after the Notice of Allowance mailed on 8/28/2018, shows no art that teaches or reasonably suggests the claimed invention. Likewise, amendments to the claims filed

⁵ Similarly, in the ’981’s grandparent ’694 application the Office once again expressly confirmed it had considered the McCloskey ’640 publication, stating in its Notice of Allowance that the “method steps of instant pending claims comprise the allowed limitation of ’767 patent, which are non-obvious improvements over the arts of the record ***and the ones cited in the IDS of April 2, 2014.***” EX2009, 130. McCloskey ’640 is the ninth reference listed in that IDS. EX2009, 75-76.

9/11/2018, only serves to further clarify *the claimed invention*, which
is free of the art.

EX1005, 306. These statements were not made in the context of double patenting, and they affirmatively confirm that the Examiner performed and considered the results of a “thorough search of the prior art” and “the newly filed IDS,” *which also included Miner*. EX1005, 285, 306; EX1013. Petitioner and its expert, Dr. Cooper, concede Miner includes the same teachings as McCloskey, namely “allow[ing] one to avoid amplification bias and measur[ing] the number of unique molecules present in an original DNA sample.” Pet.10-11 (citing Miner and McCloskey); EX1002, ¶¶92-93. Indeed, Miner uses McCloskey’s same oligonucleotide for the same purpose: a batch-stamp and barcode to identify contamination and redundant sequences in PCR. EX1013, 1; EX1004, 6. Petitioner neither acknowledges nor confronts this explicit evidence that contradicts Petitioner’s arguments of error.

As detailed above, Petitioner is clearly incorrect that the Examiner “erred by not considering the relevant teachings in the ’640 Publication” or by “failing to acknowledge the teachings in McCloskey that disclose the second tag.” Pet.71-73. McCloskey ’640 was raised by the Office, considered multiple times, and distinguished—including specifically in connection with McCloskey ’640’s purported disclosure of a second tag. *See, e.g.*, EX2002, 335-336 (McCloskey

'640 “doesn’t provide [a] composition in which all of the segments have a *multiplex identifier that uniquely identifies the individual molecule* of said contiguous region from which said segments originate”), 372-373. Thus, Petitioner’s only allegation of “error” is, itself, wrong.

Petitioner’s allegation of “error” is legally insufficient under AB part two. Even setting aside Petitioner’s unsupportable mistakes of fact, Petitioner’s bare conclusory assertion that “the Examiner materially erred by not considering the relevant teachings in the ’640 Publication” is also legally insufficient to meet Petitioner’s burden of showing a material error. Pet.71.

First, Petitioner argues that “the fact that the ’640 Publication ‘was not the basis of a rejection weighs strongly against exercising [the Board’s] discretion to deny institution.” Pet.72. But this is nothing more than “equat[ing an] Examiner’s *silence* in discussing relevant prior art to a material error,” which (even if, *arguendo*, it were factually applicable here (it isn’t)) would **not** be a showing of error. *E.g.*, *Ivantis*, IPR2022-01533, Pap.14, 19; *Eyenovia*, IPR2022-00965, Pap.7, 19 (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); *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 petitioner’s only argument of error was “the prior art references in the Petition ‘were not substantively considered during [prosecution]’”); *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20-22 (Nov. 1, 2022) (denying institution and rejecting 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 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.”); *Motorola*, 22-23.

Petitioner’s only other argument is that the “Examiner’s cursory statement that ‘the instant claims are neither obvious nor anticipated by the prior art’ was erroneous” because McCloskey taught the “second tag” sequence missing from Linnarsson. Pet.72. But as explained above, this ignores not only ’981’s second Notice of Allowance⁶—but also the substantive consideration of McCloskey’s teachings in the prosecution of related applications leading to the ’981—both of which directly contradict Petitioner’s argument that McCloskey ’640 was

⁶ In that second Notice of Allowance, the Examiner stated she affirmatively considered “the prior art in the newly filed IDS,” which included Miner. EX1005, 285, 306.

“overlook[ed]” (Pet. 72). These affirmative discussions of McCloskey ’640 and other references bely Petitioner’s attempt to limit the Office’s extensive prosecution analysis over the chain of seven non-provisional applications leading to the ’981 to only a single statement in ’981’s first Notice of Allowance. Pet.72; *supra*, §IV.

Petitioner cites an array of inapposite cases, for *AB* part two, based on its attempt to ignore the numerous related applications in ’981’s prosecution history. When the full prosecution history is considered, as it must be, Petitioner’s error in relying on these decisions is glaringly apparent. For example, while in *Cellco Partnership v. Huawei Device Co.*, IPR2020-01117, Pap.10, 13 (Feb. 3, 2021), there was no indication that the IPR reference was the basis of a rejection, here McCloskey ’640 was expressly identified by the Office in the related ’450 application as a potential basis for rejection, and was overcome by Applicant. EX2002, 335-336, 372-372. Indeed, if anything, *Cellco* supports the Board exercising its discretion and denying institution. *Becton*, 22-23 (“We are not persuaded on this record that rearranging previously substantively considered prior art, and advancing essentially the same positions raised by the Examiner during prosecution of the parent application, presents persuasive new evidence of unpatentability that was not evaluated previously by the Office.”). Similarly, unlike in *Amber.IO, Inc. v. 72LUX, Inc.*, IPR2020-00015, Pap.8, 20 (Apr. 1, 2020),

the alleged prior art teachings of McCloskey were substantively considered and distinguished in prosecution of the related applications for the same teaching of a polynucleotide-specific tag that Petitioner alleges the Examiner overlooked. Pet.72; EX2002, 335-336, 372-373. Indeed, Petitioner does not even *discuss*, let alone contend there was any error in, Applicant's or the Office's stated understanding of McCloskey '640 when it was distinguished during prosecution. Pet.72-73.

Thus, both parts one and two of *AB* point to denial, and—as a first threshold reason to deny the Petition without the need for further discussion—the Board should exercise its discretion under § 325(d) to deny institution here.

VI. Claim Construction

Terms need only be construed “to the extent necessary to resolve the controversy.” *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). PO agrees that at this time, solely for purposes of an institution decision on the Petition, no terms require explicit construction.

VII. Grounds 1 and 2: The Petition Must Be Denied Because Petitioner Fails to Allege—Let Alone Establish—That Its References Are Analogous Art To The '981 Patent

Nowhere does Petitioner assert—let alone attempt to show—that either of the two references named in its grounds (primary reference Linnarsson and secondary reference McCloskey) is analogous art *to the '981 Patent*. See Pet.52-

53. But this omission is *fatal* to the Petition: 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*, 66 F.4th at 1374. “[A] patent challenger must compare the reference *to the challenged patent*.” *Id.*

Petitioner here cannot meet its burden because it failed to perform the required analogous art analysis by addressing whether its relied-upon art is analogous *to the challenged patent*; it only asserts that McCloskey, Petitioner’s secondary obviousness reference, is analogous to Linnarsson, its primary obviousness reference. Pet.52-53; EX1002, ¶187. Thus, because Petitioner’s grounds rely entirely on obviousness and Petitioner was therefore required to establish that its obviousness art is analogous to the challenged patent as a threshold issue, Grounds 1 and 2 must both be rejected because Petitioner cannot meet its burden to establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.4th at 1380.

VIII. Ground 1: Petitioner’s Obviousness Analysis Is Also Legally Deficient Because Petitioner Fails To Sufficiently Explain How Its Proposed Combination Would Be Implemented Or Establish Motivation To Combine⁷

Petitioner failed for at least three reasons to establish that Linnarsson in view of McCloskey renders obvious “a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell.” *First*, Petitioner fails to address the incompatibilities between Linnarsson and McCloskey that are apparent on the face of the references, themselves. *Second*, Petitioner’s purported motivation to combine is premised on its erroneous and unsupported assertion that McCloskey barcodes “*each sample polynucleotide*.” Because Petitioner failed to establish the premise on which Petitioner expressly conditioned its motivation, Petitioner’s motivation argument fails. *Third*, Petitioner’s reasonable expectation of success argument is also tied to

⁷ The Petition’s Ground 1 *heading* identifies it as covering all six Challenged Claims, which conflicts with its “Identification of Challenge,” which purports to be directed to claims 1-4 and 6 only. Pet.37, 5. Petitioner’s Ground 1 discussion does not address Claim 5 and thus Petitioner cannot meet its burden of showing Claim 5 is invalid under its Ground 1.

Petitioner's same failed assertion about McCloskey tagging "each sample nucleotide" and therefore also fails.

A. Petitioner Ignores The Differences And Incompatibilities Between Linnarsson And McCloskey

Petitioner asserts that McCloskey's barcode would simply be added to Linnarsson's tagged cDNA synthesis primers ("CDSs") and/or template switching oligonucleotides ("TSOs"), but Petitioner fails to even acknowledge the differences between the two references, let alone address how those differences would be resolved in combining them. Indeed, Linnarsson is focused on gene *expression* (based on mRNA transcribed from the genes to be expressed). *See* EX1003, 1 (Abstract); Pet.6. Linnarsson's tags are added to track the cell of origin of the transcribed mRNA when reverse-transcribing the mRNA to cDNA as part of the creation of a comprehensive cDNA *library*. EX1003, 9:24-25, 10:32-33; Pet.24-25. McCloskey, in contrast, is not about gene expression. Rather, McCloskey is about tagging copies of the DNA of a *particular gene*. EX1004, 6; Pet.30. McCloskey's oligonucleotides anneal only to a specific binding site on a gene, and are used when amplifying a gene of interest via PCR in a bulk analysis to identify whether the gene (including any allele or mutation) is present in the tested sample, but provides no information about whether or not that gene is expressed (EX1004, 4; Pet.30, 33).

Petitioner vaguely refers to the use of Linnarsson's "CDS and/or TSO" in the combination, but fails to address, for example, that Linnarsson's *CDS* tags are designed to analyze gene expression and anneal to **every** mRNA molecule in the sample in connection with reverse-transcribing it into cDNA—indeed, Petitioner admits that the tags in Linnarsson's CDSs anneal to **every** mRNA molecule—for example, to mRNA's poly-A tail. Pet.25; EX1003, 24:13-20, Figure 2. Similarly, Linnarsson's *TSO* tags are designed as part of the gene expression analysis to universally anneal "to the series of cytosine nucleotides at the end of the newly-synthesized [cDNA] strand." Pet.26-27; EX1003, 18:19-26. In other words, Linnarsson's tags are designed to anneal to **each and every** mRNA and/or cDNA to analyze gene expression, and they are **not** designed to anneal solely to a **particular** gene or allele; nor does Petitioner claim they are. McCloskey's tag, in contrast, has a "3' genomic target binding site" that anneals **only** to a DNA sequence specific to the genomic target binding site and is particular **only** to the specific gene (and targeted DNA sequence) to which it is designed to bind. EX1004, 3-4; Pet.30-31. But nowhere does Petitioner address the distinction between the tags in McCloskey, which anneal to a specifically-targeted sequence, and the CDS and TSO tags in Linnarsson, which generically anneal to each and every mRNA and reverse-transcribed cDNA strand, respectively. EX1003, 18:19-30. Indeed, McCloskey's tag is not designed to anneal to Linnarsson's mRNA

sample polynucleotides or a series of cytosine nucleotides at the end of a newly-synthesized and reverse transcribed strand, which Petitioner does not establish are present in McCloskey. Petitioner ignores these distinctions in summarily asserting that there would be a motivation to combine and reasonable expectation of success.

B. Petitioner’s Motivation To Combine Fails Because Petitioner Fails To Establish The Premise Underlying Its Argument

With respect to motivation to combine, Petitioner relies on “McCloskey’s method of including a second tag sequence on the MID to distinguish sample polynucleotides” as solving Linnarsson’s problem of “amplification bias.” Pet.53. Petitioner asserts there is a motivation to combine Linnarsson with McCloskey because McCloskey “provides the exact solution. By incorporating a second tag in an oligonucleotide that uniquely identifies *each sample polynucleotide* prior to amplification, McCloskey ‘*solve[s]*’ this source-uncertainty problem for DNA sequences generated by standard PCR.” Pet.53-54; *see also* EX1002, ¶190.

First, Petitioner does not establish that McCloskey identifies *each sample polynucleotide*. Indeed, as discussed above, McCloskey tags *only* copies of a *particular* gene of a cell’s DNA. Petitioner fails to explain how McCloskey could solve any alleged amplification bias problem (in the context of Linnarsson’s creation of a cDNA library based on mRNA of genes expressed in a cell) *when McCloskey teaches tagging only a particular gene to solve the problem of false-positives due to contamination, and does not teach how to tag, let alone*

distinguish, each and every gene, let alone each expressed mRNA molecule

within a sample. EX1004, 1-2. Indeed, Petitioner identifies no teaching in McCloskey of a second tag “that uniquely identifies *each* sample polynucleotide” in a sample, as Petitioner argues is necessary to motivate the combination. Pet.53-54. And because McCloskey’s tags are specific to copies of a particular gene, McCloskey does not teach giving each mRNA molecule (or even each DNA molecule) in a cell its own barcode.

Second, Petitioner ignores that Linnarsson itself addresses the amplification bias issues that could interfere with its process and explains how to address them. Pet.54. Petitioner does not explain how any remaining amplification bias in Linnarsson creates any issues with its own process, how any amplification bias “solution” from McCloskey would improve Linnarsson, or why POSITA would have been motivated to address in Linnarsson an issue that Linnarsson already addresses. Pet.54; *Life Spine, Inc. v. Globus Med., Inc.*, IPR2022-01603, Pap.8, 40 (June 12, 2023) (denying institution where petitioner “has not articulated sufficient reasoning to explain why a POSITA would modify [its base reference] to address a concern [it] already addresses via a different mechanism.”); *Google LLC v. Jawbone Innovations, LLC*, IPR2022-00889, Pap.12, 20 (Nov. 14, 2022) (denying institution where petitioner failed to explain “motiv[ati]on to solve a problem [the reference] already solves.”).

In addition, while Petitioner argues about Linnarsson’s amplification bias “problem,” Petitioner’s citations relate instead to “source-uncertainty,” not “amplification bias.” Pet.54-55. For example, Petitioner asserts that McCloskey solves the amplification bias problem by use of a barcode, and includes a single citation to McCloskey with the following quote: “We have developed and applied molecular encoding principles to solve this source-uncertainty problem for DNA sequences generated by standard PCR.” Pet.53-54. But the *source-uncertainty* issue identified in McCloskey is purportedly solved by McCloskey’s batch-stamps—*not* by its barcodes (which Petitioner urges are the “tags” that should be added to Linnarsson). Pet.51, 53-54; EX1004, 6 (“Contaminant sequences were identified by batch-stamps....”); *see also* EX1004, 1 (“Batch-stamps specify the date and sample identity.”). In the same section Petitioner again points to McCloskey “*solv[ing]*” this source-uncertainty problem for DNA sequences generated by standard PCR.” Pet.54. Again, the source-uncertainty was solved by McCloskey’s batch-stamps. ***And all the batch-stamps used in an experiment are identical:*** “The assigned batch-stamp is registered for a specific sample run on a specific date and is used only once.” EX1004, 4. This reliance on batch-stamps cannot suffice in view of Petitioner’s apparent reliance on barcodes—not batch-stamps—for a second tag. Petitioner’s internally inconsistent, confusing motivation arguments fail for this reason, too.

C. Petitioner Fails To Establish Reasonable Expectation of Success

Petitioner's reasonable expectation of success also fails, as it, too, expressly depends on Petitioner's unexplained and unsupported assumption that McCloskey has a tag that "uniquely identif[ies] each sample polynucleotide." Pet.55.

Petitioner does not explain how *each* sample nucleotide in Linnarsson would be tagged based on McCloskey's teachings, especially where Linnarsson's CDS tags anneal to a sequence present in *all mRNA* molecules and Linnarsson's TSO tags anneal to a generic repeat sequence ("a series of cytosine nucleotides") present in *recently synthesized cDNA created from cellular mRNA* (and therefore cannot target a particular sequence). In other words, McCloskey's tags anneal *only* to copies of a *particular gene* and *only* copies of *that particular gene* receive a unique barcode. Thus, because Petitioner has made no showing that McCloskey even tags—let alone "uniquely identif[ies]"—*each polynucleotide in the sample* (as opposed to, say, specific alleles (different versions of the same gene)), Petitioner cannot satisfy its own specified condition for showing a reasonable expectation of success, which is expressly conditioned on McCloskey disclosing tags that "uniquely identify each sample polynucleotide." Pet.55.

IX. Ground 2: Ground 2 Additionally Fails Because It Lacks Particularity, Relies On Improper Evidence, And Fails To Show A Motivation To Combine

Ground 2 purports to build from and add to the Linnarsson-McCloskey combination of Ground 1, but adds some unspecified number of additional references to the combination in attempting to cover the additional limitations of dependent claim 5. Ground 2 fails, including at least for the same reasons as Ground 1.

In addition, Ground 2 fails to identify with particularity the art it actually relies on. Ground 2 purports to be “Linnarsson in View of McCloskey, and Further in View of *the Knowledge of a POSA*.” Pet.66. But, Petitioner cites to alleged admissions of PO⁸ (in a different litigation on different patents), as well as the Hug, Okayama, Shibata, and Hayazhizaki references. Pet.67-68. It is thus unclear whether Petitioner is relying on each of these references separately, together, or in sub-combinations, or on all of these potential permutations to teach the “ligation reaction” limitation.

⁸ IPRs are limited in scope to printed publications and patents. §311(b). To the extent Petitioner purports to rely on alleged admissions for a substantive claim limitation, Ground 2 is additionally improper for that reason, as well.

If instituted, PO would be forced to guess which combination of reference(s), alleged admission(s) (from an unrelated litigation on unrelated patents in arguments unrelated to obviousness), and/or “Knowledge of a POSA” comprises Petitioner’s Ground 2. Pet.66-68. As a result, it would be near impossible for PO to meaningfully address each of these many options in the appropriate level of detail, and Ground 2’s ambiguities might tempt Petitioner to improperly shift theories in response to PO’s argument. *Avant Tech., Inc. v. Anza Tech., Inc.*, IPR2018-00828, Pap.7, 13-14 (Oct. 16, 2018). This lack of particularity is insufficient to meet Petitioner’s burden and denies PO due process, as PO has no meaningful opportunity to respond to such an amorphous Ground. *ADT LLC v. Vivint, Inc.*, IPR2022-00634, Pap.7, 14-15 (Oct. 4, 2022) (noting that petitioner’s lack of particularity in its obviousness ground would, if instituted, prejudice patent owner where petitioner mapped multiple references to each limitation so it was not clear which teachings from which reference were used in the combination); *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Pap.20, 22-23 (Mar. 6, 2019) (informative) (“The extent to which these additional documents may be relied upon to fill gaps in the asserted references with respect to the claimed subject matter increases our concern that the Petition lacks the required particularity, and, instead, turns the Petition into an empty invitation for the Board and Patent Owner to search the record for evidence that might support the full breadth of Petitioner’s

contentions.”); *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.”); *see also* §312(a)(3). This is improper and this, too, requires denial under, *inter alia*, §§314(a) and 312(a)(3). *Adaptics*, IPR2018-01596, Pap.20, 24.⁹

X. Conclusion

As detailed above, Petitioner has failed to meet its burden to show there is a reasonable likelihood it 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.

⁹ *See also Jiangsu Sainty Sumex Tools Corp. v. Milwaukee Elec. Tool Corp.*, IPR2021-00373, Pap.19, 23-24 (July 6, 2021) (denying institution under §314(a) where petitioner’s asserted combinations included “one or more of” five references “in combination with one or more of common knowledge [or] common sense,” explaining this “approach [] raises a formidable number of possible prior art combinations” and finding “no good reason to subject Patent Owner to the burden and expense of a trial based on so many possible prior art combinations”).

Respectfully submitted by:

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S 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 11,621 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S 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:

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