

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

10X GENOMICS, INC.,
Patent Owner

Case IPR2023-00955
Patent 10,240,197

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

LIST OF EXHIBITS

Exhibit	Description
EX2001	File History of U.S. App. No. 15/677,957
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., IPR2023-00876, Pap.1, (April 20, 2023)
EX2009	File History of U.S. App. No. 14/172,694
EX2010	Declaration of Sayem Osman

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Challenged Claims Are Directed To A Novel, Non-Obvious Invention...4	
III.	Petitioner’s Recycled References	6
	A. Linnarsson (EX1003)	6
	B. McCloskey (EX1004)	8
	C. McCloskey II (EX1055)	10
IV.	Petitioner Ignores The Bulk Of 197’s Prosecution History	10
	A. The Examiner’s “Second Tag” Art Included McCloskey II.....	11
	B. The Examiner’s Reliance On Linnarsson.....	17
V.	Institution Should Be Denied Under 35 U.S.C. §325(d).....	22
	A. Advanced Bionics Part One	23
	B. Advanced Bionics Part Two	36
VI.	Claim Construction	46
VII.	Grounds 1-3: The Petition Must Be Denied Because Petitioner Fails to Allege—Let Alone Establish—That Its References Are Analogous Art To The ‘197 Patent	46
VIII.	Grounds 1-3: The Merits Of Petitioner’s Obviousness Analysis Is Also Legally Deficient	47
	A. Petitioner Fails To Sufficiently Explain How Its Proposed Combination Would Be Implemented Or Establish Motivation To Combine	48
	1. Petitioner Ignores The Differences And Incompatibilities Between Linnarsson And McCloskey	48

2.	Petitioner’s Motivation To Combine Fails Because Petitioner Fails To Establish Its Amplification Bias Premise	51
3.	Petitioner Fails To Establish Reasonable Expectation of Success.....	54
B.	Petitioner Fails To Show McCloskey Discloses “using the... second tag sequence to count a number of sample polynucleotides...”	56
IX.	Ground 2: Ground 2 Additionally Fails Because It Lacks Particularity, Relies On Improper Evidence, And Fails To Show A Motivation To Combine.....	58
X.	Conclusion	60

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>3Shape A/S v. Align Tech., Inc.</i> , IPR2019-00160, Pap.9 (June 11, 2019).....	34
<i>ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.</i> , 694 F.3d 1312 (Fed. Cir. 2012)	57
<i>Adaptics Ltd. v. Perfect Co.</i> , IPR2018-01596, Pap.20 (Mar. 6, 2019)	59, 60
<i>ADT LLC v. Vivint, Inc.</i> , IPR2022-00634, Pap.7 (Oct. 4, 2022)	59
<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH</i> , IPR2019-01469, Pap.6 (Feb. 13, 2020)	<i>passim</i>
<i>Alarm.com, Inc. v. Vivint, Inc.</i> , IPR2022-00728, Pap.6 (Nov. 1, 2022)	26
<i>Amber.IO, Inc. v. 72LUX, Inc.</i> , IPR2020-00015, Pap.8 (Apr. 1, 2020).....	45
<i>Autel Intelligent Tech. Corp. v. Orange Elec. Co.</i> , IPR2021-01545, Pap.8 (Apr. 8, 2022).....	22, 26
<i>Avant Tech., Inc. v. Anza Tech., Inc.</i> , IPR2018-00828, Pap.7 (Oct. 16, 2018)	59
<i>Axon Enter., Inc. v. Digital Ally, Inc.</i> , IPR2017-00515, Pap.10 (July 6, 2017)	54, 57
<i>Becton, Dickinson and Co. v. B. Braun Melsungen AG</i> , IPR2017-01586, Pap.8 (Dec. 15, 2017).....	<i>passim</i>
<i>Cellco Partnership v. Huawei Device Co.</i> , IPR2020-01117, Pap.10 (Feb. 3, 2021).....	45

<i>Cuozzo Speed Techs., LLC v. Lee</i> , 579 U.S. 261 (2016).....	60
<i>Darfon Elecs. Corp. v. Shipman</i> , IPR2022-01008, Pap.11 (Dec. 2, 2022).....	26
<i>Eyenovia, Inc. v. Sydnexis</i> , IPR2022-00965, Pap.7 (Nov. 7, 2022)	31, 44
<i>Google LLC v. Jawbone Innovations, LLC</i> , IPR2022-00889, Pap.12 (Nov. 14, 2022)	52
<i>Ivantis, Inc. v. Sight Scis., Inc.</i> , IPR2022-01529, Pap.16 (Mar. 21, 2023)	16, 24, 31, 38
<i>Ivantis, Inc. v. Sight Scis., Inc.</i> , IPR2022-01533, Pap.14 (Mar. 27, 2023)	30, 44
<i>Jiangsu Sainty Sumex Tools Corp. v. Milwaukee Elec. Tool Corp.</i> , IPR2021-00373, Pap.19 (July 6, 2021)	60
<i>John Crane, Inc. v. Finalrod IP, LLC</i> , IPR2016-01827, Pap.6 (Jan. 31, 2017).....	56, 57
<i>Keysight Techs., Inc. v. Centripetal Networks, Inc.</i> , IPR2022-01421, Pap.9 (Mar. 22, 2023)	31
<i>Life Spine, Inc. v. Globus Med., Inc.</i> , IPR2022-01603, Pap.8 (June 12, 2023).....	52
<i>Limelight Networks, Inc. v. Akamai Techs., Inc.</i> , IPR2016-01631, 2016 WL 8115506 (P.T.A.B. Dec. 30, 2016).....	35
<i>Microsoft Corp. v. AlmondNet, Inc.</i> , IPR2022-01319, Pap.9 (Jan. 30, 2023).....	44
<i>Microsoft Corp. v. Parallel Networks Licensing, LLC</i> , IPR2015-00486, Pap.10 (July 15, 2015)	34
<i>Microsoft Corp. v. ThroughPuter, Inc.</i> , IPR2022-00757, Pap.10 (Nov. 1, 2022)	31, 44

<i>Motorola Mobility LLC v. Maxell, Ltd.</i> , IPR2022-01287, Pap.11 (Feb. 2, 2023)	22, 31, 37, 44
<i>Personal Web Techs., LLC v. Apple, Inc.</i> , 848 F.3d 987 (Fed. Cir. 2017)	54
<i>Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.</i> , 66 F.4th 1373 (Fed. Cir. 2023)	3, 46, 47
<i>Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.</i> , 200 F.3d 795 (Fed. Cir. 1999)	46
Statutes	
35 U.S.C. §312(a)(3)	60

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 1-26 (the “Challenged Claims”) of U.S. Pat. No. 10,240,197 (the “’197 Patent”/“’197”) are “routine and conventional” (Pet.2), but concedes they are *novel*: Petitioner advances no §102 ground, and instead argues only that ’197’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 three grounds assert obviousness based on recycled references (**Linnarsson**, and **McCloskey**, and **McCloskey II**) 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 and overcome, and featured prominently in the

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.

initial Notice of Allowance of the related U.S. Patent No. 10,155,981 (the “’981 Patent”/“’981”), against which the ’197 is terminally disclaimed. EX2001, 238; EX1005, 114. **McCloskey**, Petitioner’s secondary reference (EX1004), is simply a less detailed version of “US20070020640” to McCloskey *et al.* (“McCloskey II”) (EX1055), Petitioner’s other secondary reference. ***McCloskey II, was also asserted by the Office, substantively considered, and then overcome*** applications leading to ’197. *See, e.g.*, EX2002, 335-336, 372-373. Petitioner either misunderstands or simply ignores the relevance of the prosecution history of related patents to §325(d).

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 Linnarsson, McCloskey, and McCloskey II—is palpably false, as Linnarsson and McCloskey II (of which McCloskey is cumulative) were ***substantively considered*** in ’197’s priority applications, including ’981. This is exactly the case §325(d) was meant to prevent.

Second, Petitioner also entirely fails to assert or analyze whether its references are analogous art to the ’197 Patent—instead discussing only whether they are analogous to one another (and only in Ground 1, so McCloskey II is never discussed). This failure impacts all three grounds and requires denial. *See, e.g.*,

Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc., 66 F.4th 1373 (Fed. Cir. 2023) (reversing a Final Written Decision for this failure).

Even setting aside these fatal threshold errors, Petitioner’s purported motivation to combine with a reasonable expectation of success fails for its Ground 1 claim 1 argument, on which all other claims and Grounds depend. Linnarsson is focused on gene *expression* and tagging *all* of the mRNA transcribed from expressed genes. *See* EX1003, 1 (Abstract). In contrast, McCloskey is about stamping only copies of a *particular gene*. McCloskey 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.41-42. 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 attempts to sidestep the fact 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.

Finally, Petitioner suggests that the Challenged Claims lack written description or are somehow invalid because PO made §101 arguments about unrelated patents in an unrelated proceeding (Pet.10-13). 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 ’197, “Methods For Analyzing Nucleic Acids From Single Cells,” claims priority to an August 20, 2009 provisional. EX1001, 1; Pet.6. ’197’s Challenged Claims are directed to innovative methods of counting 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*, thus facilitating counting the number of polynucleotides originating from each cell. EX1001, 6:33-7:22, cl.1 (30:16-39). 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 ’197 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, McCloskey, and McCloskey II cannot. EX1001, 6:33-7:22, cl.1 (30:16-39). The specification explains that combinatorially tagging a 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 polynucleotide 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 ’197 Patent, like many other patents, discloses multiple inventions. EX1001, 1:50-62. One of the other inventions disclosed in the ’197 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 References³

A. Linnarsson (EX1003)

Linnarsson, a patent publication identifying Sten Linnarsson as sole inventor (EX1003 (“Linnarsson”), 1), is cited on ’197’s face and was the basis of multiple rejections by the Office in the ’957 application that matured into the related ’981 (against which ’197 is terminally disclaimed), as well as ’981’s parent (’094) application. EX1001, 2; EX1005, 114; EX2001, 153-156; 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.17. As part of this process, “single cells are placed in separate wells of a 96-well plate and lysed....” EX1003, 4:8-13; Pet.28. Each of those cells “contain[s] a plurality of mRNA molecules.” EX1003, 3:26-30; Pet.28.

³ Petitioner (apparently hoping to evade its word limit) purports to incorporate by reference the “technical background sections” (totaling six pages) in a separate petition filed by Petitioner on a related patent (as well as the supporting expert declaration). Pet.5-6. This is improper, and these six pages *far* exceed (by more than 1,000 words) the 38 words Petitioner says remain below its 14,000-word limit. *See* Pet.77; Pet.5 (citing EX2008, §IV).

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.17. The CDSs and/or TSOs identify the cell from which a tagged polynucleotide originated. EX1003, 19:4-7; Pet.17-19.

According to Petitioner, “Linnarsson discloses a cDNA synthesis primer... that includes a sequence of thymines....” Pet.17-18. Because every mRNA molecule has a poly-A tail, “a sequence of thymines... hybridiz[e] with a sequence of adenines making up a poly-A tail... of an mRNA strand.” Pet.17-18; EX1003, 24:13-20, Fig.2. Thus, such CDSs are able to anneal to every mRNA molecule in a well.

Similarly, TSOs have a poly-guanosine sequence. EX1003, 18:19-21; Pet.18-19. 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.18-19. The poly-guanosine sequence in TSOs “‘anneals transiently’ to the series of cytosine nucleotides at the end of [a] newly-synthesized strand.” Pet.18-19; 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 during 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.19-20.

Linnarsson's method results in all the mRNA extracted from a single cell being tagged with the same barcode as it is reverse transcribed 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, 1. McCloskey purports to address a "source-uncertainty" problem that arises when pooled DNA samples are amplified. EX1004, 1, 2. To address this problem, McCloskey adds an "encoding oligonucleotide" with a batch-stamp and barcode via primer extension as part of the DNA amplification process. EX1004, 2-4; Pet.22. The batch-stamp identifies the batch sample from which the cells originated to identify contamination (*i.e.*, to identify sequences originating from a different patient or sample left over 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.22.⁴ 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.22-23.

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), *it does not tag other genes* (which, in McCloskey's process, are not amplified). EX1004, 2, 4-5.

McCloskey discloses that its incorporation of oligonucleotides into the amplified 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

⁴ Alleles are different versions of the same gene. EX2003, 3.

interest is amplified. 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.*

C. McCloskey II (EX1055)

Petitioner's EX1055 is, as Petitioner admits, "a sister patent application that goes along with the McCloskey publication" and, "similar to McCloskey, McCloskey II also discloses a method for tagging polynucleotides with 'a molecular barcode and batch-stamp.'" Pet.26. Thus, McCloskey II shares McCloskey's deficiencies. Pet.26. Notably, McCloskey II is relied on only in Ground 3 for the "addition[al]" teaching that the "barcode sequence may comprise up to 30 nucleotides." Pet.26.

IV. Petitioner Ignores The Bulk Of 197's Prosecution History

Clearly hoping to lead the Board *away* from the Office's extensive analysis during prosecution of the eight non-provisional applications in '197's direct family tree, Petitioner myopically focuses solely on the single application (16/197,047

(“’047 application”)) that matured directly into the ’197 Patent. Pet.10 (“Prosecution History Overview” discussing only the ’047 application); EX1005 (attaching only the ’047 application’s prosecution history). But ***the seven other applications in ’197’s family*** contain exhaustive discussion confirming both that (1) the substantive teachings of Petitioner’s three cited references—Linnarsson, McCloskey, and McCloskey II—were squarely before the Office (indeed, it was the Office that raised and substantively addressed both Linnarsson and the more detailed McCloskey II in prosecution), and (2) Petitioner’s regurgitation of those references and related arguments here fails to render the ’197’s claims obvious.

A. The Examiner’s “Second Tag” Art Included McCloskey II

Petitioner now argues (Pet.27-46, 55, 65) that McCloskey should be used in all of its recited Grounds to provide disclosure of ’197’s “second tag” (the ***polynucleotide-specific*** tag that Petitioner urges “distinguish[es]... other sample polynucleotides”). Pet.37-44. But during prosecution of ’197’s family the Office expressly *declined* to find a molecule-specific tag in a more detailed version of McCloskey (McCloskey II)—along with a raft of *other* references (such as Kanda and Miner) over which McCloskey is, at best, *cumulative*. EX2002, 335-336 (distinguishing Petitioner’s EX1055 “US20070020640”).

For example, during prosecution of App. No. 13/387,343 (“’343 application”)—the first non-provisional application, which, like ’197, claimed use

of a combination of tags (or 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 ’197’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; EX1001, 2, 6:33-7:22, cl.1. 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* (EX2007)—that is cited in McCloskey (EX1004, 2, 7) and whose lead author is also a co-author of McCloskey (EX1004, 1). EX2005, 807-817. Specifically, the Office asserted Laird disclosed the claimed multiplex identifier (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 (and amended the claims to specify the length of the polynucleotide of interest (EX2005, 844-851)), the Office allowed the remaining claims. EX2005, 865-867. The Office’s

“Reasons for Allowance” stated that “Laird alone or in combination with the art of record *does not disclose or make* it [sic] *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 Petitioner’s McCloskey II. EX2002, 335-336, 372-373, 383. In particular, the Office raised a number of references and, in July 24 and 26, 2013 interviews, “requested that the Applicants provide a brief

summary of how the claims are distinguished from [them].” EX2002, 335-336.

One reference raised and successfully distinguished was McCloskey II, 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 [III]* (cited in the previous interview)” (EX2002, 372-373)—the Office indicated that while “tagging of sample or a nucleic acid of interest” was known:

it would not have been obvious to [POSITA] to modify the references of the [sic] record... to arrive at the claimed composition... wherein... 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.

During prosecution of the '450's great-grandchild '957 application—which issued as '981, and against which '197 is terminally disclaimed (EX1005, 114)—after Applicant overcame the Examiner's anticipation rejection using *Linnarsson* by arguing Linnarsson lacked the second tag, the Examiner concluded in a second

Notice of Allowance that none of the art of record, “*including the prior art submitted in the newly filed IDS*” reasonably suggested the claimed invention. EX2001, 306; *infra*, §IV.B; *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*”); *Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01529, Pap.16, 15-18 (Mar. 21, 2023) (considering the prosecution histories of continuations “determined by Examiner to not be patentably distinct” from the parent application). The “newly filed IDS” noted by the Examiner was *one page* and contained just 13 references (EX2001, 285), one of which was “MINER et al., ‘Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR.’” EX2001, 285; EX1013, 1.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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.	Tr
	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		

EX2001, 285; *see also* EX1005, 109, 150. Miner, which is discussed in McCloskey as applying to “hairpin-bisulfite PCR” the same principles used in McCloskey (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 McCloskey teachings that Petitioner argues disclose the claimed “second tag.” Pet.37-46; EX1013, 1; EX1004, 1; EX1001, cl.1 (30:16-39). The Examiner allowed ’981’s claims over Linnarsson *with Miner in hand*, and ’197 was later terminally disclaimed against ’981. EX2001, 283-284; EX1005, 114.

B. The Examiner’s Reliance On Linnarsson

Petitioner’s obviousness arguments urge combining these recycled McCloskey teachings with Linnarsson as the base reference asserted to provide disclosure of ’197’s method of analyzing a plurality of cells and tagging polynucleotides within those cells with a “first” tag (the *cell-specific* tag). Pet.27-46. 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 ’981’s parent and ’981; but Applicant overcame Linnarsson and obtained ’981’s claims (against which ’197’s claims are terminally disclaimed) because Linnarsson

alone *or in combination with the art of record* (see §IV.A) did not anticipate or render them obvious.

During prosecution of '981's *parent* application (No. 14/792094 ("094 application")), the pending claims—like '197'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 the '197's family's prosecution, the Office identified and asserted Petitioner's primary Linnarsson reference (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 ’957 application that matured into ’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.

EX2001, 64. During '981's prosecution, the Office rejected these then-pending claims as anticipated by Linnarsson (EX2001, 154), but later withdrew that rejection after further argument (EX2001, 181-182) (and an amendment clarifying "the first tag sequence is a different sequence for different single cells in the plurality of single cells" (EX2001, 178)). As the Office correctly concluded in '981's initial August 28, 2018 Notice of Allowance, "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.*” EX2001, 238. The Examiner confirmed even more broadly in a second Notice of Allowance, after reviewing an additional IDS (EX2001, 283-284), that Linnarsson’s gap 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.*” EX2001, 306.

As discussed above, the “newly filed IDS” was *one page* and contained just 13 references (EX2001, 285), including Miner. EX2001, 285; EX1005, 109, 150; 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 Linnarsson-McCloskey combination (Pet.37-44)—*after Applicant distinguished Linnarsson for lacking the “second tag,”* and allowed the

claims—finding they were neither anticipated nor obvious. EX2001, 306.

The '197 issued after Applicant filed a terminal disclaimer against its parent, the '981. EX1005, 114.

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 McCloskey⁵ to argue claim 1 is obvious. Instead, Petitioner offers just a conclusory assertion—without support—that the “Examiner materially erred *by not considering the relevant teachings in the* [sic] *Linnarsson and McCloskey II.*” Pet.72. Not only is this factually incorrect, but it is also legally insufficient to show “error.” *Becton*, 22-23; *Autel Intelligent Tech. Corp. v. Orange Elec. Co.*, IPR2021-01545, Pap.8, 26-27 (Apr. 8, 2022) (conclusory arguments fail to demonstrate Office error); *see Motorola Mobility LLC v. Maxell, Ltd.*, IPR2022-01287, Pap.11, 16 n.8 (Feb. 2, 2023).

⁵ McCloskey II is also recycled and used only in Ground 3—for certain dependent claims—solely to modify the length of McCloskey's tag. Pet.65-69.

Petitioner's secondary McCloskey reference is at best cumulative of the more detailed McCloskey II, 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 McCloskey II disclosure was *successfully distinguished and overcome by Applicant* in the face of the Office's contemplated rejection. Petitioner never acknowledges that prosecution history, never disputes McCloskey is cumulative of McCloskey II, and never demonstrates any error in the Office's prior substantive consideration of McCloskey II. And Petitioner *ignores* its primary reference, Linnarsson, was expressly overcome during prosecution of the '981 (against which the '197 is terminally disclaimed). The Office found Linnarsson lacked this teaching of a polynucleotide-specific tag, which the Office also found (with Laird) McCloskey II was inadequate to supply. Pet.73; *see also* EX2001, 238; EX2002, 335-336, 372-373, 383; EX1005, 114. 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.

Petitioner argues that the “Examiner did not cite or discuss McCloskey II or Linnarsson in any rejection or in any remarks in response to a rejection.” Pet.71. This is wrong, as both were raised by the Office in prosecution of related patents and the Office used each for the same purposes as Petitioner here, including in the ’197’s parent, the ’981 (against which the ’197 is terminally disclaimed).

First, the Office has clearly considered “the same or substantially the same prior art” before. Each of Petitioner’s Grounds relies on two recycled references to render claim 1 is obvious: *Linnarsson* and *McCloskey*. *Linnarsson* was the basis of explicit rejections—both in the application that issued as the ’981 Patent (which the Challenged Claims are terminally disclaimed against) and in its parent ’094 application—which Applicant ultimately overcame. EX2001, 193-196; EX2004, 1085-1087; *Ivantis*, IPR2022-01529, Pap.16, 15-17. To argue claim 1 obvious, Petitioner points now to the *same Linnarsson disclosures* previously cited by the Office, and advances the *same arguments* that the Office made in prosecution. For example, Petitioner points to Linnarsson pages 2 and 36 (Pet.27) as disclosing the

preamble, Linnarsson's Figure 3 and page 4 as disclosing the ("first") cell tag (Pet.31-32, 36), and Linnarsson's disclosure of a "cDNA sample [with] a combination of tags" (Pet.32). 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." EX2001, 195; EX2004, 1086 (arguing Linnarsson disclosed "[t]he cell specific tag (e.g., see figure 3)"). And the Office, like Petitioner, also asserted that Linnarsson discloses "a distinct tag or combination of tags" such that "each cDNA sample comprised 2 distinct tags." EX2001, 196; EX2004, 1086 (arguing Linnarsson disclosed "[d]ifferent tags"); Pet.43. Petitioner is, thus, repeating the *same* Linnarsson *prior art disclosures* and *arguments*, which the Office rejected, in hopes of reaching a different result.

The same is true for Petitioner's cited ***McCloskey*** article (EX1004), whose substantive teachings that Petitioner argues should be combined with Linnarsson's were already (like Linnarsson) raised *by the Office*, argued, and overcome during prosecution leading to the '197 patent in the form of the more detailed ***McCloskey II*** (EX1055) (which Petitioner adds in Ground 3). Petitioner does not dispute ***McCloskey*** is cumulative of ***McCloskey II***, which is cited on the face of the '197 *and was raised and argued by the Office* in prosecuting the related '450 application in '197's priority chain (Pet.71; EX1001, 1; EX2002, 335-336, 372-

373, 383). This alone is reason enough to find *AB* part one is met, as Petitioner is plainly wrong that neither's teachings were "considered" by the Examiner—both were cited and discussed. Pet.71-72; *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) (similar).

Indeed, Petitioner concedes the parallels between McCloskey and McCloskey II. Petitioner admits here:

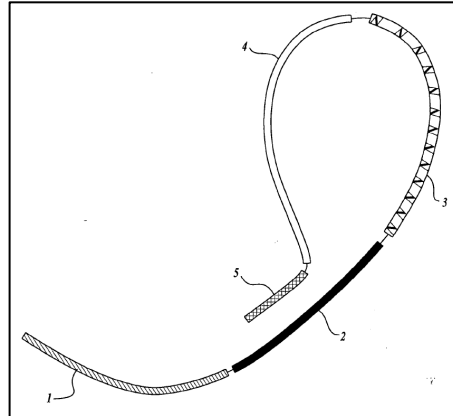
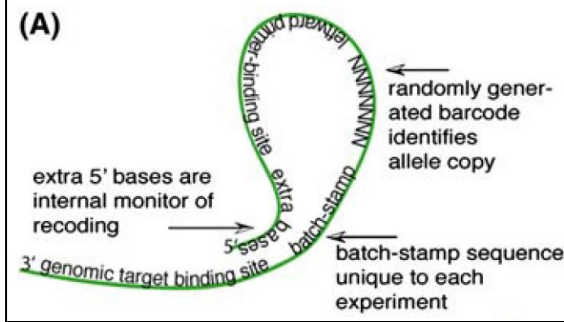
McCloskey II is a *sister patent application that goes along with the McCloskey publication discussed in the immediately preceding section. Thus, similar to McCloskey, McCloskey II also discloses a method for tagging polynucleotides with 'a molecular barcode and batch-stamp.'*

Pet.26. And Petitioner essentially acknowledges that McCloskey II 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” McCloskey II—not McCloskey. *See* Pet.72-73.

Moreover, a review of both references confirms the more detailed McCloskey II raised and argued by the Office (and overcome by PO) during prosecution of ’197’s related ’450 application *already included the teachings on which Petitioner purports to rely*—and at minimum McCloskey is cumulative of the previously-considered McCloskey II. 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 ’197’s requirement of a “second” polynucleotide-specific tag. Pet.37-46. But McCloskey II includes the very same teaching, as Petitioner admits (Pet.26), and includes more detail. EX1055, 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 II, *e.g.*:

McCloskey (EX1004)	McCloskey II (EX1055)
<u>“Batch-stamp” disclosures</u> Pet.37 (citing EX1004 at Fig. 1).	Fig.1 and [0013], <i>see also</i> Fig.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.

Pet.38 (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”))

¶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.”

“Barcode” disclosures

Pet.43 (quoting EX1004, 2 (“Our method utilizes an encoding oligonucleotide with five distinct informational regions[:] the random barcode distinguishes among

¶21: “The bar-coded oligonucleotide further comprises a second sequence that provides a random barcode. The term ‘random barcode’ refers to an arbitrary sequence than can uniquely identify a target nucleic acid in an experiment...”

sequences arising from different cell or allele copies”))	¶¶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.38 (quoting EX1004 1, 5 (“batch-stamps and barcodes [should] be used when amplifying irreplaceable DNAs and cDNAs for... single cell... analyses”)) Pet.38 (quoting EX1004, 1, 5 (“to single-stranded cDNA templates”))	¶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 biomedical, ancient DNA, and forensic purposes.”

Pet.40 (quoting EX1004, Abstract (“The risks of... biased amplification ...are especially high when limited amounts of template DNA are used.”))	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.”
---	---

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 II (EX1055) and the other art that was already considered by the Office. Indeed, this would have been the case even if McCloskey II 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.72-73. But in fact, as detailed *supra* §IV.A, ***McCloskey II*** *was discussed and distinguished* to avoid a potential rejection in the prosecution leading to ’197.

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 Ivantis*, IPR2022-01529, Pap.16, 15-17. 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 credited—is irrelevant and need not be reached by the Board since the ***art*** is not new. *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). Moreover, Petitioner’s arguments are ***not*** new, and Petitioner’s assertion that “***no arguments*** were made during examination with respect to any of these references” is wrong. Pet.71.

During prosecution of the related '981 Patent, 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 '981's 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.*" EX2001, 238, 306. This prior art already of record *included McCloskey II*, 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 II**, and **Miner**—and determined the claims of the '981—against which the '197 was terminally

disclaimed—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.*, EX2001, 238, 306. And as detailed above (§IV.A), in the prosecution of ’197’s related ’450 predecessor application, McCloskey II’s oligonucleotide was specifically distinguished from the claimed MID to overcome a potential rejection: “US20070020640 [McCloskey II]... 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 any of these references” is wrong—and, indeed, strains credulity.⁶ Pet.71 (emphasis original).

⁶ Petitioner is well aware of the prosecution history of the related ’981 Patent, having filed a Petition seeking *inter partes* review of the ’981 weeks before the present Petition was filed. EX2008, 17-19. Petitioner nonetheless failed to

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 II* (a more detailed version of *McCloskey* (EX1004)) *were* substantively considered during the prosecution of the '197's related applications.

In fact, the Office *explicitly* considered obviousness combinations for both *Linnarsson* and *McCloskey II* in those applications. The Office asserted *Linnarsson* in an obviousness-type double patenting rejection in combination with PO's '149 patent during '981's prosecution (EX2001, 157), and considered

acknowledge (let alone address) that prosecution history, which is undisputedly relevant as confirmed by, *e.g.*, the *Becton* case Petitioner cited in its Petition. Pet.70 (citing informative *Becton* decision, which considered the prosecution history of the parent application); *see Becton*, 22 (“[the references] were substantively considered... *during prosecution of the parent application* from which the [challenged] patent issued....”).

McCloskey II in a potential obviousness combination with Laird in another 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 [III]***”). And the second ’981 Notice of Allowance expressly concluded the art of record (including Linnarsson, McCloskey II, 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.” EX2001, 306. Thus, although Petitioner wholly ignores these aspects of ’197’s prosecution history, Petitioner’s third pre-*AB* case, *Limelight*,⁷ and *Weber* (an institution decision that issued one day after *AB* issued), which Petitioner cites as support for this argument, are also inapposite, as both of Petitioner’s references were considered in obviousness rejections in related applications for the same teachings and therefore are not “new” arguments. Pet.72 (citing *Limelight Networks, Inc. v. Akamai Techs., Inc.*, IPR2016-01631, 2016 WL

⁷ Additionally, the secondary references in *Limelight* were neither before the examiner nor cumulative of references that were—whereas here, McCloskey is cumulative of references previously cited by the Office, including *e.g.*, McCloskey II, Kanda, and Miner. *See supra*, §IV.A; *Limelight Networks, Inc. v. Akamai Techs., Inc.*, IPR2016-01631, 2016 WL 8115506, at *5 (P.T.A.B. Dec. 30, 2016).

8115506, at *5 (P.T.A.B. Dec. 30, 2016) and *Weber, Inc. v. Provisur Tech., Inc.*, IPR2019-01467, Pap.7, 9-10 (Feb. 14, 2020)).

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 [sic] Linnarsson and McCloskey

II.” Pet.72. Petitioner is, to begin with, wrong on the facts: Linnarsson and McCloskey II *were* raised by the Office and substantively considered during prosecution of applications leading to the ’197 Patent, and were distinguished by Applicant. (With consideration of the more detailed McCloskey II, the Examiner also clearly considered the teachings of McCloskey.) And Petitioner is also wrong on the law: Petitioner’s conclusory assertion fails to show any actual Examiner “error.”

Petitioner is factually incorrect, ignoring the prosecution history of ’197’s parent applications where the Office raised and expressly considered (and Applicant expressly distinguished) both Linnarsson and McCloskey II.

Petitioner completely fails to address the prosecution history of ’197’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 related to ’197, (1) the Applicant explicitly overcame a Linnarsson rejection, (2) the Applicant expressly distinguished McCloskey II from the claimed MID and overcame a potential rejection based on McCloskey II (EX2002, 335-336, 372-373, 383), (3) the Examiner made other rejections regarding the MID that were overcome (*supra*, §IV), (4) the Examiner

expressly acknowledged the IDS that listed McCloskey II (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”)) and (5) the Examiner confirmed in the second Notice Allowance of the ’981 that the claims were patentable over the newly filed IDS containing Miner (EX2001, 285, 306). Petitioner fails to explain how the teachings of Linnarsson or McCloskey II, summarized in McCloskey, were purportedly “overlook[ed]” in light of this prosecution history. *E.g.*, Pet.72-73. This is especially unlikely where the Applicant filed a terminal disclaimer against ’981, which issued over Linnarsson and other references of record, including, *e.g.*, McCloskey II and Miner. *See Ivantis*, IPR2022-01529, Pap.16, 15-18 (considering prosecution histories of continuations with “claims that are substantially similar” to claims in the parent application). Petitioner also fails to explain why *Becton* factor “(c)” weighs against exercising the Board’s discretion to deny institution where both Linnarsson and McCloskey II were the basis of actual or expressly contemplated rejections by the Office. Pet.72-73; EX2002, 335-336, 372-373, 383.

Linnarsson. In the prosecution of ’981 and its parent application, the Examiner raised Linnarsson as a rejection. *Supra*, §§IV.B, V.A. Indeed, as detailed above, the Examiner made the same arguments Petitioner does here, and Applicant overcame them. *Supra*, §§IV.B, V.A. Petitioner is aware of this

prosecution history, as it acknowledged some of it in its Petition seeking *inter partes* review against '981. EX2008, 3, 17-19, 72. For example, Petitioner wholly ignores (both here and in its '981 Petition) the Examiner's statements in '981's 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... further clarify ***the claimed invention***, which ***is free of the art***.

EX2001, 306. These statements 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*, and concluded Linnarsson (which Applicant had just overcome) together with this other art did not “teach[] or reasonably suggest[] the claimed invention.” EX2001, 285, 306; EX1013.

Petitioner and its expert, Dr. Cooper, rely on Miner for the same teachings as McCloskey, namely “removing amplification bias” and “counting... molecules.” EX1002, ¶¶90-92; EX2008, 10-11 (citing EX1013, Miner). 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 regarding Linnarsson (and McCloskey and McCloskey II via Miner).

McCloskey II. In the ’450 application, 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 II. *Id.* Applicant explained that McCloskey II “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*, 14-15] 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 [III]* (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 II during the prosecution leading to the '197 (Pet.72)—to the contrary, McCloskey II 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 '197 claims priority, and over which McCloskey and McCloskey II are 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 Kanda, cited on '197's face, taught the "limitation of broadly recited multiplex identifier 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 the "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 [one] 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. And, finally, the Examiner confirmed the related ’981 was allowed—*after a Linnarsson rejection*—over the art in a newly filed IDS containing Miner, *which discloses McCloskey’s batch-stamp and barcode* approach. EX2001, 285, 306. 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 II and similar art did not disclose or render obvious the Challenged Claims’ polynucleotide-distinguishing tag.⁸

⁸ Similarly, in the ’197’s related ’694 application the Office once again expressly confirmed it had considered McCloskey II, stating in its Notice of Allowance that

As detailed above, Petitioner is clearly incorrect that the Examiner “erred by not considering the relevant teachings in the [sic] Linnarsson and McCloskey II.” Pet.72-73. Both Linnarsson and McCloskey II were raised by the Office, considered multiple times, and distinguished—including specifically in connection with Linnarsson’s purported disclosures of a first tag and McCloskey II’s purported disclosure of a second tag. *See, e.g.*, EX2001, 193-94 (discussing rejection in part because Linnarsson purportedly discloses a first tag); EX2002, 335-336 (McCloskey II “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” here 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 “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 II is the ninth reference listed in that IDS. EX2009, 75-76.

the relevant teachings in the [sic] Linnarsson and McCloskey II” is also legally insufficient to meet Petitioner’s burden of showing a material error. Pet.72.

First, Petitioner argues that “the fact neither Linnarsson nor the ’640 Publication was ‘the basis of a rejection weighs strongly against exercising [the Board’s] discretion to deny institution.” Pet.72-73. 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) (no error even though art was not the basis of a rejection); *Motorola*, 22-23.

Petitioner cites an array of inapposite cases, for *AB* part two, based on its attempt to ignore the numerous related applications in ’197’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. Petitioner's reliance on *Cellco Partnership v. Huawei Device Co.*, IPR2020-01117, Pap.10, 13 (Feb. 3, 2021) is misplaced. Pet.73. There, petitioner's reference was not the basis of a rejection during prosecution, which weighed against exercising discretion to deny institution. Here, in contrast, both Linnarsson and McCloskey II *were* expressly identified by the Office in the related applications as actual and contemplated bases for rejection, and both were overcome by Applicant. EX2002, 335-336, 372-372. Indeed, if anything, *Cellco* supports the Board exercising its discretion and denying institution. *See Cellco*, IPR2020-01117, Pap.10, 12-13. Similarly, unlike in *Amber.IO, Inc. v. 72LUX, Inc.*, IPR2020-00015, Pap.8, 20 (Apr. 1, 2020), the alleged prior art teachings of Linnarsson and McCloskey II were substantively considered and distinguished in prosecution of the related applications for the same teachings Petitioner uses here—and Petitioner never identifies any specific teaching it 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 Linnarsson or McCloskey II when they were distinguished during prosecution of related applications. 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 1-3: The Petition Must Be Denied Because Petitioner Fails to Allege—Let Alone Establish—That Its References Are Analogous Art To The ’197 Patent

Nowhere does Petitioner assert—let alone attempt to show—that any of the three references named in its grounds (primary reference Linnarsson and secondary references McCloskey and McCloskey II) are analogous art *to the ’197 Patent*. See Pet.39 (the only analysis of analogous art, asserting only that Linnarsson and McCloskey are analogous *to each other*). (Indeed, Petitioner does not perform even its *incorrect* analysis for McCloskey II in Ground 3.) 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 not addressing whether its relied-upon art is analogous *to the challenged '197 patent*; it only asserts that McCloskey, Petitioner's secondary reference, is analogous to Linnarsson, its primary obviousness reference. Pet.39; EX1002, ¶163. (Petitioner does not even allege McCloskey II is analogous to Linnarsson.) Because Petitioner's Grounds rely entirely on obviousness and Petitioner was therefore required to establish that its obviousness art is analogous to the challenged '197 patent as a threshold issue, Grounds 1, 2, and 3 must each be rejected because Petitioner cannot meet its burden to establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.4th at 1380.

VIII. Grounds 1-3: The Merits Of Petitioner's Obviousness Analysis Is Also Legally Deficient

Petitioner's Ground 1 is based on the combination of Linnarsson and McCloskey. As discussed below, Petitioner's argument that one would modify Linnarsson to incorporate a "second tag" from McCloskey ignores incompatibilities between its two references and fails to prove the premise underlying both its motivation to combine and reasonable expectation of success arguments. Relatedly, Petitioner fails to show McCloskey discloses a "second tag sequence to count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell" (Pet.44) or explain how or why POSITA would modify Linnarsson to incorporate the material Petitioner argues from McCloskey.

Petitioner's Grounds 2 and 3 build on its Ground 1 arguments, and accordingly fails for at least all of the reasons that Ground 1 fails.

A. Petitioner Fails To Sufficiently Explain How Its Proposed Combination Would Be Implemented Or Establish Motivation To Combine

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. *See* Pet.37-44. *Second*, Petitioner's purported motivation to combine is premised on its erroneous and unsupported assertion that McCloskey barcodes “*each sample polynucleotide*.” *See* Pet.40-42. Because Petitioner failed to establish the premise on which Petitioner expressly conditioned its motivation argument, Petitioner's motivation argument fails. *Third*, Petitioner's reasonable expectation of success argument is also tied to Petitioner's same failed assertion about McCloskey tagging “each sample nucleotide” and therefore also fails. *See* Pet.42-43.

1. 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); see EX1002, ¶103. 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.16-21. McCloskey, in contrast, is not about gene expression. Rather, McCloskey is about tagging copies of the DNA of a *particular gene*. EX1004, 6; Pet.22. 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.22-25).

Petitioner vaguely refers to the use of Linnarsson's "CDS and TSO" (*e.g.*, Pet.39) in its 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 *CDS*s anneal to *every* mRNA molecule—for example, to mRNA's poly-A tail. Pet.17; EX1003, 24:13-20, Fig.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.18-19; 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.21-23. 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.

**2. Petitioner's Motivation To Combine Fails Because
Petitioner Fails To Establish Its Amplification Bias Premise**

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.41-42. 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.41-42; *see also* EX1002, ¶166.

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.41-

42. 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 attempts to sidestep the fact that Linnarsson itself addresses the amplification bias issues that could interfere with its process and explains how to address them. Pet.41-42. Petitioner does not explain how remaining amplification bias, if any, 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.41-42; *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 "motivat[ation] 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.41-42. 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.41. 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.38, 41-42; 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.42. 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.

3. Petitioner Fails To Establish Reasonable Expectation of Success

Petitioner's reasonable expectation of success also fails for both its alternatives,⁹ as it, too, expressly depends on Petitioner's unexplained and

⁹ Petitioner's second "[a]lternativ[e]" theory is unclear. Pet.43. To the extent Petitioner is attempting to argue a single-reference obviousness theory based on Linnarsson, that Ground is not identified (Pet.5) and fails because Petitioner identifies no "second tag" disclosure and does not articulate a motivation to combine or reasonable expectation of success, or a Linnarsson-only theory for Cl.1H. Pet.43; *see also* Pet.44-45. To the extent Petitioner is instead arguing either the CDS or TSO's cell-tag would be replaced with a tag from McCloskey that "uniquely identifies each sample polynucleotide," Petitioner does not explain how that theory differs from the theory in the previous paragraph of its argument. Pet.43; *Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017) (reversing obviousness determination where there was no "clear, evidence-supported account of the contemplated workings of the combination" which "is a prerequisite to adequately explaining and supporting a conclusion" of obviousness); *Axon Enter., Inc. v. Digital Ally, Inc.*, IPR2017-00515, Pap.10, 18-19 (July 6, 2017) (denying institution, stating neither petitioner nor its expert

unsupported assumption that McCloskey has a tag that “uniquely identif[ies] each sample polynucleotide.” Pet.43. 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

“explains in sufficient detail the nature of Petitioner’s proposed modification... Petitioner does not explain in sufficient detail *how* the proposed modification is supposed to work”).

McCloskey disclosing tags that “uniquely identify each sample polynucleotide.” Pet.43.

B. Petitioner Fails To Show McCloskey Discloses “using the... second tag sequence to count a number of sample polynucleotides...”

Petitioner also fails to show McCloskey discloses a “second tag sequence to count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell.” Pet.44. Petitioner asserts that McCloskey “discloses that these tags allow the precise count of sample polynucleotides *in each sample single-cell* to be determined.” Pet.44-45. Not so. As laid out above, McCloskey discloses tagging only allele copies, and does not disclose tagging or counting all polynucleotides from a sample, let alone from “each sample single-cell.” *Infra*, §VIII.A-C. Thus, McCloskey does not provide a way to count each polynucleotide in the cell, and for this reason too, Petitioner fails.

Even assuming, *arguendo*, Linnarsson in view of McCloskey does render obvious a “second tag sequence to count a number of sample polynucleotides,” Petitioner failed to present an obviousness argument for limitation 1H, where it seemingly relies on secondary reference McCloskey without explaining *how* Linnarsson’s method would be *modified* to include McCloskey’s sequence counting approach or *why* POSITA would have been motivated to make the modification. Pet.44-46; *John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827,

Pap.6, 13-14 (Jan. 31, 2017) (“Merely identifying where limitations may be found in several prior art references is not sufficient... without articulating **how** and why **specific teachings of the references would have been combined.**”); *ActiveVideo Networks, Inc. v. Verizon Commc’ns, Inc.*, 694 F.3d 1312, 1327-28 (Fed. Cir. 2012) (affirming reversal of obviousness verdict where expert “failed to explain how specific references could be combined” including “how any specific combination would operate or read on the asserted claims”); *Axon*, IPR2017-00515, Pap.10, 18-19 (denying institution, stating neither petitioner nor its expert “explains in sufficient detail the nature of Petitioner’s proposed modification... Petitioner does not explain in sufficient detail *how* the proposed modification is supposed to work”). Petitioner entirely skips that required analysis and simply asserts “the combination of Linnarsson and McCloskey discloses and renders obvious” the limitation.¹⁰ Pet.46. This is insufficient to meet Petitioner’s burden.

¹⁰ Petitioner also cites the ’197 as support that these counting methods were “well-known and routine.” Pet.45. The relevance of this discussion is unclear. To the extent Petitioner argues that some combination with such disclosures would render obvious this limitation, Petitioner has failed to sufficiently articulate that argument, and has again not provided the required obviousness analysis. *John Crane*, IPR2016-01827, Pap.6, 13-14.

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 challenges a handful of claims that depend from claim 1. The ground 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.55. But, for claim 5, Petitioner cites to alleged admissions of PO (in a different litigation on different patents), as well as the Hug, Okayama, Shibata, and Hayazhizaki references. Pet.58. 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. Similarly, for claim 12 Petitioner points to the “Brenner 2000 prior art article (EX1035)” as support for its argument (Pet.60) and for claim 26 Petitioner points to “Albert’s method,” as explained in EX1057, to target a specific polynucleotide for tagging (Pet.64). And for each of these claims, Petitioner does not explain whether or how the methods described in various exhibits that are not part of Ground 2 would be combined with

Linnarsson or McCloskey, or why POSITA would have considered those teachings pertinent. Pet.55-65.

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 various Ground 2 arguments. Pet.55-61, 63-65. 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, 24.¹¹

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

¹¹ *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”).

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

Respectfully submitted by:

Dated: September 21, 2023

/J. Steven Baughman/

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

Megan Raymond (Reg. No. 72,997)

Attorneys For Patent Owner 10x

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 12,584 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

Dated: September 21, 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 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:

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
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: September 21, 2023

Respectfully submitted,

By: /Sayem Osman
Sayem Osman