Patent Owner 10x Genomics, Inc.'s Demonstrative Slides

Parse Biosciences, Inc.
v.
10x Genomics, Inc.

IPR2023-00958
Inter Partes Review of U.S. Patent No. 10,697,013

Patent Trial and Appeal Board
United States Patent and Trademark Office
November 6, 2024

Table Of Abbreviations

'013 Patent	EX1001, U.S. Patent No. 10,697,013
Pet.	Paper 1, Petition for *Inter Partes* Review
ID.	Paper 9, Granting Institution of *Inter Partes* Review
POR.	Paper 21, Patent Owner's Response
Rep.	Paper 27, Petitioner's Reply to Patent Owner's Response
SurRep.	Paper 33, Patent Owner's Sur-Reply
STRT	Single-cell Tagged Reverse Transcription
NGS	Next Generation Sequencing

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

Illustrative ’013 Claim

1. A method for multiplexed analysis of nucleic acids from single cells, the method comprising:

(a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides;

(b) performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:

(A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and

(B) ligating a second oligonucleotide tag to said extension product, and

wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises:

(i) a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides;

(ii) a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells; and

(iii) a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell;

(c) amplifying said tagged polynucleotide, thereby generating a plurality of amplified polynucleotides corresponding to the tagged polynucleotide; and

(d) sequencing said plurality of amplified polynucleotides to determine sequences of the amplified polynucleotides corresponding to the sample sequence, the first tag sequence, and the second tag sequence of the tagged polynucleotide; and

(e) using the sequences determined in step (d) to count sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells

EX1001 (’013 Patent), Cl.1

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Linnarsson's Method

Linnarsson's Method Analyzes Gene Expression In Single Cells

- Linnarsson is directed to preparing a cDNA library by reverse-transcribing mRNA produced by genes to analyze gene expression.

EX1003 (Linnarsson), 1 (Abstract); EX2013 (Quackenbush Decl.), ¶¶33-47; POR.6-9; SurRep.12-15.

- Petitioner admits Linnarsson analyzes "substantially all" mRNA molecules of a cell.

EX1003 (Linnarsson), 12:4-8; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 41:10-44:22; POR.7-8, 49 n.26; SurRep.21-22.

Further, the purpose of Linnarsson's method is gene expression analysis, which a POSA would have understood contemplates the analysis of substantially all mRNA molecules of a cell. EX1002 ¶ 222; EX1003 at 1:11-12, 1:25-26 ("direct sequencing of the ***all***, or parts, ***of the mRNA content*** of a tissue is being increasingly used."); EX1015 at 1:10-11, 1:31-33. Thus, a POSA would have understood that such a method was designed to be applied to substantially all mRNA molecules of a given cell.

EX2021 (Petition IPR2023-00955), 70-71.

Linnarsson's Method Analyzes Gene Expression In Single Cells

- Dr. Cooper also admits that Linnarsson analyzes "substantially all" mRNA molecules of a cell.

EX2022 (Cooper IPR2023-00955 Decl.), ¶222; SurRep.21-22.

222. Linnarsson's method begins with "releasing mRNA from each single cell to provide a plurality of individual mRNA samples." Ex. 1003 at 3:26-28; Ex. 1015 at 2:30-32. A POSA would understand that because the mRNA is indiscriminately released from each single cell, and because Linnarsson does not describe any additional elimination or filtration, the released mRNA sample comprises substantially all mRNA molecules of said cell. As discussed above, Linnarsson's method then tags these sample polynucleotides for the purpose of gene expression analysis. A POSA would understand that the purpose of such a method would be to analyze substantially all mRNA molecules of a cell—therefore, this method would provide associating a tag with substantially every sample mRNA molecule. Ex. 1003 at 1:11-12, 1:25-26 ("direct sequencing of the ***all***, or parts, ***of the mRNA content*** of a tissue is being increasingly used."); Ex. 1015 at 1:10-11, 1:31-33. Thus, a POSA would understand that Linnarsson describes a method which is designed to be applied to substantially all mRNA molecules of a given cell.

EX2022 (Cooper IPR2023-00955 Decl.), ¶221.

238. Similarly, Linnarsson teaches attaching a tag to each individual mRNA sample. *See* 16:18-20 ("A template-switching oligonucleotide (TSO) that includes a portion which is at least partially complementary to a portion of the 3'd end of the first strand of cDNA can be added to ***each*** individual mRNA sample…"), 18:27-30 ("If the lysis is achieved partially by heating, then the CDS and/or the TSO can be added to ***each*** individual mRNA sample during cell lysis…"), 46:22-24 ("wherein a template-switching oligonucleotide (TSO) is added to ***each*** individual mRNA sample ….").

EX1002 (Cooper Decl.), ¶221.

Linnarsson's Method Analyzes Gene Expression In Single Cells

- Petitioner admits Linnarsson deals with "analysis of gene expression in single cells."

Pet.27; EX1003 (Linnarsson), 9:23-10:2; Rep.27.

- And Linnarsson states that its methods "provide the advantage of generating a cDNA library representative of RNA content in a cell population by using single cells."

Pet.27; EX1003 (Linnarsson), 9:23-10:2; Rep.27.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods and compositions for the analysis of gene expression in single cells or in a plurality of single cells. In particular, the invention provides methods for preparing a cDNA library from a plurality of single cells. The methods are based on determining gene expression levels from a population of individual cells, which can be used to identify natural variations in gene expression on a cell by cell level. The methods can also be used to identify and characterize the cellular composition of a population of cells in the absence of suitable cell-surface markers. The methods described herein also provide the advantage of generating a cDNA library representative of RNA content in a cell population by using single cells, whereas cDNA libraries prepared by classical methods typically require total RNA isolated from a large population (see Example I). Thus, a cDNA library produced using the methods of the invention provide at least equivalent representation of RNA content in a population of cells by utilizing a smaller subpopulation of individual cells along with additional advantages as described herein.

Pet.27; EX1003 (Linnarsson), 9:23-10:2; Rep.26.

Linnarsson's Approach Reduces Amplification Bias By Reducing The Number Of Necessary PCR Cycles

- According to Petitioner, Linnarsson's method reduces "cell-to-cell amplification bias" because it uses large amounts of polynucleotides from 96 cells, and therefore has to perform fewer rounds of amplification.

EX1003 (Linnarsson), 37:22-32; Pet.17-22, 35-36.

To incorporate a well-specific (and hence cell-specific) barcode, the reverse transcriptase template-switching mechanism (Schmidt et al., Nucleic Acids Res. 27:e31 (1999)) was used whereby a helper oligo directs the incorporation of a specific sequence at the 3' end of the cDNA molecule (**Figure 10A**). A different helper oligo was used in each well, with distinct five-base barcodes and universal primer sequence. After cDNA synthesis, the 96 reactions were pooled, purified and amplified by single-primer PCR in a single tube. Cell-to-cell amplification bias was thus reduced, and the number of PCR cycles could be kept low since amplification started from 96-fold more material. The amplified samples were then adapted for sequencing using standard methods. The procedure was named 'STRT' (single-cell tagged reverse transcription). For details, see the Methods section and **Figure 11**.

EX1003 (Linnarsson), 37:22-32; Pet.16-22.

Figure 11 Depicts Generating A cDNA Library, Including Fragmentation And Capture With Biotin

- Linnarsson's method involves preparing a cDNA library for sequencing by reverse-transcribing mRNA initially produced by transcription of genes expressed in the cells in the sample.

  EX1003 (Linnarsson), 1 (Abstract), 3:25-4:2, 12:4-8, 5:10-11, 23:1-4, 37:31-32, Fig.11; *see also* Pet.17-18; EX2013 (Quackenbush Decl.), ¶33-47; POR.6-9; SurRep.18-23.

- "single cells are placed in separate wells of a 96-well plate and lysed…."

  EX1003 (Linnarsson), 3:26-30, 4:8-13; Pet.28; EX2013 (Quackenbush Decl.), ¶¶33-47; POR.6-9.

- CDSs and TSOs are then incorporated into cDNA during reverse transcription from mRNA.

  EX1003 (Linnarsson), 18:32-33; *see also* Pet.17-18; EX2013 (Quackenbush Decl.), ¶33-47; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 25:22-26:12; POR.6-11; SurRep.18-23.

- After reverse transcription is completed, the cDNA (now including a CDS and TSO) from each well is amplified, at which point a biotin is added to the 5' fragment, and then the cDNA is fragmented.

  EX2013 (Quackenbush Decl.), ¶40; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 28:19-29:7; POR.10-13; SurRep.18-27.

- The biotinylated fragments, the "5' fragments" and "3' fragments," are bound to the beads and ***the internal fragments are washed away***.

  EX1003 (Linnarsson), 6:3-12, 26:21-26, Fig.11; EX2013 (Quackenbush Decl.), ¶¶40-44; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 29:8-13; POR.13-14, 33-36; SurRep.18-27.

- The "***5' fragment***" is then released by BtsCI digestion, adapter sequences are added, and ***it is sequenced***, and ***the 3' fragment remains bound to the bead***.

  EX1003 (Linnarsson), 6:5-12, 18:27-19:11; Pet.28; EX2013 (Quackenbush Decl.), ¶¶41-44; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 31:12-22, 32:7-14, 43:21-44:22; POR.13-16, 33-36; SurRep.18-27.

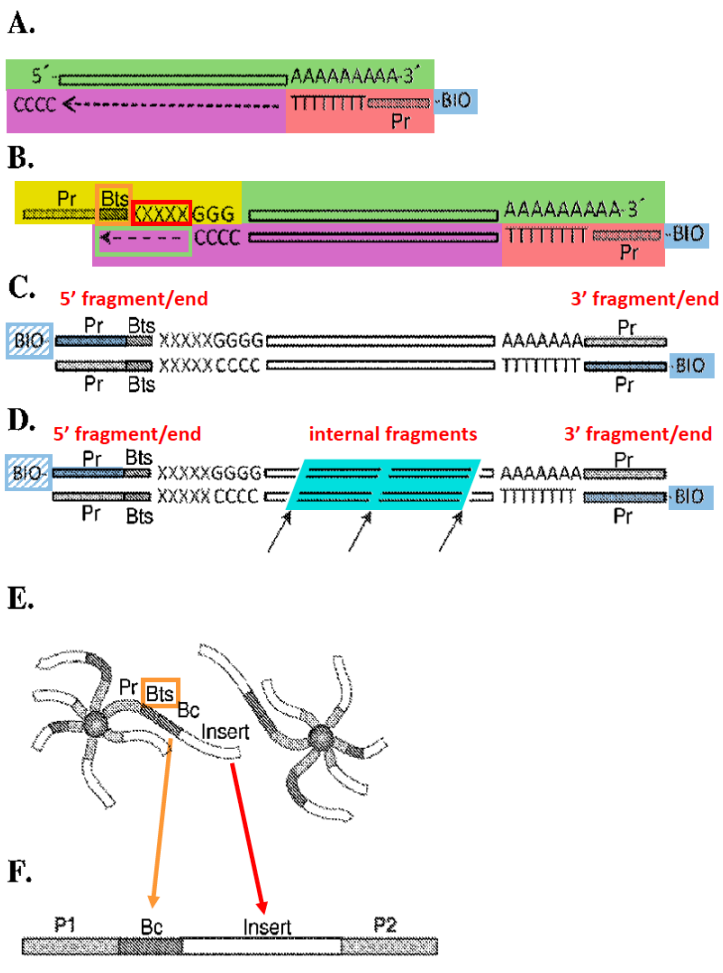


Figure 11

Linnarsson's Disclosed Method(s) All Use Fragmentation And Capture With Biotin

- Petitioner and Dr. Cooper assert that fragmentation and capture with biotin and restriction enzymes are optional because the description of Figure 11 states: "Figure 11, panels A-F, show a graphical representation of steps optionally used in the STRT method." EX1003 (Linnarsson), 5:28-6:12, Fig.11; SurRep.4-6.

- But that description never specifies what aspects are optional, and it does not disclose any other embodiments that function without any aspects/steps deemed "optional."

  EX1003 (Linnarsson), 5:28-6:12, Fig.11; SurRep.24-25.

- And Dr. Cooper lacks any reasoned basis for deciding which parts of Figure 11 are "optional."

  SurRep.24-25.

  - Dr. Cooper agrees the CDS, TSO, and amplification steps in Panels A-C are ***required***.

    EX2040 (Cooper Reply Dep. Tr.) 51:21-56:4; SurRep.24-25.

  - But Dr. Cooper asserts that fragmentation and capture in Panels D-E are ***optional***.

    EX2040 (Cooper Reply Dep. Tr.) 56:20-57:17; SurRep.24-25.

Linnarsson's Disclosed Method(s) All Use Fragmentation And Capture With Biotin

- Linnarsson's fragment and capture method ***requires biotin*** for capture.

  EX2013 (Quackenbush Decl.), ¶¶64-65; POR.31-33; SurRep.3-6, 18-23.

  - Linnarsson consistently discloses fragmentation and capture with biotin, including in both of its Examples (Examples I and II) and in Figure 11.

    EX2013 (Quackenbush Decl.), ¶¶64-65; EX1003 (Linnarsson), Fig.11, 5:28-6:12; 23:1-37:32; EX2040, (Cooper Reply Dep. Tr.), 28:21-31:9; POR.31-33; SurRep.3-6, 23-26.

  - Biotin is critical in Linnarsson's method, as it allows for tagged polynucleotides to be isolated from untagged polynucleotides.

    POR.22-23; EX2013 (Quackenbush Dec.), ¶¶64-65; POR.31-33; SurRep.18-23, 3-6.

    - Without such purification, tagged and untagged polynucleotides would be sequenced and the resulting information would be muddled.

      SurRep.25-26; POR.31-33; EX2013 (Quackenbush Decl.), ¶64.

    - As Dr. Quackenbush explains, "*Linnarsson discloses that the biotin captures the tagged fragments and enables their purification. … Without biotin, all the fragments would be 'washed away.*"

      EX2013 (Quackenbush Decl.), ¶64; POR.30-32; SurRep.25-26.

Linnarsson Discloses That Further Fragmenting May Be Needed To Generate The cDNA Library

- Linnarsson's "cDNA Library" is already fragmented: it is "a collection of cloned complementary DNA (cDNA) ***fragments***."

EX1003 (Linnarsson), 12:4-8; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 41:10-44:22; POR.43-45; SurRep. 18-23.

- And as Petitioner's Dr. Cooper admits, Linnarsson discloses that, after generating the cDNA library, ***additional*** fragmentation may be required for, *e.g.*, next-generation sequencing ("NGS") or for shotgun sequencing.

> "certainly one could contemplate many fragmentation steps if one wanted to."

EX1003 (Linnarsson), 22:5-21; EX1081 (Cooper Reply Dep. Tr.), 97:17-103:19, 111:8-113:16; SurRep.18-23.

  - For example, Dr. Cooper confirms the cDNA in the cDNA library ***must be fragmented to a suitable size*** for the next-generation sequencing ("NGS") Linnarsson discloses:

> "[A]t some point, you need to fragment to get them – to make them suitable for the particular sequencer machine that you're using."

EX1003 (Linnarsson), 6:9-12, 12:4-8; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 32:7-14, 42:11-43:3; POR.13-14, 43-45; SurRep.18-23.

Linnarsson's Only Two Examples (I And II) Both Employ Fragmentation And Capture With Biotin

- As Petitioner's Dr. Cooper admits, ***Figures 3 and 4 are both introduced as part of Example I***.

EX1081 (Cooper Reply Dep. Tr.), 90:9-92:19, 94:8-97:11 & 118:5-13 (acknowledging Figures 3 and 4 are in Example I, but arguing Figures 3 and 4 are "incompatible with a fragmentation and capturing approach" while Example I "discloses fragmentation and capture"); EX1003 (Linnarsson), 23:1-37:32; EX2013 (Quackenbush Decl.), ¶¶84-85; SurRep.18-23.

- And Example I and Example II, in turn, are both fully consistent with Figure 11—both explicitly require ***biotin*** and ***fragmentation***:
  - Both use a ***biotinylated*** CDS and a TSO with a restriction enzyme ***cut site***,
  - Both add a ***biotin*** to each TSO during PCR amplification,
  - Both ***fragment*** the amplified polynucleotides, and then
  - Both sequence just the 5' ***fragment***.

Rep.11-20; EX2013 (Quackenbush Decl.), ¶84; EX1003 (Linnarsson), 23:9-19, 31:3-32:27; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 23:15-25:21, 29:14-30:2; EX1081 (Cooper Reply Dep. Tr.), 96:12-97:11, 118:5-8; EX2015 (Guan), 1; POR.29-33; SurRep.18-21.

Figures 3 And 4 Are Both Disclosed As Part Of (And Are Fully Consistent With) Example I's Fragmentation And Capture With Biotin

- Petitioner argues Figures 3 and 4 "include neither a ***biotin*** nor a restriction enzyme cut site."

  Rep.17-18 (citing EX1070 (Cooper Reply Decl.), ¶¶42-56, 117-122).

- But as part of illustrating Example I's process, which generates a cDNA library with the STRT process's fragmentation and capture approach, Petitioner failed to show Figures 3 and 4 teach anything other than poly***nucleotide sequences*** for a compatible TSO and CDS.

  EX1003 (Linnarsson), Figs.3-4; SurRep.18-23.

- Consistent with Example I's STRT disclosures, Figures 3 and 4 include, *inter alia*, a primer (APS) and cell-tag.

  EX1003 (Linnarsson), Figs.3-4; SurRep.18-23.

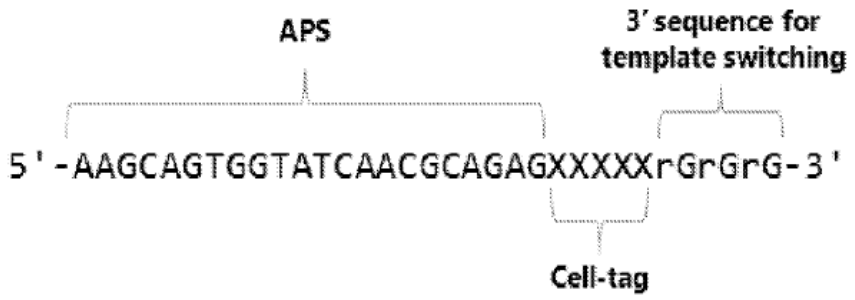


Figure 3

Figure 4

Figures 3 And 4 Are Both Disclosed As Part Of (And Are Fully Consistent With) Example I's Fragmentation And Capture With Biotin *(cont'd)*

- Petitioner argues Figures 3 and 4 "include neither a biotin nor a ***restriction enzyme cut site***."

Rep.17-18 (citing EX1070 (Cooper Reply Decl.), ¶¶42-56, 117-122).

Dr. Cooper testified that:

> "***biotin*** (in the case of both the CDS and TSO) and ***restriction enzyme cut site*** (in the case of the TSO) are ***part and parcel of the fragmentation method*** used in Figure 11."

EX1070 (Cooper Reply Decl.), ¶37; *see also* EX1081 (Cooper Reply Dep. Tr.), 128:17-129:7; SurRep.18-21.

And, attempting to distinguish them from Figure 11, Dr. Cooper repeatedly opined that Figures 3 and 4 do not contain ***"any" "restriction enzyme cut site at all"***:

> "Figures 3 and 4 ***do not include… a restriction enzyme cut site at all***…."

> "Linnarsson's Figure 3 and Figure 4 show exemplary TSO and CDS that do not contain a biotin and ***do not contain any restriction enzyme cut site***."

E.g., EX1070 (Cooper Reply Decl.), ¶¶89, 117-118, 48 ("The lack of a restriction enzyme cut site… in Figure 3 is critical"); Pap.41 (PO's Opposition), at 4.

Figures 3 And 4 Are Both Disclosed As Part Of (And Are Fully Consistent With) Example I's Fragmentation And Capture With Biotin *(cont'd)*

- EX2015 is from New England Biolabs.
  - EX2015 identifies **GCAGTG** as an enzyme restriction site.

EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 121:2-21, 133:22-134:20; SurRep.18-23.

- As Dr. Cooper admits, "a restriction enzyme cut site is part and parcel of the fragmentation method," which is the method used in Linnarsson's Figure 11.

EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 123:11-125:4, 129:2-7; Rep.17-18 n.7 ((admitting BtsI sequence appears in Figures 3 and 4); EX1070 (Cooper Reply Decl.), ¶37, 55-56; EX2040 (Cooper Reply Dep. Tr), 37:16-21; SurRep.18-23.

Linnarsson (EX1003)

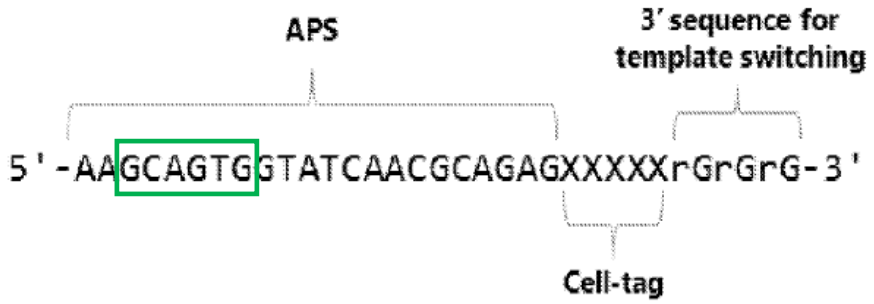


Figure 3

Figure 4

McCloskey Does Not Disclose Single Cell Analysis

McCloskey Discloses A Process For Identifying Contamination Across Different Batches

- McCloskey describes a process for identifying contamination across different batches (*e.g.,* between samples from different patients).

EX1004 (McCloskey), 2-4; EX2013 (Quackenbush Decl.), ¶¶49-52; POR.18-20, 39-42.

- McCloskey's method involves lysing the cells and ***combining their contents*** (including the DNA) ***before tagging*** the copies of a particular gene.

EX1004 (McCloskey), 2-4; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 34:19-35:3; EX2013 (Quackenbush Decl.), ¶¶49-52; POR.18-20 (between samples from different patients).

McCloskey's Encoding Oligonucleotide

- McCloskey describes adding an "encoding oligonucleotide" to copies of alleles for a particular gene.

EX1004 (McCloskey), 2-4; EX2013 (Quackenbush Decl.), ¶49; POR.18-20.

- McCloskey's encoding oligonucleotide includes (1) a batch-stamp, (2) a random barcode, and (3) a genomic target-binding site that targets the specific gene on the chromosomal DNA to be barcoded.

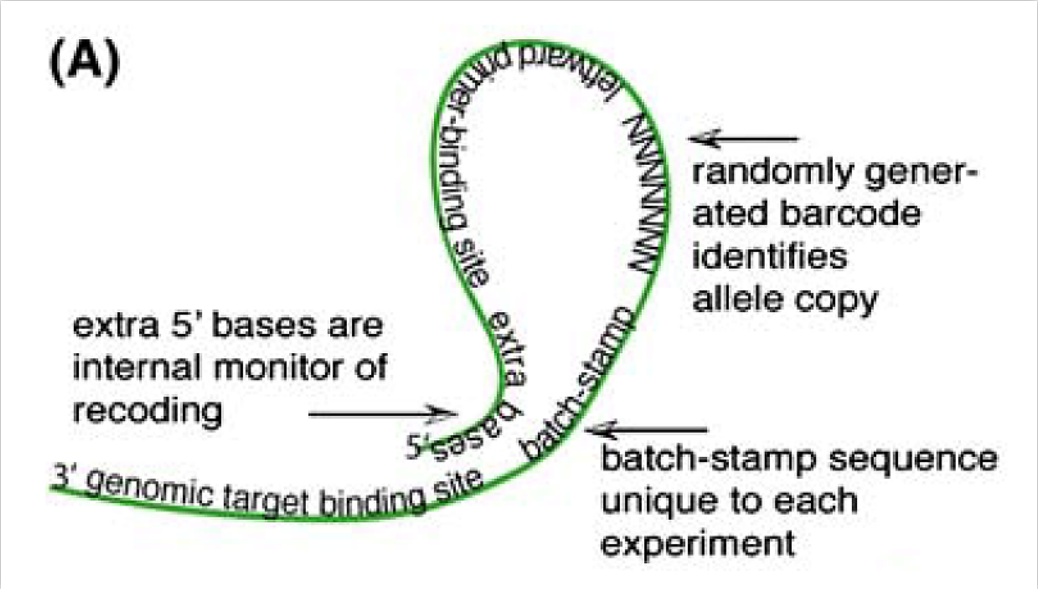
EX1004 (McCloskey), 2; EX2013 (Quackenbush Decl.), ¶49; POR.18-20.

- McCloskey's ***batch-stamp*** identifies the batch sample from which a polynucleotide originates in order to identify contamination, and is 6-8 nucleotides long.

EX1004 (McCloskey), 2-4; EX2013 (Quackenbush Decl.), ¶49; POR.18-20.

- McCloskey's ***barcode*** distinguishes between copies of an allele for a particular gene in the sample, and is 7 nucleotides long.

EX1004 (McCloskey), 2-4; EX2013 (Quackenbush Decl.), ¶49; POR.18-20.



EX1004 (McCloskey3).

McCloskey's Approach Cannot Identify The Cell From Which A Polynucleotide Originates

- As Dr. Quackenbush explained, single cell analysis involves analyzing multiple cells from the same sample while maintaining information on a cell-by-cell basis.

EX2013 (Quackenbush Decl.), ¶68; EX1002 (Cooper Decl.), ¶67 ("Single cell genomics is the study of polynucleotides and proteins at a cell-by-cell resolution."); POR.5-6, 18-20.

1. A method for multiplexed analysis of nucleic acids from single cells, the method comprising:

(a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides;

(b) performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:

(A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and

(B) ligating a second oligonucleotide tag to said extension product, and
wherein said tagged polynucleotide of the plurality of tagged polynucleotides comprises:

(i) a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides;

(ii) a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells; and

(iii) a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell;

(c) amplifying said tagged polynucleotide, thereby generating a plurality of amplified polynucleotides corresponding to the tagged polynucleotide; and

(d) sequencing said plurality of amplified polynucleotides to determine sequences of the amplified polynucleotides corresponding to the sample sequence, the first tag sequence, and the second tag sequence of the tagged polynucleotide; and

(e) using the sequences determined in step (d) to count sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells

EX1001 ('013 Patent), Cl.1.

McCloskey's Approach Cannot Identify The Cell From Which A Polynucleotide Originates

- Petitioner and Dr. Cooper say McCloskey teaches single cell analysis.

Pet.26; EX1002 (Cooper Decl.), ¶¶166-167; POR.18-20.

- But McCloskey does ***not*** disclose analysis of a sample consisting of a plurality of cells where the sample can be analyzed on a cell-by-cell basis.

Pet.26; EX1002 (Cooper Decl.), ¶¶166-167; EX2013 (Quackenbush Decl.), ¶¶ 49-51; POR18-20.

  - McCloskey teaches that ***each sample uses the same batch-stamp***, regardless of sample size:

> "The assigned batch-stamp is registered for a specific sample run on a specific date and is used only once."

EX1004 (McCloskey), 4; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 35:4-19; EX2013 (Quackenbush Decl.), ¶¶ 49-51; POR.18-20.

  - And McCloskey teaches lysing all the cells in a sample and ***pooling all of their DNA <u>prior to tagging</u>***, which makes it impossible to determine from which cell in the multi-cell sample a particular allele originated.

EX1004 (McCloskey), 2, 5; EX2013 (Quackenbush Decl.), ¶¶49-51; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 33:3-35:19; POR.18-20, 39-42; *see also* EX1002 (Cooper Decl.), ¶70 ("isolation of single cells from a cell population" is the first step of "Single Cell Genomics").

  - McCloskey only discloses the possibility of tagging (for detecting contamination) when the *sample itself consists only of a "single cell"*—not "single cell analysis" as Petitioner argues.

EX1004 (McCloskey), Abstract, 7; EX2013 (Quackenbush Decl.), ¶¶ 49-51; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 38:6-39:17; POR.18-20.

Ground 1: Ligation Theory Fails To Establish A Motivation To Combine, And Adding Ligation Fails To Meet The Limitations Of Claim 1

The Petition Guides The Life Of Petitioner's IPR

- **Petitioner is the master of its Petition.**

The rest of the statute confirms, too, that the petitioner's petition, not the Director's discretion, is supposed to guide the life of the litigation. For example, § 316(a)(8) tells the Director to adopt regulations ensuring that, "after an inter partes review has been instituted," the patent owner will file "a response to the petition." Surely it would have made little sense for Congress to insist on a response to the petition if, in truth, the Director enjoyed the discretion to limit the claims under review. What's the point, after all, of answering claims that aren't in the proceeding? If Congress had meant to afford the Director the power he asserts, we would have expected it to instruct him to adopt regulations requiring the patent owner to file a response to the Director's institution notice or to the claims on which the Director instituted review. Yet we have nothing like that here. And then and again there is § 318(a). At the end of the proceeding, § 318(a) categorically commands the Board to address in its final written decision "any patent claim challenged by the petitioner." In all these ways, the statute tells us that the petitioner's contentions, not the Director's discretion, define the scope of the litigation all the way from institution through to conclusion.

SAS Inst., Inc. v. Iancu, 138 S. Ct. 1348, 1353, 1355-57 (2018); SurRep.1-2.

Ground 1 Fails To Explain How And Why POSITA Would Modify Linnarsson

- Petitioner's combination relies on knowledge of a POSITA to attempt to cover this ligation limitation.

  Pet.34-39; POR.36-42.

- But there must be an explanation as to ***how and why POSITA would incorporate these additional teachings into the proposed combination***, and Petitioner failed to provide this.

  POR.22-42; SurRep.3-8.

> "It does not suffice to meet the motivation to combine requirement to recognize the two alternative arrangements…were both known in the art."

Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc., 97 F.4th 882, 886-87 (Fed. Cir. 2024); SurRep.6-8.

  - Relying on the knowledge of a POSITA still requires a petitioner to establish POSITA would be ***motivated to incorporate that knowledge*** into the proposed combination, and to ***explain how the teaching would be incorporated into the proposed combination*** to render the claims obvious.

Applied Materials, Inc. v. Demaray LLC, IPR2021-00103, Pap.52, 36-42 (June 29, 2022) (rejecting petitioner's argument that references evidencing POSITA's knowledge alone "sufficiently explain how such teachings apply to [the reference's] system"); *see also DSS Tech. Mgmt., Inc. v. Apple Inc.*, 885 F.3d 1367, 1374 (Fed. Cir. 2018) (identifying "three caveats" to using common sense in obviousness analysis, warning it is not "typically invoked" "to supply a missing claim limitation"); *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) ("Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment."); POR.39.

Petitioner's Modifications Would Add Complexity Without Benefit

- Petitioner asserted "POSA would have been motivated to utilize this design choice because it would allow for added flexibility in selecting tag sequences during an experiment."

  Pet.38-39.

- But Petitioner, in its Reply, does not dispute ligation requires adding additional steps and complexity.

  POR.23-26; SurRep.6-8.

- And Petitioner argued the result would be "entirely equivalent," which undermines any motivation to combine: "As Dr. Cooper explains, this approach would be *entirely equivalent to the method already disclosed by Linnarsson*, except that instead of having the tag sequence be part of the CDS or TSO prior to extension, the second tag sequence is added to the CDS or TSO after extension."

  EX1002 (Cooper Decl.), ¶ 149; Pet.39; POR.23-26; EX2013 (Quackenbush Decl.) ¶¶59-61; SurRep.6-8.

- POSITA would not be motivated to introduce complexity to achieve an equivalent method.

  POR.23-26; SurRep.6-8.

  - *In re Schweickert*, 676 F. App'x 988, 995 (Fed. Cir. 2017) (non-precedential) (reversing Board's obviousness determination where modification to prior art system that "already" performs function of proposed modification was "unnecessary" and "would do little more than add unwanted cost and complexity to the system").

    POR.26.

  - "It does not suffice to meet the motivation to combine requirement to recognize that two alternative arrangements…were both known in the art." *Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 887-89 (Fed. Cir. 2024).

    SurRep.4-7.

Petitioner's Assertions About Increasing Flexibility Are Conclusory

- Petitioner asserted only that ligation "would allow for added flexibility in selecting tag sequences during an experiment," and Dr. Cooper's opening declaration merely parroted this conclusory assertion near-verbatim, with no explanation. Pet.39; EX1002 (Cooper Decl.), ¶149; POR.23-27; SurRep.6-8.

- This unexplained, conclusory testimony cannot be credited.

Markforged Inc. v. Continuous Composites, Inc., IPR2022-00679, Pap.24, 28-29 (Sept. 26, 2023) (rejecting motivation to combine where "Petitioner's statement [wa]s nothing more than an unsupported conclusory assertion regarding a possible benefit" without "providing the requisite rationale sufficient to support a conclusion of obviousness"); *ExtractionTek Sales LLC v. Gene Pool Techs., Inc.*, IPR2022-00832, Pap.32, 28-30 (Oct. 23, 2023) (concluding claims not unpatentable where petitioner and expert provided conclusory assertions of combination's "advantage"); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15-16 (Aug. 24, 2022) (precedential) ("the cited declaration testimony is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight"); POR.26-27; *see also* SurRep.6-8.

- As Dr. Quackenbush confirmed:

> "Dr. Cooper has not identified any 'flexibility' that is gained when *ligating* a tag rather than, *e.g.*, adding it via primer extension, (which Dr. Cooper asserts would have been obvious in other proceedings) *before* further modifying its combination with ligation. Assuming one could add a tag via ligation in Linnarsson's method [], those same tag sequences could be added via primer extension with the CDS and/or TSO."

EX2013 (Quackenbush Decl.), ¶60; POR.26-27; *see also* SurRep.6-8.

Petitioner's Assertions About Increasing Flexibility Are Conclusory *(cont'd)*

- Dr. Cooper's reply declaration made the new assertion that adding tags via ligation provides flexibility to add shorter barcodes later in the process if tagging a small number of molecules. EX1070 (Cooper Reply Decl.), ¶¶74-77; Rep.8-9.
- But even in his reply declaration Dr. Cooper ***never explains how POSITA would know at the outset whether only a small number of endogenous molecules are present***, such that POSITA would know it could use shorter barcodes via ligation. EX1070 (Cooper Reply Decl.), ¶77; SurRep.7-8.
- Indeed, ***the very purpose of the claimed method is to determine that number of molecules in the sample***—POSITA would not know the number of molecules prior to tagging and sequencing. SurRep.6-8.
- Further, neither Petitioner nor Dr. Cooper explain how this supposed added flexibility is specifically ***achieved by ligation*** as opposed to its Ground 1 combination. EX1070 (Cooper Reply Decl.), ¶77; Rep. 8-9; EX2013 (Quackenbush Decl.), ¶¶59-61; POR.26-27; SurRep.6-8.
- Petitioner additionally argued the result would be "entirely equivalent," which undermines any claim of additional flexibility. Pet.38-39; EX2013 (Quackenbush Decl.), ¶¶59-61; POR.26-27; SurRep.6-8.
- And Petitioner provides no other explanation for why the ability to add the barcode later in the process is advantageous. EX1070 (Cooper Reply Decl.), ¶77; SurRep.7-8.

Hug's Linker Approach Does Not Cure The Issues Of Ligating To The CDS Or TSO

- The Petition also asserts that "[a] POSA could use Hug's method as one exemplary method to ligate the oligonucleotide… a POSA could have designed a linker to hybridize to Linnarsson's CDS and/or TSO as well as the oligonucleotide…"

  Pet.39; POR.38-42.

  - But Hug's linkers are ***not designed to link a series of random nucleotides***—like McCloskey's barcode—***with another sequence***—like Linnarsson's CDS or TSO.

    EX2013 (Quackenbush Decl.), ¶¶72-79; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 49:8-50:9; POR.38-42.

  - And Petitioner never explains how Hug's linker approach could be modified to ligate a random sequence to the TSO or CDS.

    EX2013 (Quackenbush Decl.), ¶¶ 72-79; POR.41-42.

  - Regardless, Hug's linker approach ***does not permit a tag to be ligated to a biotin***.

    EX2013 (Quackenbush Decl.), ¶79; POR.38-42.

  - And Hug's linker approach does not prevent the second tag from remaining bound to the bead if ligated to the TSO because it would still be ligated to the 5' end of the restriction cut site, and thus not sequenced.

    EX2013 (Quackenbush Decl.), ¶¶65, 79; POR.29-42.

Petitioner Never Explains How Its Proposed Combination Would Work Without Biotin And Fragmentation

- Petitioner and Dr. Cooper rely on Figure 11 and repeatedly *equated* Figures 2-4 and Figure 11.

  Pet.17-22, 31-34, 41-42; EX1002 (Cooper Decl.), ¶¶101, 104, 108, 135-140, 155-156, 199, 200; POR.32; SurRep.24.

- And Petitioner and Dr. Cooper never offered modifications to Linnarsson to eliminate its biotin or fragmentation, and never explained whether or how the method would work without these features in the Petition and Opening Declaration.

  POR.32; SurRep.5-6.

- But neither Dr. Cooper nor the Petition explains how Linnarsson's method would work *without* biotinylated cDNA.

  EX2020 (Cooper Depo Tr.), 12:7-13:11; EX2013 (Quackenbush Decl.), ¶¶64-65; POR.32; SurRep.4.

Ground 1: Petitioner's Failed Argument That Linnarsson Discloses Sequencing The Entire Polynucleotide

Petitioner's Sequencing Assertions Fail—Linnarsson Does Not Sequence The Entire Tagged Polynucleotide

- The ***Petition argued*** that, in its combination, Linnarsson meets the sequencing limitation because ***Linnarsson teaches sequencing the entire tagged polynucleotide***.
  - The Petition and Dr. Cooper equated the "tagged cDNA" to the full-length cDNA molecules generated by reverse transcription.

    Pet.18, 31-32, 39-40; EX2013 (citing EX1002 (Cooper Decl.), ¶138), ¶54; POR.42-46; SurRep.17-18.
  - The ***Petition argued*** "Linnarsson teaches that after generating ***the tagged polynucleotides***, 'sequencing is performed' ***thereon***."

    Pet.39-40, 44; POR.43-44; SurRep.17-18.

- But ***Linnarsson does not teach sequencing the entire polynucleotide***.

  Pet. 39-40, 44; POR.43-44; EX2013 (Quackenbush Decl.), ¶¶81-84; SurRep.17-26.
  - Petitioner ignored that Linnarsson sequences only the "5' fragment" and failed to address whether or how sequencing only the "5' fragment" is sufficient to meet the claim element based on Petitioner's argument.

    EX2018 (Cooper IPR2023-00876 Dep. Tr.), 44:10-44:22; EX2013 (Quackenbush Decl.), ¶¶81-85; POR.42-45; SurRep.27.
    - **Petitioner repeatedly relied on Figure 11 in its mappings, and on Reply Petitioner admits "in Figure 11 of Linnarsson, the CDS is not sequenced."**

      Rep.19-20; EX2013 (Quackenbush Decl.), ¶85; Pet.41-42 (mapping Fig.11 to [1D], [1F]); EX1002 (Cooper Decl.), ¶¶135-140, 155-156 (same, to [1D], [1F]); *see also* EX2040 (Cooper Dep. Tr.), 74:10-75:19; EX2018 (Cooper IPR2023-00876 Dep. Tr.), 43:21-44:22; POR.47-48; SurRep.23-24, 27.

Petitioner's Sequencing Assertions Fail—Linnarsson Does Not Sequence The Entire Tagged Polynucleotide

- But ***Linnarsson does not teach sequencing the entire polynucleotide***. *(cont'd)*
  - Petitioner's three citations to Linnarsson provide no details and never identify ***what*** is sequenced, let alone show the ***entire*** tagged polynucleotide is sequenced.
    - Linnarsson's Figure 1 is only an "***overview of a method***" that says "sequencing is performed" ***without specifying <u>what</u> is sequenced***.

      EX1002 (Cooper Decl.), ¶185; EX1003 (Linnarsson), 4:8-13; EX2013 (Quackenbush Decl.), ¶84; POR.43-44; SurRep.17-23.
    - Linnarsson's 19:28-32 similarly indicates ***something*** is sequenced, ***but not <u>what</u>*** is sequenced.

      EX1002 (Cooper Decl.), ¶186; EX1003 (Linnarsson), 19:28-32; EX2013 (Quackenbush Decl.), ¶84; POR.43-44.
    - Linnarsson's 21:13-25 confirms the entirety of the tagged polynucleotide is not sequenced (only a ***fragment*** is) and discloses ***<u>further</u> fragmenting*** may be needed: "the cDNA library can be processed by fragmenting the cDNA library (e.g., with DNase) to obtain a short-fragment 5'-end library."

      EX1003 (Linnarsson), 21:13-25; EX2013 (Quackenbush Decl.), ¶84; EX1002 (Cooper Decl.), ¶186; POR.16, 43-45; SurRep.21-23.
      - "cDNA library" is itself defined in Linnarsson as "a collection of cloned complementary DNA (cDNA) ***fragments***."

        EX1003 (Linnarsson), 12:4-8; EX2013 (Quackenbush Decl.), ¶83; POR.43-44; SurRep.21-23.

Petitioner's Sequencing Assertions Fail—Linnarsson Does Not Sequence The Entire Tagged Polynucleotide *(cont'd)*

- Further, **Petitioner and Cooper explicitly and repeatedly relied on *Figure 11***, which indisputably incorporates the fragmentation and capture approach, and therefore cannot sequence the entirety.

Pet.32-33, 41-42 (mapping Fig.11 to [1D], [1F]); EX1002 (Cooper Decl.), ¶¶135-140, 155-156 (same, to [1D], [1F]); EX2018 (Cooper IPR2023-00876 Dep. Tr.), 23:15-25:21, 29:14-30:2; EX2013 (Quackenbush Decl.), ¶¶37-47, 63; POR.10 n.7, 31-33; SurRep.23-26.

  - Dr. Cooper admitted he relied on Figure 11:

> **Q.** And so, you rely on these steps [in Figure 11] and others described in Linnarsson in coming to your opinions about Linnarsson; is that correct?
>
> **A.** Correct. I use some of the -- you know, figure 11 is part of the evidence of -- of all of the disclosure that's in Linnarsson, yes.

EX2018 (Cooper IPR2023-00876 Dep. Tr.), 23:15-20, 29:14-30:2; POR.10 n.7, 56; SurRep.10-12.

  - Indeed, both Petitioner and Dr. Cooper ***repeatedly equated Figures 2 and 11,*** **and** ***treated them and Figures 3-4 as a single embodiment*** without explaining how or why POSITA would mix-and-match across them.

Pet.29-32, 34-35 ("As shown in Figures 2 and 11… Figure 11… ***discloses the same***…"), 32-33 ("As shown in Figure 2 below, ***a*** TSO… ***Figure 11 discloses the same***… Figure 3… ***similarly discloses a*** TSO…"); EX1002 (Cooper Decl.), ¶¶136-138 ("As demonstrated in Figures 2 and 11, above, the CDS…"), 139-140 ("The TSO… is shown in Figures 2 and 11… Figure 3 depicts an example of a TSO…"), 150-151 ("Linnarsson's Figures 2 and 11, depicted below, show…"); EX2013 (Quackenbush Decl.), ¶45-47, 97; SurRep.23-26.

Petitioner's Sequencing Assertions Fail—Linnarsson Does Not Sequence The Entire Tagged Polynucleotide *(cont'd)*

- With respect to sequencing, the Petition ignored that in the method of Figure 11, Linnarsson sequences only the "5' fragment," not the entire tagged polynucleotide. Petitioner's assertion that [1J] is met by Linnarsson teaching that sequencing is performed on the tagged polynucleotide is plainly wrong

EX2018 (Cooper IPR2023-00876 Dep. Tr.), 41:10-44:22; EX2013 (Quackenbush Decl.), ¶¶80-86; POR.42-48; SurRep.18-23.

- Petitioner also admits that "in Figure 11 of Linnarsson, the CDS is not sequenced."

Rep. 19-20; EX2013 (Quackenbush Decl.), ¶85; Pet.32-33, 41-42 (mapping Fig.11 to [1D], [1F]); EX1002 (Cooper Decl.), ¶¶135-140, 155-156 (same, to [1D], [1F]); POR.47-48; *see also* SurRep.23-25.

- And neither Petitioner nor Dr. Cooper ever identified a complete embodiment (from tagging through sequencing) *without* fragmentation-and-capture.

Pet.44; EX1002 (Cooper Decl.), ¶¶ 183-187; Rep.17-19; EX2013 (Quackenbush Decl.), ¶¶45-47, 97; POR. 31 n.16; SurRep.25.

Petitioner's New Sequencing Reply Theories Fail

- Petitioner belatedly argued that when the cDNA is fragmented, it could "be done in various ways" including in ways that sequence the "full complement of fragments."

  Rep.19; EX1070 (Cooper Reply Decl.), ¶¶50-51, 99-104; SurRep.21-23.

- But the fragmentation Petitioner addresses relates to processing of the "cDNA library" itself, which only consists of fragments to begin with.

  EX1003 (Linnarsson), 12:4-8, 22:5-21; EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 103:8-19; SurRep.21-23.

Petitioner's New Sequencing Reply Theories Fail *(cont'd)*

- Petitioner belatedly argued the sequencing limitation is met because "Linnarsson does not require fragmentation."

  Rep.18-19; EX1070 (Cooper Reply Decl.), ¶¶59, 127; SurRep.18-19, 22-23.

  - Dr. Cooper repeatedly argued Figures 3 and 4 do not include a BtsCI cut site, and previously testified that Figures 3 and 4 "do not contain any restriction enzyme cut site."

    E.g., EX1070 (Cooper Reply Decl.), ¶¶36-59, 114-117; EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 118:14-130:5, 133:19-137:10; SurRep.19-20 n.9, 20 n.11.

  - Dr. Cooper also testified that the "biotin (in the case of both the CDS and TSO) and restriction enzyme cut site (in the case of the TSO) are part and parcel of the fragmentation method used in Figure 11."

    EX1070 (Cooper Reply Decl.), ¶37; Rep.6; SurRep.20 n.11.

- But fragmentation is not optional in Linnarsson's method(s).

  EX1003 (Linnarsson), 21:13-25, Fig.11, 26:9-20, 35:17-27; EX2013 (Quackenbush Decl.), ¶62-67, 81-84; POR.30-33, 43-45; SurRep.17-23.

  - Consistent with Dr. Cooper's "part and parcel" opinion, ***Figures 3 and 4 <u>are</u> part of the fragmentation and capture approach, and they <u>do</u> have restriction enzyme cut sites***.

    EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 123:11-125:4, 129:2-7, 133:22-137:10; Rep.17-19; EX1070 (Cooper Reply Decl.), ¶37; SurRep.19-21.

  - And this is consistent with Linnarsson, which *introduces Figures 3 and 4 within Example I, which uses fragmentation and capture*.

    EX1003 (Linnarsson), 23:1-24:20; EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 96:12-97:11, 118:5-8 (admitting Ex.I includes "fragmentation and capture"); EX1070 (Cooper Reply Decl.), ¶¶ 36-48; SurRep.18-23.

Petitioner's New Sequencing Reply Theories Fail *(cont'd)*

- Petitioner and Dr. Cooper also belatedly assert Linnarsson Claims 1 and 27 are evidence that "Linnarsson does not require fragmentation."
  - Petitioner argues Linnarsson's claim 27 "recite[s] fragmenting," which means fragmenting is not required.

    Rep.18-19; EX1070 (Cooper Reply Decl.), ¶¶59, 127; EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 97:17-101:22, 111:8-113:16; SurRep.22-23.
  - Dr. Cooper also suggested for the first time in his Reply declaration that Linnarsson claim 1 evidenced fragmentation's supposed optionality because it did not identify fragmentation as a requirement.

    EX1070 (Cooper Reply Dep. Tr.), ¶¶59, 127; SurRep.22-23.
- But Linnarsson's claims do not indicate fragmentation is not required.
  - And Dr. Cooper agreed it may be necessary to further fragment the cDNA to sequence it.

    EX1003 (Linnarsson), 22:5-21; EX1081 (Cooper Reply Dep. Tr.), 97:17-103:19, 111:8-113:16; SurRep.18-23.
  - Petitioner's reliance on Linnarsson's claim 27 is late, and its "fragmenting the cDNA library" language only confirms there may be an ***additional*** fragmentation step after creation of the cDNA library.

    Rep.7; EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 101:9-103:7; SurRep.22-23.
    - Linnarsson defines "cDNA library" as "a collection of cloned complementary DNA (cDNA) ***fragments***."

      EX1003 (Linnarsson), 12:4-8; EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 97:17-98:20; POR.17; SurRep.21-23.
    - And Dr. Cooper concedes ***additional*** fragmentation may be required for, *e.g.*, the NGS or shotgun sequencing Linnarsson discloses.

      EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 111:8-113:16; EX1003 (Linnarsson), 22:5-21; SurRep.22-23.
  - Petitioner's reliance on Linnarsson's claim 1 is also late, and it does not exclude biotin or fragmentation: it is a "comprising claim" and is simply silent on those features.

    In re Benno, 768 F.2d 1340, 1345-46 (Fed. Cir. 1985); *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1262 (Fed. Cir. 1989); EX1070 (Cooper Reply Decl.), ¶¶61, 106; EX1003 (Linnarsson), 46:3-12; SurRep.22-23.

Ground 1: Petitioner's Combination Fails To Satisfy Its Argued Motivation To Combine Linnarsson And McCloskey And Reasonable Expectation Of Success

Petitioner Must Prove Its Combination Provides The Solution Petitioner Argued For

- Whether the claims requiring tagging "substantially all" mRNA molecules in a cell uniquely is irrelevant—Petitioner must show its combination would have provided the solution it argued for.

The Board, therefore, was justified in finding that, "despite having acknowledged the quantitative deblocking requirement in Tsien (Pet. 37), the Petition ***did not provide a specific or credible explanation why an ordinary artisan would have expected Zavgorodny's azidomethyl protecting group to meet Tsien's quantitative deblocking requirement*** under conditions suitable for use in Tsien's sequencing methods." ***While this shortcoming is irrelevant to a finding that there was no reasonable expectation of success in meeting the claims of the '537 patent, which do not require quantitative deblocking at all, it is central to a finding of no motivation to combine***. This is ***because the petitioner's sole argument for why one of skill in the art would be motivated to combine*** Zavgorodny's azidomethyl group with Tsien's SBS method ***was because it would meet Tsien's quantitative deblocking requirement***.

Intelligent Bio-Sys., Inc. v. Illumina Cambridge, Ltd., 821 F.3d 1359, 1367-69 (Fed. Cir. 2016) (citations omitted); POR.43-46.

Linnarsson's Method Tags Substantially All mRNA Molecules Of A Given Cell

- The "sample polynucleotides" of Linnarsson's method are "substantially all mRNA molecules of a given cell."

EX1003 (Linnarsson), 1 (Abstract); EX1002 (Cooper Decl.), ¶¶ 124, 125, 129; EX2013 (Quackenbush Decl.), ¶¶88-90; POR.7-10; SurRep12-15.

Further, the purpose of Linnarsson's method is gene expression analysis, which a POSA would have understood contemplates the analysis of substantially all mRNA molecules of a cell. EX1002 ¶ 222; EX1003 at 1:11-12, 1:25-26 ("direct sequencing of the ***all***, or parts, ***of the mRNA content*** of a tissue is being increasingly used."); EX1015 at 1:10-11, 1:31-33. Thus, a POSA would have understood that such a method was designed to be applied to substantially all mRNA molecules of a given cell.

EX2021 (IPR2023-00955 Petition), 55; EX2022 (Cooper IPR2023-00955 Decl.), ¶222.

Petitioner's Argued Motivation to Combine Depends On Tagging "Substantially All" mRNA Molecules Uniquely

- Petitioner and Cooper asserted POSITA would have been motivated to modify Linnarsson to "solve" amplification bias (or "source-uncertainty") by tagging "each"/"every"/"substantially all" mRNA molecules in Linnarsson using McCloskey's teachings of a second tag. Pet.34-36; EX1002 (Cooper Decl.), ¶¶87, 174; EX2022 (Cooper IPR2023-00955 Decl.), ¶222; Rep.20-21; *see also* POR.48-49; SurRep.11.

Linnarsson attempts to address the issue of amplification bias by using a cell-tag to distinguish single cells, but recognizes its solution is not perfect as it only "reduces," rather than eliminating, amplification bias. *See* Linnarsson (Ex. 1003) at 11:6-9; Linnarsson Provisional (Ex. 1015) at 3:14-18 ("[t]his reduces amplification bias."). McCloskey recognizes the issue of amplification bias, and expressly discloses that its method of including a second tag sequence on the oligonucleotide "solve[s]" this problem.

EX1002 (Cooper Decl.), ¶171-174 ; Pet.34-36; EX1003 (Linnarsson), 2:3-13; SurRep.10-15

Solving Amplification Bias Requires Tagging All Polynucleotides Uniquely

- "Solv[ing]" amplification bias requires tagging all sample polynucleotides uniquely.

EX1003 (Linnarsson), 1 (Abstract); EX2013 (Quackenbush Decl.), ¶¶87-94; POR.48-49 & n.26; SurRep12-15.

87. To solve this problem, it was well-known and very common to add molecular tags (as discussed above at X.C.1) to target sequences prior to the amplification step. *See, e.g.*, Miner at 1 (Ex. 1013.001), McCloskey at 766 (Ex. 1004.006), Stöger at 6 (Ex. 1060.006), Genereux at 2 (Ex. 1061.002), Nicolas at 0371 (Ex. 1062.008). Every sample and the polynucleotides within every given sample are first uniquely tagged before being amplified and thereafter sequenced. By uniquely tagging the sample and the polynucleotides, researchers can track the number of polynucleotides and their source by counting the number of unique tags. The number of unique tags correspond to the number of unique polynucleotides in every sample. This results in addressing amplification bias by keeping a track of the polynucleotides in the original sample. EX1013.001; EX1004.006.

EX1002 (Cooper Decl.), ¶87.

Petitioner's Ground 1 Theory Is Limited To McCloskey's 7-Nucleotide Barcode

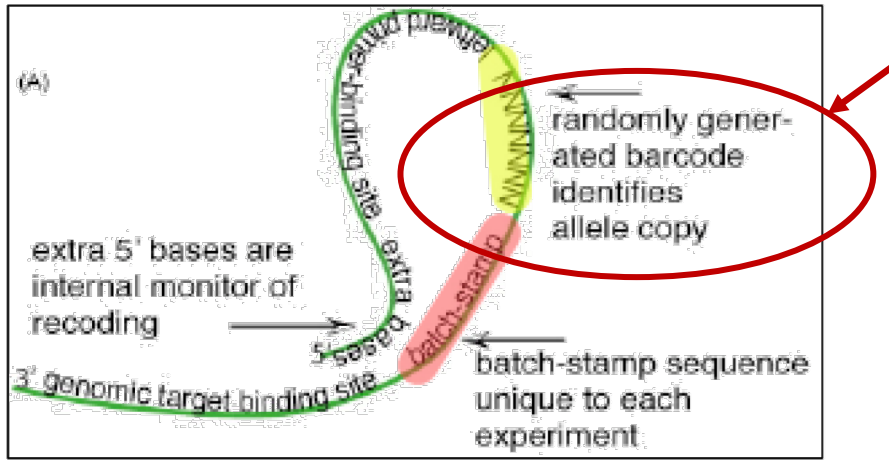
- The Petition never mentioned (let alone relied on) 4^n and never included McCloskey II for Ground 1.

  EX1070 (Cooper Reply Decl.), ¶132 (citing EX1002, (Cooper Decl.), ¶¶256-257 (Ground 2 opinions)); Pet.60-62; Rep.25-26 (arguing Ground 1 but citing EX1002, ¶¶254-258); POR.48-49 n.25, n.26; SurRep.15-17.

- To the extent Petitioner can be credited with actually identifying a barcode from McCloskey, it can only be the barcode actually used in McCloskey—which Petitioner acknowledges is "seven nucleotides."

  Pet.34-35; Rep.21; SurRep.15-17

McCloskey teaches an "encoding oligonucleotide" as depicted below in Figure 1:



EX1004 at Fig. 1. As shown above, McCloskey's encoding oligonucleotide comprises two tag sequences: (1) a "batch-stamp" sequence (highlighted in red, above) to identify the experimental batch or genomic source (*e.g.*, a single cell) and (2) a "barcode" (highlighted in yellow, above) to distinguish polynucleotide sequences "arising from different cell or allele copies." *See* EX1004.001-002

Petitioner's Ground 2 Theory *Modifies* McCloskey's 7-Nucleotide Barcode: Adding McCloskey II And Applying 4^n

C. The Asserted Prior Art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §[1]	Basis
1–12, 19–28	103(a)	Linnarsson,[2] McCloskey,[3] and "further in view of the knowledge of a [person of ordinary skill in the art]"
13–18	103(a)	Linnarsson, McCloskey, McCloskey II[4] and "further in view of the knowledge of a [person of ordinary skill in the art]"

Pap.9 (Institution Decision), 6.

Petitioner's Ground 2 Theory *Modifies* McCloskey's 7-Nucleotide Barcode: Adding McCloskey II And Applying 4^n

- Only in Ground 2 did the Petition first rely on the "4^n" formula and the additional McCloskey II reference to modify Petitioner's Ground 1 Linnarsson-McCloskey combination to provide a longer barcode to cover claim 13.

EX1002, (Cooper Decl.), ¶¶255-257; Pet.60-61; SurRep.15-17.

Furthermore, it would have been obvious to design molecular tags to have a sufficient number of randomly selected nucleotides to ensure that each sample polynucleotide is tagged with a ***unique*** second tag sequence. McCloskey teaches that using second tag sequences each containing *n* number of random base pairs "enables one to distinguish 4^n allele copies per reaction." EX1004.004. It would have been a simple design choice to design the second tag sequences with appropriate number of nucleotides to ensure sufficient number of distinct second tag sequences in the reaction mixture (e.g., at least 100 times for than the number of sample polynucleotides) such that each sample polynucleotide is uniquely tagged. EX1002 ¶ 256.

For example, McCloskey II teaches using molecular-tags each comprising 30 random base pairs, which would allow the creation of 4^{30} (1.15×10^{18}) unique second tag sequences. EX1055 at [0021] ("the length of the second sequence is between 3 and 30 nucleotides"). Linnarsson also teaches that its tag sequence can comprise at least 20 nucleotides, which would allow the creation of 4^{20} (1.10×10^{12}) unique barcodes. Using molecular tags comprising 30 or 20 nucleotides would more than ensure that each sample polynucleotide from a single cell is tagged with a unique tag sequence. A typical mammalian cell comprises approximately between 50,000 to 360,000 mRNA molecules. *See* EX1002 at ¶ 257.

Pet.60-61.

The Petition's Theory Does Not Provide Enough Tags To Tag Each mRNA Molecule In Linnarsson

- Petitioner asserted "It would have been a simple design choice to design the second tag sequences with appropriate number of nucleotides to ensure sufficient number of distinct second tag sequences in the reaction mixture (e.g., ***at least 100 times [more] than the number of sample polynucleotides) such that each sample polynucleotide is uniquely tagged***."

  Pet.61; EX1002 (Cooper Declaration), ¶ 256; EX2013 (Quackenbush Decl.), ¶ ¶87-94; POR.48-49 & n.26; SurRep.9-12.

- But per the admissions of Petitioner and its expert, Dr. Cooper, McCloskey's 7-nucleotide barcode wouldn't provide enough tags (only up to 16,348):

  POR.48-49, nn.25-26; SurRep.9-12.

  - Fails for mammals: Tagging between 50,000 and 300,000 expected mRNA molecules per cell would require 5,000,000 to 30,000,000 tags.

    EX1002 (Cooper Declaration), ¶ 257; EX1054 (Marinov), 1; EX2013 (Quackenbush Decl.), ¶91; POR.48-49 & n.26; POR.48-49, nn.25-26; SurRep.9-12.

  - Fails for yeast: Tagging between 15,000 and 60,000 expected mRNA molecules per yeast cell would require 1,500,000 to 6,000,000 tags.

    EX1002 (Cooper Declaration), ¶ 257; EX1054 (Marinov), 1; EX2013 (Quackenbush Decl.), ¶91; POR.48-49, nn.25-26; SurRep.9-12.

  - Fails for bacteria: Tagging between 1,380 expected mRNA molecules per E. Coli cell would require 138,000 tags.

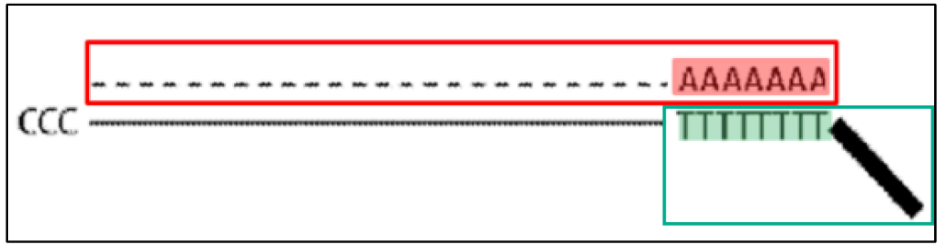
    EX1002 (Cooper Declaration), ¶ 257; EX1054 (Marinov), 1; EX2013 (Quackenbush Decl.), ¶91; POR.48-49, nn.25-26; SurRep.9-12.

The Petition's Theory Cited Linnarsson's Disclosures Of Tagging Eukaryotic mRNA

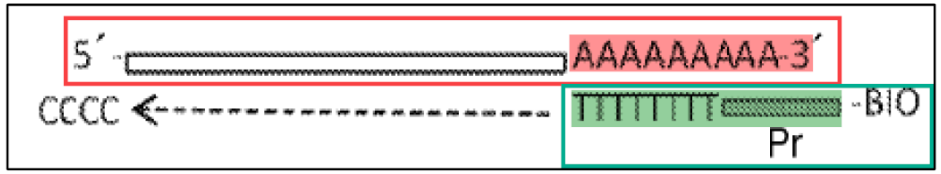
- In the Petition, Petitioner and Dr. Cooper exclusively relied on mRNA with a poly-A tail and a CDS with a poly-T sequence and asserted Petitioner's asserted combination worked for Linnarsson's "tissue of interest."

EX1002 (Cooper Decl.), ¶135; Pet.28, 31-33, 39-42; SurRep.11-12.

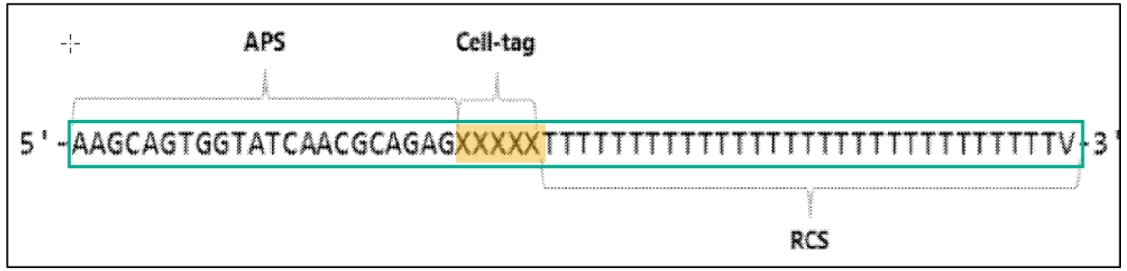
"As shown in ***Figures 2 and 11***, ***a*** CDS (boxed in green, below)… As shown in ***Figure 4***, Linnarsson discloses that ***the*** CDS (boxed in green)…."



EX1003 at Fig. 2



Id. at Fig. 11



EX1003 at Fig. 4

EX1002 (Cooper Decl.), ¶135; Pet.31-33, 39-42; SurRep.11-12.

The Petition's Theory Relied On Linnarsson's Disclosures Of Tagging Eukaryotic mRNA *(cont'd)*

- According to Petitioner's Dr. Cooper, the purpose of the poly(A) tail is to "allow[] it to be exported from the nucleus":

61. Protein-coding gene expression is achieved by two major steps – transcription and translation. Transcription is the copying of genetic information from a DNA sequence into a specific type of RNA: messenger RNA (mRNA), which is made up of nucleotides that are complementary to the DNA sequence. During transcription, an enzyme called RNA polymerase catalyzes the formation of a pre-mRNA molecule using the DNA sequence as a template for complementary base-pairing. The pre-mRNA is then processed to form mature mRNA. Clancy at 1 (Ex. 1030.001). A poly(A) tail, which is a sequence of adenine nucleotides, is added to the 3' end of the mature mRNA (circled in red, below) and makes the mRNA molecule more stable and allows it to be exported from the nucleus to carry out the next step, translation.

EX1002 (Cooper Decl.), ¶61.

Tagging A Subset Of Molecules Fails

- Petitioner argues the ***claims*** "do not require tagging ***all*** the mRNA molecules in such a cell." Rep.24; SurRep.12-15.

- But Petitioner's ***motivation to combine*** ***<u>does</u>*** require tagging "substantially all" mRNA molecules in the cell, as done in Linnarsson. SurRep.12-15; *see also* POR.48-49, nn.25-26.

- Petitioner never proposed any modification to Linnarsson to tag less than "substantially all mRNA molecules" in the cell, and never explained how amplification bias could be "solved" by tagging less than all. EX2013 (Quackenbush Decl.), ¶92; Pet.34-36; EX1002 (Cooper Decl.), ¶¶87, 174; EX2022 (Cooper IPR2023-00955 Decl.), ¶¶91, 222; POR.48-49, nn.25-26; SurRep.12-15.

- And ***merely "<u>reduc[ing]</u> amplification bias"*** (as Petitioner first suggests in Reply) is ***not sufficient for Petitioner's theory, which depends on "<u>solv[ing]</u>" amplification bias***. Petitioner's Dr. Cooper expressly contrasted this against Linnarsson's "only '***reduc[ing]***'" amplification bias. EX1002 (Cooper Decl.) ¶171; Pet.35-37; POR.48-49; EX2013 (Quackenbush Decl.), ¶92; Rep.23-26; SurRep.12-15.

- And tagging the subset of mRNA molecules in bacteria that have a poly-A would identify mRNA "bound for degradation," not those being expressed. EX2103 (Llorens-Rico), 4; EX1081 (Cooper IPR2023-00876 Reply Dep. Tr.), 74:18-76:3, 64:16-71:14, esp.64:16-65:1, 65:8-21, 66:5-69:20; Rep.22-25; SurRep.12-15.

Petitioner's Analogous Art Analysis Is Deficient

Petitioner's Analogous Art Argument Failed

- The Petition affirmatively made an analogous art argument for McCloskey and Linnarsson.

Pet.35; EX1002 (Cooper Decl.), ¶170; *see Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373, 1380 (Fed. Cir. 2023) (petitioner cannot meet its burden when it "argue[s] that [a prior art reference] is analogous to another prior art reference and not the challenged patent."); POR.51-53; *see also* SurRep.29.

- But that affirmative Petition argument failed on its merits: Petitioner didn't dispute that—while it affirmatively argued analogousness—it failed to show analogousness ***to the '013 patent***.

Rep.27-28; SurRep.29.

- Petitioner now asserts it can change its analogous art argument and do so without limitation on Reply (citing *Sanofi-Aventis Deutschland GmbH v. Mylan Pharms.*, 66 F.4th 1373, 1379 (Fed. Cir. 2023)).

Rep.27-28; SurRep.29.

- But PO's Response did not invite a broadening reply.

Cf. Corephotonics, Ltd. v. Apple Inc., 84 F.4th 990, 1004-1010 (Fed. Cir. 2023) (declining to find Board abused discretion in allowing argument responding to patentee's affirmative assertions against analogousness, noting, *inter alia*, "petitions were ambiguous; they did not make clear whether [petitioner] was stating [references] are in the same field… as the Challenged Patents or, instead, merely… one another"; petitioner permitted to respond both by ***bolstering*** its field of endeavor argument and by adding" pertinent-to-the-problem argument); SurRep.29.

- Petitioners should not be permitted to rewrite a deficient Petition argument where Petitioner affirmatively argued analogousness but did so incorrectly.

SurRep.29.

Petitioner Failed To Establish McCloskey Is Prior Art

Petitioner Failed To Establish McCloskey Is Prior Art

- Petitioner asserted McCloskey (EX1004) is prior art ***based on EX1028***.

  Pet.22 (citing EX1028 (Hall-Ellis Declaration)); Rep.4-5; POR.20-21; SurRep.27-28.

- But ***EX1028 does not even mention McCloskey***, let alone establish it was publicly accessible before the priority date.

  EX1028 (Hall-Ellis Decl.); POR.20-21.

- And McCloskey itself provides ***no admissible evidence it was disseminated or otherwise made publicly available prior to the priority date.***

  SurRep.27-28.

  - The ***date in McCloskey itself is hearsay***.

    Standard Innovation Corp. v. Lelo, Inc., IPR2014-00148, Pap.41, 18-28 (Apr. 23, 2015) (concluding claims not unpatentable where reference not qualified as a printed publication because, *inter alia*, dates within the exhibit were inadmissible hearsay); *Medivis, Inc. v. Novarad Corp.*, IPR2023-00042, Pap.35, 27-30 (Mar. 6, 2024) (copyright date "is not sufficient [even] at... institution... to demonstrate public accessibility") POR.20-21; SurRep.27-28.

  - And even if the hearsay date were considered, it would be ***insufficient to establish*** McCloskey was ***publicly accessible***.

    Medivis, Inc. v. Novarad Corp., IPR2023-00042, Pap.35, 27-30 (Mar. 6, 2024) (copyright date and unsubstantiated argument that reference appeared online insufficient to demonstrate public accessibility); SurRep.27-28.

Petitioner's Reply Arguments Should Not Be Considered

- Months later, on Reply, Petitioner first sought to fix its evidentiary failings with a brand new (late) Hall-Ellis Declaration:

> "Nonetheless, Dr. Sylvia Hall-Ellis in her non-hearsay testimony confirms McCloskey's public availability and prior art status. *See* EX1085 ¶¶ 44-45, 50 ("…it is my opinion that the McCloskey article…was publically available on or shortly after January 3, 2008…". Submitting a supporting declaration is allowed on reply. *See, e.g., Hulu v. Sound View*, IPR2018-01039, Paper 29 at 15 (P.T.A.B. Dec. 20, 2019) (precedential)."

Rep.4-5; SurRep.27-28.

- To begin, the Reply's citation without discussion to the improper new Hall-Ellis declaration is also ***improper incorporation by reference***, and should not be considered.

SurRep.27-28; Rep.4-5.

- Petitioner's improper new evidence is ***not responsive to the POR***. As in *Sirius XM*, PO here "simply pointed out the defect in the Petition"—the Petition's failure to establish the reference was prior art.

Sirius XM, IPR2018-00690, Pap.63, 13-15 (July 23, 2020) (refusing to consider reply evidence that reference was prior art where "Patent Owner's Response simply pointed out the defect in the Petition"); Rep.4-5; POR.20-21; SurRep.27-28.

  - *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Pap.29, 15 (Dec. 20, 2019)—cited by Petitioner—does not support considering the new Hall-Ellis Declaration because it is not responsive evidence, as *Hulu* requires.

Rep.4-5; SurRep.27-28.

Patent Owner's Motion To Exclude

Patent Owner's Motion To Exclude

- Patent Owner timely objected to McCloskey as irrelevant under FRE 402 and its date as hearsay, stating in part: "To the extent that Petitioner attempts to rely on any date that may appear in EX1004… to establish public accessibility as a printed publication, any such date is hearsay."

  Pap.12 (PO's Objections to Evidence); Pap.38 (PO's Motion to Exclude), 1; Pap.42 (PO's Reply), 4..

- Petitioner failed to serve supplemental evidence within the time period required under 37 C.F.R. § 42.64(b)(2).

  Pap.38 (PO's Motion to Exclude), 3, 8-10.

- Instead, on Reply and without authorization, Petitioner purportedly supplied an authenticating declaration from Sylvia Hall-Ellis, purporting to confirm McCloskey's prior art status.

  Rep.4-5.

- Patent Owner timely moved to exclude McCloskey (EX1004) and the new Hall-Ellis Declaration (EX1085), and any reliance thereon.

  Pap.38 (PO's Motion to Exclude), 1.

McCloskey Should Be Excluded

- Petitioner's opposition identifies ***no hearsay exception*** that would permit McCloskey's purported publication date to be considered for the truth of the matter asserted.

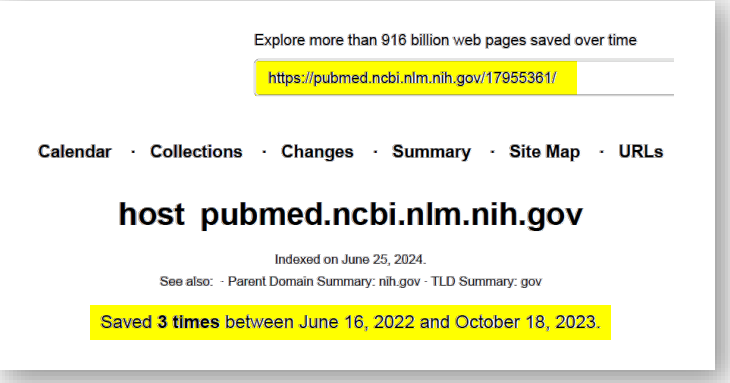
Pap.40 (Petitioner's Opposition), 4-10; Pap.42 (PO's Reply), 1-3; Fed.R.Evid.802.

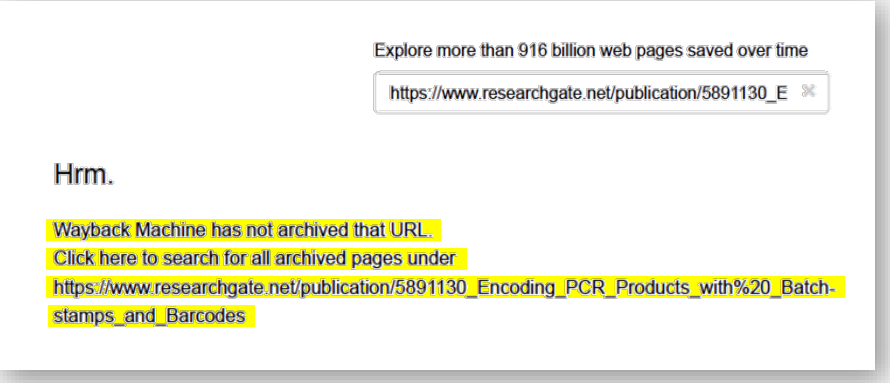
- Instead, the opposition points to different "evidence" that McCloskey is a printed publication. Petitioner cites the Board's ruling in a related IPR, argues "McCloskey is properly considered because it bears all conventional markers of publication," and cites the McCloskey II and Fodor Patents as supposedly confirming availability.

Pap.40 (Petitioner's Opposition), 7-8, 11 (citing EX1029 and EX1053); Pap.42 (PO's Reply), 1.

  - But Petitioner relies on the web-based version of McCloskey, and there is no evidence McCloskey was available online as of 2009, let alone publicly accessible.

Pap.42 (PO's Reply), 1-3.





EX2041 (Wayback Capture for Springer), 1; EX2042 (Wayback Capture for National Library of Medicine), 1; EX2043 (Wayback Capture for ResearchGate), 1; Pap.42 (PO's Reply), 1.

No Evidence McCloskey Was Available Online As Of The Priority Date

- "Conventional markers of publication" do not establish that the dates on McCloskey are not hearsay or prove public accessibility of McCloskey.

Pap.40 (Petitioner's Opposition), 4-6; Pap.42 (PO's Reply), 2-3.

- Petitioner identifies no purported evidence of public accessibility other than a (hearsay) publication date recited in the McCloskey document, itself.

Pap.40 (Petitioner's Opposition), 4-10; Pap.42 (PO's Reply), 1-3.

No Evidence McCloskey Was Available Online As Of The Priority Date

- And publication dates are insufficient to establish accessibility.

Pap.42 (PO's Reply), 2-3.

The remainder of Petitioner's argument in support of public accessibility is terse. Petitioner states, "Chen . . . appeared online on April 13, 2015, and in print in June 2015. . . . Chen was cited by seven publications by January 2017." Reply 27 (citing Exs. 1009, 1028). In support, Petitioner relies in part on the face of Chen, which states that it was "[a]vailable online 13 April 2015." *Id.*; Ex. 1009, 1. This statement does not prove public accessibility because any reference can state it was published without actually being published. Not only that, but there is no indication in this statement whether Chen was "made available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *SRI*, 511 F.3d at 1194. Moreover, Petitioner's assertion that Chen was cited by seven publications does not establish public accessibility. Petitioner does not even supply these publications as exhibits for our inspection to verify these citations. *See* Ex. 1028 ¶ 15 (listing seven alleged publications but not including them as exhibits).

Medivis, Inc. v. Novarad Corp., IPR2023-00042, Pap.35, 28 (Mar. 6, 2024); Pap.42 (PO's Reply), 2-3.

No Evidence McCloskey Was Available Online As Of The Priority Date

- And publication dates are insufficient to establish accessibility. *(cont'd)*

Pap.40 (PO's Reply), 1-3.

And, a copyright notice *may* be evidence of publication[10], but generally such a notice does not "establish when a document was publicly accessible under patent law." *Stryker Corp. v. Karl Storz Endoscopy-Am., Inc.*, Case IPR2015-00677, slip op. at 18–19 (PTAB Sept. 2, 2015) (Paper 15); *see also Microsoft Corp. v. Corel Software, LLC*, Case IPR2016-01083, slip op. at 13–14 (PTAB Dec. 1, 2016) (Paper 14) ("The copyright notice, alone, however, sheds virtually no light on whether the document was publicly accessible as of that date, therefore additional evidence is typically necessary to support a showing of public accessibility.").

Schlumberger Tech. Corp. v. Integrated Drive Sys. LLC, IPR2018-00603, Pap.40, 12-22 (Sept. 3, 2019); Pap.42 (PO's Reply), 2.

In an *inter partes* review, a petitioner bears the burden of establishing unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 316(e). That burden includes establishing that references relied upon as prior art are printed publications. Furthermore, as the Federal Circuit has explained, "'if the fact trier of the issue is left uncertain, the party with the burden loses.'" *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378–79 (Fed. Cir. 2015) (*quoting Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326–27 (Fed. Cir. 2008)). In this case, we determine that evidence merely demonstrating publication to the internet is not "a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l*, 511 F.3d at 1194 (Fed. Cir. 2008).

Celltrion, Inc. v. Biogen, Inc., IPR2016-01614, Pap.65, 19-20 (Feb. 21, 2018); Pap.42 (PO's Reply), 2.

McCloskey II And The Fodor Patents Cannot Establish Accessibility

- Parse asserts that McCloskey II and the Fodor Patents establish McCloskey was published in 2007.

  Pap.40 (Petitioner's Opposition), 6-8; Pap.42 (PO's Reply), 3-4.

- But the accessibility of McCloskey II does not establish McCloskey was publicly accessible

  Pap.40 (Petitioner's Opposition), 6-7; Pap.42 (PO's Reply), 3-4.

- And the Fodor Patents were not even filed until after McCloskey's 2009 critical date and simply repeat McCloskey's hearsay date.

  Medivis, Inc. v. Novarad Corp., IPR2023-00042, Pap.35, 28 (Mar. 6, 2024) (statement that reference "[a]vailable online 13 April 2015" did not establish public accessibility, as "any reference can state it was published without actually being published");; Pap.40 (Petitioner's Opposition), 7-8; Pap.42 (PO's Reply), 3-4.

(12) **United States Patent**
Fodor et al.

(10) **Patent No.: US 8,835,358 B2**
(45) **Date of Patent: Sep. 16, 2014**

(54) **DIGITAL COUNTING OF INDIVIDUAL MOLECULES BY STOCHASTIC ATTACHMENT OF DIVERSE LABELS**

(75) Inventors: **Stephen P. A. Fodor**, Palo Alto, CA (US); **Glenn K. Fu**, Dublin, CA (US)

(73) Assignee: **Cellular Research, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 619 days.

(21) Appl. No.: **12/969,581**

(22) Filed: **Dec. 15, 2010**

6,040,138	A	3/2000	Lockhart et al.
6,046,005	A	4/2000	Ju et al.
6,060,596	A	5/2000	Lerner et al.
6,117,631	A	9/2000	Nilsen
6,124,092	A	9/2000	O'Neill et al.
6,138,077	A	10/2000	Brenner
6,140,489	A	10/2000	Brenner
6,172,214	B1	1/2001	Brenner
6,197,506	B1	3/2001	Fodor et al.
6,235,475	B1	5/2001	Brenner et al.
6,268,152	B1	7/2001	Fodor et al.
6,284,460	B1	9/2001	Fodor et al.
6,309,822	B1	10/2001	Fodor et al.
6,309,823	B1	10/2001	Cronin et al.
6,326,148	B1	12/2001	Pauletti et al.
6,355,431	B1	3/2002	Chee et al.
6,355,432	B1	3/2002	Fodor et al.
6,395,491	B1	5/2002	Fodor et al.
6,406,848	B1	6/2002	Bridgham et al.

(Continued)

EX1029 (U.S. Patent No. 8,835,358), 1.

(12) **United States Patent**
Fodor et al.

(10) **Patent No.: US 9,708,659 B2**
(45) **Date of Patent: Jul. 18, 2017**

(54) **DIGITAL COUNTING OF INDIVIDUAL MOLECULES BY STOCHASTIC ATTACHMENT OF DIVERSE LABELS**

(71) Applicant: **Cellular Research, Inc.**, Palo Alto, CA (US)

(72) Inventors: **Stephen P. A. Fodor**, Palo Alto, CA (US); **Glenn K. Fu**, Dublin, CA (US)

(73) Assignee: **Cellular Research, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/540,029**

(22) Filed: **Nov. 12, 2014**

5,149,625	A	9/1992	Church et al.
5,200,314	A	4/1993	Urdea
5,424,186	A	6/1995	Fodor et al.
5,424,413	A	6/1995	Hogan et al.
5,445,934	A	8/1995	Fodor et al.
5,604,097	A	2/1997	Brenner
5,635,352	A	6/1997	Urdea et al.
5,635,400	A	6/1997	Brenner
5,648,245	A	7/1997	Fire et al.
5,654,413	A	8/1997	Brenner
5,656,731	A	8/1997	Urdea
5,658,737	A	8/1997	Nelson et al.
5,714,330	A	2/1998	Brenner et al.
5,744,305	A	4/1998	Fodor et al.
5,759,778	A	6/1998	Li et al.
5,763,175	A	6/1998	Brenner
5,800,992	A	9/1998	Fodor et al.
5,846,719	A	12/1998	Brenner et al.
5,854,033	A	12/1998	Lizardi
5,871,928	A	2/1999	Fodor et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EX1053 (U.S. Patent No. 9,708,659), 1.

The Hall-Ellis Declaration Is Untimely Supplemental Evidence And Should Be Excluded

- The Hall-Ellis Declaration is belated, unauthorized, supplemental evidence filed well past the deadline under 37 C.F.R. §§ 42.123, 42.223 and should be excluded.

  Pap.38 (PO's Motion to Exclude), 8-10.

- Petitioner asserts that the Hall-Ellis Declaration is responsive evidence that was proper on reply.

  Pap.40 (Petitioner's Opposition), 10-15; Pap.42 (PO's Reply), 4-5.

- But Patent Owner only pointed out a defect in the Petition—its failure to establish McCloskey was prior art—and this did not invite new evidence.

  Pap.42 (PO's Reply), 4-5; POR.20-21.

  - The Board in *Sirius XM* similarly refused to consider reply evidence purportedly showing a reference was prior art because "Patent Owner's Response simply pointed out the defect in the Petition."

    Sirius XM Radio Inc. v. Fraunhofer-Gesellschaft Zur Forderung Der Angewandten Forschung E.V., IPR2018-00690, Pap.63, 10, 13-15 (July 23, 2020); Pap.40 (Petitioner's Opposition), 15; Pap.42 (PO's Reply), 4-5

- Petitioner also now requests for the Board to waive the requirements of 37 C.F.R. § 42.64(b)(2).

  Pap.40 (Petitioner's Opposition), 15.

  - But Petitioner's request is both late and unauthorized, and does not meet the good cause standard.

    Pap.42 (PO's Reply), 5.

  - Petitioner waited over ***five months*** after Patent Owner objected to McCloskey and never sought permission to serve it late or file it as supplemental information.

    Pap.42 (PO's Reply), 5.

Petitioner’s Motion To Exclude

The Petitioner's Motion To Exclude

- Petitioner's Motion should be denied for seeking to exclude portions of the Sur-Reply to which it didn't object, based on rules it didn't cite.

  Pap.41 (PO's Opposition), 2-3.

- More fundamentally, Petitioner's Motion is improper because it fails to identify any evidence it seeks to exclude—it is, instead, directed to arguments.

  Pap.41 (PO's Opposition), 3.

  - Petitioner's Motion is like the one rejected by the Board in *Unified Patent LLC v. Mobilepay LLC*, IPR2019-00466, Pap.36, 11 (July 29, 2020), as "improper for failing to identify any evidence to exclude with reference to a proper objection" and "not 'challeng[ing] the admissibility of evidence,' but rather request[ing] the striking of arguments submitted."

    Pap.41 (PO's Opposition), 3.

The Petitioner's Motion To Exclude *(cont'd)*

- Petitioner seeks to exclude arguments related to BtsI as irrelevant. Pap.39 (Petitioner's Motion to Exclude), 2-3.

- But arguments regarding BtsCI are *clearly relevant* because they *contradict Petitioner's substantive arguments that fragmentation is optional because Figures 3 and 4 do not contain any restriction enzyme cut site*.

  EX1070 (Cooper Reply Decl.), ¶¶31-59, 114-127 (testifying Fig.3 & 4 "do not include… any restriction enzyme cut site"); Rep.11-13; Pap.41 (PO's Opposition), 4, 6.

  - Dr. Cooper admits restriction enzymes other than BtsCI are within the scope of Linnarsson.

    EX2040 (Cooper Reply Dep. Tr.), 37:16-21; Pap.41 (PO's Opposition), 1-3, 7.

  - And Dr. Cooper admits Figures 3 and 4 do contain a restriction enzyme cut site

    EX2040 (Cooper Reply Dep. Tr.), 25:21-31:9; SurRep.18-21; Pap.41 (PO's Opposition), 4.

The Petitioner's Motion To Exclude *(cont'd)*

- Petitioner also argues the arguments should be excluded because of the danger of unfair prejudice or confusion that could be caused because Bts "happens to have a name highly similar to the enzyme that is used in Linnarsson," BtsCI.

Pap.39 (Petitioner's Motion to Exclude), 8-9.

- But there is no danger of unfair prejudice or confusion:

Pap.39 (Petitioner's Motion to Exclude), 9; Pap.41 (PO's Opposition), 12-14.

  - Unlike a lay jury, the Board is not in need of Rule 403's protection.

See Medtronic Vascular, Inc. v. TMT Sys., Inc., IPR2021-01532, Pap.56, 46-48 (Mar. 7, 2023); *Spinal Elements, Inc. v. Spectrum Spine IP Holdings, LLC*, PGR2021-00050, Pap.47, 54-55 (Aug. 17, 2022) ("Rule 403 has limited applicability, if any, to bench trials like this proceeding"); *Fox Factory, Inc. v. SRAM, LLC*, IPR2017-00472, Pap. 64, 60 (Apr. 18, 2018) ("As the factfinder, we are able to consider this evidence, in light of the parties' arguments, and give it the appropriate weight."); *Neste Oil Oyj v. Reg Synthetic Fuels, LLC*, IPR2013-00578, Pap.53, 10-11 (Mar. 12, 2015) (proceedings "before the Board are not jury trials; in the absence of a jury, the risk of unfair prejudice against which Rule 403 guards is diminished, if not eliminated entirely"); *see also United States v. Preston*, 706 F.3d 1106, 1117 (9th Cir. 2013), *rev'd on other grounds*, 751 F.3d 1008 (9th Cir. 2014) (*en banc*) ("Rule 403 is inapplicable to bench trials."); Pap.41 (PO's Opposition), 12-14.

  - And Patent Owner's Sur-Reply is clear that the BtsI enzyme and the BtsCI enzyme are not the same.

SurRep.19-21; Pap.41 (PO's Opposition), 12-14.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S 10X GENOMICS, INC.'S DEMONSTRATIVES has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

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