

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

10X GENOMICS, INC.,
Patent Owner

Case IPR2023-00876
Patent 10,155,981

**PATENT OWNER'S SUBMISSION OF UNRESOLVED
OBJECTIONS TO PETITIONER'S DEMONSTRATIVES**

Pursuant to 37 C.F.R. §42.70(b), and the Board’s May 31, 2024 Order Setting Oral Argument (Paper 32), Patent Owner 10x Genomics, Inc. (“PO”) respectfully submits the below list of unresolved objections to Petitioner’s demonstratives. Following each objection is a copy of the objected-to slide with objectionable portions within red rectangles.

- **Slide 6:** This slide reflects new argument regarding a different number of times the “Reflex” Method is mentioned and includes an excerpt of Figure 1 of the ’981 Patent, which is not supported by the citations to the brief on the slide.

“Reflex” Method: Mentioned Over 250 Times

The diagram illustrates the 'Reflex' method in several steps. It starts with a 'First Domain' containing a 'REFLEX' site (102) and a 'Site A' (106). Step 1 involves annealing complementary 'REFLEX' sites (104, 108). Step 2 involves extending from the 3' end (110). The process then involves denaturing (112, 114) and optionally removing a double strand (116, 118). Finally, a copy is made in inverse polarity (120, 122, 124, 126, 128, 130).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’981 Petition at 20)

EX1001 (’981 Patent) at Fig. 1
Parse 6

- **Slide 7:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on

the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr Quackenbush: Does Not Know If Claims Cover "Reflex" Method



John Quackenbush
10X's Expert

Q. Do you know whether the reflex method as described in the '981 patent embodies the claims in the '981 patent?

A. So I don't believe Dr. Cooper offers opinions about whether or not the reflex method is embodied in the claims of the '981 patent. The figure legend says that this is, I believe, an exemplary embodiment, but I haven't performed the analysis, and I'm not prepared to offer an opinion.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 99:11-101:13
Parse 7

- **Slide 11:** This slide reflects new argument regarding how the highlighted language in the excerpts of EX1053 purportedly map to the challenged claim

language, which is not supported by the citation on the slide.

Disputed Claims In *Becton-Dickinson* Case Included Dual Tagging And Single Cell

13. A system for counting *n*, wherein *n* is a number of nucleic acid target molecules that are present in a single cell from a sample comprising cells, the system comprising:

a) a diverse set of labels comprising a plurality of oligonucleotides attached to each bead of a plurality of beads, wherein the set of labels comprises *m* different labels, wherein $m > n$, and wherein each oligonucleotide of the plurality of oligonucleotides comprises a common sequence, a variable target label sequence, and a target-specific recognition sequence capable of attaching to or hybridizing to the target molecule;

b) a plurality of reaction vessels comprising a single cell from said sample comprising cells and a single bead from said plurality of beads, wherein each reaction vessel is used for attaching a label from the diverse set of labels attached to the bead contained therein to each occurrence of the nucleic acid target molecules from the single cell contained therein to generate a set of labeled nucleic acid target molecules, wherein the individual labeled nucleic acid target molecules comprise all or a portion of the complementary sequence of a nucleic acid target molecule and a label from the diverse set of labels; and

c) processing software for counting *n* from a number of labeled nucleic acid target molecules detected.

} dual tags

} single cell

} attaching to molecules from single cell

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(‘981 Petition at 13)

EX1053 (‘659 Patent) at Claim 13
Parse 11

- **Slide 16:** This slide reflects new argument regarding how the highlighted language in the excerpts of EX1053 purportedly map to the challenged claim

language, which is not supported by the citation on the slide.

Disputed Claims In *Becton-Dickinson* Case Included Dual Tagging And Single Cell

13. A system for counting n , wherein n is a number of nucleic acid target molecules that are present in a single cell from a sample comprising cells, the system comprising:

a) a diverse set of labels comprising a plurality of oligonucleotides attached to each bead of a plurality of beads, wherein the set of labels comprises $m > n$, and wherein each oligonucleotide of the plurality of oligonucleotides comprises a common sequence, a variable target label sequence, and a target-specific recognition sequence capable of attaching to or hybridizing to the target molecule;

b) a plurality of reaction vessels comprising a single cell from said sample comprising cells and a single bead from said plurality of beads, wherein each reaction vessel is used for attaching a label from the diverse set of labels attached to the bead contained therein to each occurrence of the nucleic acid target molecules from the single cell, contained therein to generate a set of labeled nucleic acid target molecules, wherein the individual labeled nucleic acid target molecules comprise all or a portion of the complementary sequence of a nucleic acid target molecule and a label from the diverse set of labels; and

c) processing software for counting n from a number of labeled nucleic acid target molecules detected.

dual tags

single cell

attaching to molecules from single cell

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’981 Petition at 13)

EX1053 (’659 Patent) at Claim 13
Parse 16

- **Slide 22:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Objective Indicia Evidence



John Quackenbush
10X's Expert

Q. If you turn to paragraph 19 of your report. Do you have that in front of you?

A. I do, yes.

Q. And in terms of the fourth factor, objective indicia, what did you do to investigate whether there was objective indicia supporting your position?

A. So to the best of my recollection, I didn't offer any opinions on objective indicia. I don't believe Dr. Cooper provided any arguments regarding that.

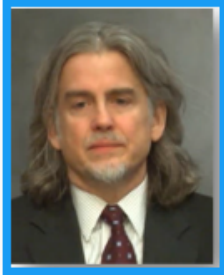
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 15:10-25
Parse 22

- **Slide 23:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Objective Indicia Evidence



John Quackenbush
10X's Expert

Q. What did you do to investigate whether there were objective indicia supporting your position?

A. So I believe I answered that question to the best of my ability – or to the best of my recollection. I didn't provide any opinions here about objective indicia. I don't believe Dr. Cooper offered any opinions regarding objective indicia.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 16:8-17:3
Parse 23

- **Slide 24:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Objective Indicia Evidence



John Quackenbush
10X's Expert

Q. Did you do anything to investigate whether there were objective indicia supporting 10x?

A. I don't believe – I think I answered the question twice. I don't believe I provided any opinions in my report regarding objective So to the best of my recollection, I didn't offer any opinions on objective indicia. I don't believe Dr. Cooper provided any arguments regarding that.

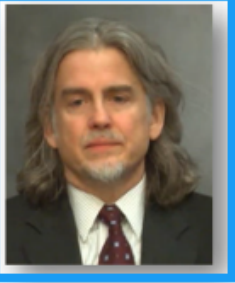
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 16:8-17:3
Parse 24

- **Slide 25:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Commercial Success



John Quackenbush
10X's Expert

Q. Are the claimed inventions of the '981 patent commercially successful?

A. So I haven't done an analysis of the '918 [sic] patent. I don't know if 10x claims they're practicing the invention of the '918 [sic] patent. I didn't provide an opinion about that, and I'm not prepared to offer an opinion today.

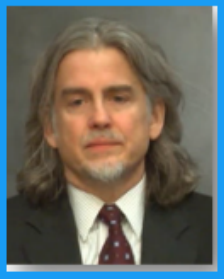
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 20:25-22:15
Parse 25

- **Slide 26:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Unexpected Results



John Quackenbush
10X's Expert

Q. Do the claimed inventions of the patents-in-suit – can you identify any **unexpected results** offered by the claimed inventions of the patent – – of the '981 patent?

A. I haven't performed that analysis, and I'm **not prepared to offer an opinion today**. I haven't formed that analysis in the context of this matter.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 20:25-22:15
Parse 26

- **Slide 27:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Copying



John Quackenbush
10X's Expert

Q. Are you aware of any – can you identify any copying of the claimed inventions of the patents-in-suit?

A. Again, I have not done that analysis in the context of the matter we're discussing today, and I'm not prepared to provide an opinion.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 20:25-22:15
Parse 27

- **Slide 28:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Praise



John Quackenbush
10X's Expert

Q. Can you identify any **praise** by those in the field for the claimed inventions?

A. So I don't believe Dr. Cooper offered any opinions for me to respond to. I didn't do that analysis in the context of the matter we're discussing today, and **I'm not prepared to offer any opinions now.**

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 20:25-22:15
Parse 28

- **Slide 29:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Long-Felt Need



John Quackenbush
10X's Expert

Q. Did you investigate whether there was a long-felt need for the claimed inventions?

A. My assignment here was to respond to Dr. Cooper's arguments. I don't believe I did that analysis, and it doesn't appear in my report, so I'm not prepared to offer an opinion today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 23:1-8
Parse 29

- **Slide 30:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Teaching Away



John Quackenbush
10X's Expert

Q. Do you have an opinion here one way or the other whether there is **teaching away** as an objective indicia of nonobviousness?

A. **I don't recall rendering such an opinion.** If you can point me to places in my report where I offered such an opinion, I'd be happy to refresh my memory.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 29:6-13
Parse 30

- **Slide 31:** The slide fails to include the context of Dr. Quackenbush's testimony by omitting the entirety of the question and answer, the heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide, and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Whether '981 Patent Is Inventive



'So I haven't done a thorough analysis of the inventiveness of the '981 patent.'

John Quackenbush
10X's Expert

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 1)

EX1057 (Quackenbush Depo) at 190:3-4
Parse 31

- **Slide 32:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on

the slide, and includes Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Opinion On Whether '981 Patent Is Inventive



John
Quackenbush
10X's Expert

- Q. Are you able to describe, based on all your work on this matter, what you think is inventive about any of the claims in the '981 patent? Let's say someone wanted to know and asked you.
- A. I haven't performed that analysis, so I would be hesitant to render an opinion today since it's outside the scope of my report.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 1)

EX1057 (Quackenbush Depo) at 203:22-204:5

Parse 32

- **Slide 36, 38, 43, 57, 60, 88-89, 91, 111, 113-114, 133, 141-142, 186:** These slides include Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Claims Require Sequencing "Entirety" Of Tagged Polynucleotides



John Quackenbush
10X's Expert

Dr. Quackenbush's IPR Declaration

1. Dr. Cooper Fails To Show Linnarsson Teaches "Sequencing The Plurality of Tagged Nucleotides"

54. In my opinion, Linnarsson does not teach sequencing "the plurality of tagged polynucleotides" as required by [1G]. Dr. Cooper asserts that the "tagged polynucleotides" in Linnarsson are the cDNA generated during reverse transcription, and that, in his opinion, these tagged polynucleotides are sequenced. EX1002, ¶138 ("The tagged cDNA is the claimed 'plurality of tagged polynucleotides.'"), ¶¶195-198. In my opinion, Dr. Cooper has not shown this limitation is disclosed by Linnarsson. Dr. Cooper ignores, and therefore does not address, how Linnarsson's sequencing of only *a portion* of each tagged polynucleotide, as opposed to the entirety of the tagged polynucleotides, could satisfy this limitation. *Supra*, ¶34.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX2013 (Quackenbush Decl.) ¶ 54
Parse 36

- **Slide 39:** The slide relies on new evidence, which is not found in the citations to the brief (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Originally No Opinion On Whether Sequencing Of "Entire" Polynucleotides Is Required



John Quackenbush
10X's Expert

Q. [D]o you have an opinion one way or the other whether that has to be the entire sequence of the sample polynucleotide from Step 1B? If you're using PCR?

A. The tagged polynucleotide is – the tagged polynucleotide has its own sequence. So I believe you may be confused about the fact that sequence refers to the actual physical structure of the molecule. It might also refer to sequence determined from that molecule. The answer to your question would depend on the context in which it's used. Beyond reading the literal language here, I'm not prepared to render an opinion as to the scope of what that comprising term means in the context of claim 1 of the '981 patent and the deposition we're conducting today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 77:17-79:11
Parse 39

- **Slide 40:** The slide fails to include the context of Dr. Quackenbush's testimony by omitting the entirety of the question and answer, and includes

Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Analysis Of Claim Scope



**John
Quackenbush**
10X's Expert

"I haven't performed an analysis of the scope of the claims of the '981 patent for the – within the context of my declaration and deposition today, and so I'm not prepared to render an opinion."

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 75:3-7
Parse 40

- **Slide 41:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Analysis Of Claim Scope	
	Q. Based on your analysis of Dr. Cooper's declaration, have you identified any terms that warrant claim construction? A. So I didn't perform a thorough analysis with regard to claim construction. My opinions are laid out in the section of my report we referred to earlier, which I believe appears on claim 31. Beyond that, I don't have any further opinions to offer.
John Quackenbush 10X's Expert	
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE (Petitioner's Resp to POR at 2)	EX1057 (Quackenbush Depo) at 132:21-133:10 Parse 41

- **Slide 42:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Full Analysis Of '981 Patent And What Is Disclosed



John Quackenbush
10X's Expert

Q. When the tag nucleotides are being generated in Step 1C, can that be done using PCR?

A. So I haven't – in the context of preparing this report, I haven't done a full analysis of the '981 patent and what's disclosed in the specification. I was responding to Dr. Cooper's arguments about obviousness. And so I'm not prepared today to render an opinion about all the different ways that sample polynucleotide – that tagged polynucleotides can be prepared

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 73:6-74:8
Parse 42

- **Slide 45:** The heading reflects new unbriefed argument regarding Petitioner's characterization of the Petition's argument, which is

unsupported by the citation on the slide.

Petition: Did Not Rely On Sequencing “Entire” Polynucleotides

Page 57 Of The Petition

Linnarsson teaches that after generating the tagged polynucleotides, “sequencing is performed” thereon. See EX1003 at 4:8-13, 19:28-32, 21:13-25 (“This cDNA library can be sequenced to provide an analysis of gene expression in single cells or in a plurality of single cells.”); EX1015 at 8:22-28, 8:33-9:10, 9:35-10:6.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’981 Petition at 57)

’981 Petition at 57
Parse 45

- **Slide 47:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is not found in the citations to the brief (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Dr. Cooper Did Not Opine On Whether Entire Sample Polynucleotide Must Be Sequenced



John Quackenbush
10X's Expert

Q. Do you have an opinion as to whether the sequencing of plurality of tagged polynucleotides requires sequencing of the entire sequence of the tagged polynucleotide? Is that a claim construction issue that you evaluated?

A. So I don't believe Dr. Cooper has offered any opinions, so I haven't done that analysis, and I'm not prepared to offer testimony regarding it today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 172:9-173:20
Parse 47

- **Slide 48:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is not found in the citations to the brief (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Dr. Cooper Did Not Opine On Whether Entire Sample Polynucleotide Must Be Sequenced



John Quackenbush
10X's Expert

Q. Does that require, in terms of your understanding of the claim, that the entire sequence of the sample polynucleotide is included in the tagged polynucleotide?

A. So I haven't done that analysis. I don't believe Dr. Cooper offered any opinions regarding that that I was required to respond to, and so I'm not prepared to offer an opinion about that sitting here today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 172:9-173:20
Parse 48

- **Slide 50:** The heading reflects new unbriefed argument regarding the disclosures of McCloskey and what Petitioner has defined as “Dual

Tagging,” which is unsupported by the citation on the slide.

McCloskey: Teaches Dual Tagging

Our method utilizes an encoding oligonucleotide with five distinct informational regions (Fig. 1): (1) the batch-stamp, unique to each experiment, specifies the DNA source such as the patient or sample identification, and the date of reaction; (2) the random barcode distinguishes among sequences arising from different cell or allele copies; (3) the primer-binding site facilitates specific PCR amplification; (4) the genomic target-binding site targets the locus to be encoded prior to amplification; and (5) the extra 5' bases serve as an internal sentinel of recoding. This encoding

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’981 Petition at 30)

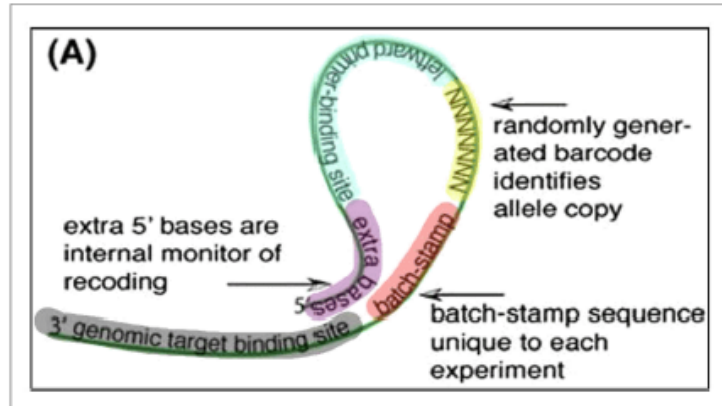
EX1004 (McCloskey et al.) at 2

Parse 50

- **Slide 51:** The heading reflects new unbriefed argument regarding the disclosures of McCloskey and what Petitioner has defined as “Dual

Tagging,” which is unsupported by the citation on the slide.

McCloskey: Teaches Dual Tagging



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(‘981 Petition at 31)

EX1004 (McCloskey et al.) at Fig. 1
Parse 51

- Slides 58-59, 71, 78-80, 95, 97, 99, 101, 103, 105, 107, 109, 147-150, 160:

These slides each include Dr. Cooper’s photo, which is not in the record.

Dr. Cooper: POSA Would Improve Linnarsson Using McCloskey’s Barcodes



Gregory Cooper
Parse’s Expert

188. Second, a POSA would have been motivated to combine Linnarsson’s method of tagging polynucleotides with McCloskey’s MID comprising two tag sequences because McCloskey teaches a solution to a problem discussed in Linnarsson, namely amplification bias. Linnarsson discloses that analyzing gene expression in single cells results in “potential amplification bias.” Linnarsson (Ex. 1003) at 2:3-15, 11:6-10; Linnarsson Provisional (Ex. 1015) at 2:6-21, 3:14-20. A POSA would have understood that avoiding amplification bias is particularly important in gene expression analysis in single cells. As explained above, single cell genomics rely on limited amounts of template DNA, thus amplification will be necessary and correcting for bias is particularly important. *Id.* Linnarsson attempts

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1002 (Cooper Decl.) ¶ 188
Parse 58

- **Slide 60:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Response On Motivation To Combine



John Quackenbush
10X's Expert

Q. Would a user of the Linnarsson process benefit from the advantages promoted by McCloskey of the barcodes that are disclosed in McCloskey of identifying redundant sequences?

A. So I'm not sure what you're asking me. I'm not sure that Dr. Cooper presented an analysis of advantages and so I haven't performed that analysis. I'm not prepared to offer an opinion today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 173:22-174:6
Parse 60

- **Slide 65:** The slide relies on new evidence, which is not found in the citations to a brief.

District Court's Construction: Not All Sequences Must Be Tagged

District Court's Claim Construction Opinion

Here, no ordinary person skilled in the art would interpret the language in Claim 13 to mean that "all polynucleotides in a cell" are being used, because the Claim is clearly referring to "sample polynucleotides." Rather, Plaintiffs' proposed construction using the term "of interest" would inject ambiguity and subjective intent to the claim, as described below. On the other hand, Defendant's proposed construction of adding "of said cell" correctly reflects the plain language of the '197 patent. See *Renishaw*, 158 F.3d at 1250 ("The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.")

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1066 (Opinion re CC) at 18
Parse 65

- **Slide 67:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Does Not Know If Claims Require Mammalian Cells



John Quackenbush
10X's Expert

Q. Do you understand that the '981 claims are limited to mammalian sources?

A. I haven't performed such an analysis. I don't believe Dr. Cooper offers any such opinions, and so it's beyond the scope of what I'm prepared to testify about today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 130:7-132:11
Parse 67

- **Slide 69:** The heading reflects new unbriefed argument mischaracterizing the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Linnarsson Could Be Applied To Yeast Cells



John Quackenbush
10X's Expert

Q. In terms of Linnarsson, is it your understanding that Linnarsson can only be used with mammalian sources?

A. So I don't believe Dr. Cooper offers any interpretation of Linnarsson saying that Linnarsson can only be used for mammalian sources. I don't believe I offered any opinions about the limitations of the application of Linnarsson beyond mammalian sources. However, Linnarsson's CDS, cDNA synthesis primer has an oligo(dT) component. And to the best of my recollection, all eukaryotic mRNAs are polyadenylated. So, for example, Linnarsson's application or Linnarsson's method could, sitting here today speculating, could be applied to analysis of single yeast cells or other eukaryotic cells.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 130:7-132:11
Parse 69

- **Slide 70:** The heading reflects new unbriefed argument mischaracterizing the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Linnarsson Can Be Applied To Yeast Cells



John Quackenbush
10X's Expert

Q. Would you have known in 2009 how to adapt the Linnarsson method to single yeast cells?

A. So I haven't fully done that analysis, but if yeast cells, if – and I believe they are; I believe the mRNA is polyadenylated. I could imagine using it for yeast cells. But, again, I haven't fully thought through all the implications, and so I haven't thought about what one would want to do in 2009, other than analyzing the methods presented here in Linnarsson in the context of Dr. Cooper's arguments.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 130:7-132:11
Parse 70

- **Slide 72:** The heading reflects new unbriefed argument regarding bacteria, which is unsupported by the citation on the slide, and relies on new

evidence, which is not found in the citations to a brief.

The Literature: Bacteria Use PolyA Tails

POLYADENYLATION OF mRNA IN PROKARYOTES

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KEY WORDS: poly(A) RNA, poly(A) polymerase, bacterial cDNA libraries, mRNA processing, mRNA degradation

ABSTRACT

The 3'-ends of both prokaryotic and eukaryotic mRNA are polyadenylated, but the poly(A) tracts of prokaryotic mRNA are generally shorter, ranging from 15 to 60 adenylate residues and associated with only 2–60% of the molecules of a given mRNA species. The sites of polyadenylation of bacterial mRNA are diverse and include the 3' untranslated and intergenic regions, and sites within the coding regions of mRNA degradation products. The diversity of polyadenylation sites suggests that mRNA polyadenylation in prokaryotes is a relatively indiscriminate process that can occur at all mRNA's 3'-ends and does not require specific consensus sequences as in eukaryotes. Two poly(A) polymerases have been identified in *Escherichia coli*. They are encoded by unlinked genes, neither of which is essential for growth, suggesting significant functional overlap. Polyadenylation promotes the degradation of a regulatory RNA that inhibits the replication of bacterial plasmids and may play a similar role in the degradation of mRNA. However, under certain conditions, poly(A) tracts may lead to mRNA stabilization. Their ability to bind S1 ribosomal protein suggests that poly(A) tracts may also play a role in mRNA translation.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX2104 (Sarkar) at 1
Parse 72

- **Slide 73:** The heading reflects new unbriefed argument regarding bacteria, which is unsupported by the citation on the slide, and relies on new evidence, which is not found in the citations to a brief.

The Literature: Bacteria Use PolyA Tails

RNA Polyadenylation in Prokaryotes and Organelles; Different Tails Tell Different Tales

Shimyn Slomovic, Victoria Portnoy, Varda Liveanu, and Gadi Schuster
Department of Biology, Technion—Israel Institute of Technology, Haifa 32000, Israel

I. INTRODUCTION

Polyadenylation is an important post-transcriptional modification of prokaryotic, eukaryotic and organellar RNA. Considerable progress has been made over the past 15 years in the study of the various polyadenylation processes and our understanding of their biological significance. In bacteria and organelles, the relationship of polyadenylation to RNA decay has been established, and the major proteins involved identified. In the nucleus and cytoplasm, the molecular mechanism of the addition of stable poly(A) tails to the 3' ends of most mRNAs and the importance of this process for translation initiation has been revealed. In addition, a quality control mechanism, including transient polyadenylation which targets the RNA for degradation by the exosome complex, has recently been described for the yeast nucleus (Lacava *et al.*, 2005; Vanacova *et al.*, 2005; Wyers *et al.*, 2005). This review seeks to provide a concise comparison of our current knowledge regarding the pathways of RNA polyadenylation and decay in several systems including bacteria, archaea, chloroplasts, mitochondria and the nucleus. Indeed, a major point of this review is the assumption that a basal mechanism of polyadenylation-dependent degradation of RNA was already present in the last universal common ancestor

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX2105 (Slomovic et al.) at 3
Parse 73

- **Slide 74:** The heading reflects new unbriefed argument regarding bacteria, which is unsupported by the citation on the slide, and includes Dr. Cooper's photo, which is not in the record.

Dr. Cooper: Bacteria Use Poly A Tails



Gregory Cooper
Parse's Expert

Q. Do you agree that only eukaryotic organisms ordinarily have mRNA with a poly-A tail?

A. I don't think that's true. I think there are evidence of polyadenylation in some prokaryotic organisms. I don't think it's used in quite the same way or has the same mes- -- same functionality. But I actually think there are examples of poly-A-tailed mRNAs in bacteria.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX2020 (Cooper Depo) at 64:16-65:1
Parse 74

- **Slide 75:** The heading reflects new unbriefed argument regarding bacteria, which is unsupported by the citation on the slide, and includes Dr. Cooper's

photo, which is not in the record.

Dr. Cooper: Bacteria Use Poly A Tails	
	Q. Would you agree that mRNA polyadenylation is absent in prokaryotic mRNAs except in transcripts bound for degradation?
	A. No, I'm not comfortable saying that one way or the other. Again, my understanding is that some bacteria have poly-A-tailed mRNAs at their ends.

	Q. So you didn't consider whether bacteria have a poly-A tail?
Gregory Cooper Parse's Expert	A. No. I believe there are some mRNAs in bacteria that have a poly-A tail.
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE	
EX2020 (Cooper Depo) at 65:8-14, 69:21-70:2	
Parse 75	

- **Slide 81:** The heading reflects new unbriefed argument regarding McCloskey, which is unsupported by any briefing by Petitioner, and relies

on new evidence, which is unsupported by any briefing by Petitioner.

PO's Position: McCloskey Is Just A "Less-Detailed" Version Of US20070020640

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(PO's Prelim Resp at 2)

PO's Prelim Resp at 2
Parse 81

- **Slide 85:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Does Not Know If Linnarsson Requires Fragmentation



John Quackenbush
10X's Expert

Q. Do you have an opinion one way or the other as to whether Linnarsson requires fragmentation for the creation of cDNA libraries using his tagging methods?

A. So I haven't done that analysis. If I look at Figure 11 and Examples 1 and 2, which are the examples presented, Linnarsson's method uses this fragmentation step using DNAs and this is consistent with his definition of the term "cDNA libraries" which appears on page 12.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 154:1-10
Parse 85

- **Slide 112:** The slide fails to include the context of Dr. Quackenbush's testimony by omitting the entirety of the question and answer, and includes

Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Ignored Figure 4



"So you are absolutely correct, I didn't cite to Figure 4."

John Quackenbush
10X's Expert

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 6)

EX1057 (Quackenbush Depo) at 170:17-18
Parse 112

- **Slide 117:** This slide reflects reliance on new evidence and argument regarding Linnarsson's disclosures, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's

Motion to Exclude.

Linnarsson Uses BtsCI

Figure 11, panels A-F, show graphical representation of steps optionally used in the STRT method. Panel A shows a reverse transcription step. A tailed oligo-dT primer directs synthesis of a cDNA strand. When the end of the template RNA is reached, reverse transcriptase adds 3-4 Cs at 3' of cDNA strand (due to its terminal transferase activity). Panel B shows a template switching step. Barcoded helper oligo anneals transiently, and cDNA synthesis proceeds using the oligo as template. As a consequence, the 3' end of the cDNA will carry barcode (XXXX), BtsCI recognition (Bts) and primer annealing (Pr) sequences. Panel C shows a single primer PCR step. The ends of the cDNA have identical sequences and are amplified using a single PCR primer, which helps suppress short amplicons. Panel D shows a fragmentation step. The amplified library is fragmented to 200 - 300 bp using controlled DNase digestion. Panel E shows an immobilization and end-repair step. Both 5' (with barcode (Br) and BtsCI site (Bts)) and 3' fragments are bound to beads, while internal fragments are washed away. Panel F shows fragment release and adapter ligation. 5' fragments are released by BtsCI digestion, leaving just the barcode (Bc) and insert (white area). 3' fragments remain stuck on the beads. Genome Analyzer paired-end compatible adapters (P1 and P2) are ligated. The library is sequenced from the P1 primer (and could optionally be sequenced also from P2). P1 reads begin with a 5 bp barcode, followed by 3-4 Gs, followed by the cDNA insert. P2 reads would yield only cDNA sequence.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 5)

EX1003 (WO2010/11762) at 5:28-6:12
Parse 117

- **Slide 118:** This slide reflects reliance on new evidence and argument regarding Linnarsson's disclosures, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's

Motion to Exclude.

Linnarsson Uses BtsCI

The fragments were released by BtsCI digestion, and simultaneously ligated to the FDV and RDV adapters. The beads were then resuspended in the reaction mix shown in Table 6.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Mtn to Exc at 6)

EX1003 (WO2010/11762) at 27:7-8
Parse 118

- **Slide 119:** This slide reflects reliance on new evidence and argument regarding Linnarsson's disclosures, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's

Motion to Exclude.

Linnarsson Uses BtsCI

5' fragments containing barcodes and cDNA inserts were released from the beads by BtsCI digestion, and adapters were simultaneously ligated to generate a sample suitable for sequencing on the Illumina Genome Analyzer. The beads were resuspended in 40 μ L of 1 mM ATP, 1 μ M SOLEXA-ADP1 adapter

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Mtn to Exc at 6)

EX1003 (WO2010/11762) at 35:28-31
Parse 119

- **Slide 120:** This slide reflects reliance on new evidence and argument regarding Linnarsson's disclosures, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Motion to Exclude, and includes Dr. Cooper's photo, which is not in the

record.

Dr. Cooper: BtsI Is Never Used In Linnarsson	
 Gregory Cooper Parse's Expert	Q. I'm asking whether it would surprise you to know that GCAGTG is a restriction enzyme cut site for BtsI?
	A. I'd have to do the details on that. It's – it could be a cut site for a different enzyme than that which is disclosed in Linnarsson.
	* * *
	Q. So if that's a restriction enzyme cut site for BtsI, it's in both Figures 3 and 4, correct?
	A. That stretch of nucleotide is there, yes. And, again, we're referring to an enzyme that Linnarsson doesn't elsewhere refer to.
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE (Paper 34 at 5)	
EX2020 (Cooper Depo) at 150:14-151:1 Parse 120	

- **Slide 121:** The heading reflects new unbriefed argument regarding the scope of Linnarsson's disclosures, which is unsupported by the citation on the slide, and relies on new evidence, including claim 1 of Linnarsson,

which is not found in the citations to the brief.

Linnarsson: Claims Are General

- No biotin
- No restriction enzyme
- No capture
- No fragmentation

1. A method of preparing a cDNA library from a plurality of single cells, the method comprising the steps of:

- (i) releasing mRNA from each single cell to provide a plurality of individual mRNA samples, wherein the mRNA in each individual mRNA sample is from a single cell;
- (ii) synthesizing a first strand of cDNA from the mRNA in each individual mRNA sample and incorporating a tag into the cDNA to provide a plurality of tagged cDNA samples, wherein the cDNA in each tagged cDNA sample is complementary to mRNA from a single cell;
- (iii) pooling the tagged cDNA samples; and
- (iv) amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner’s Resp to POR at 25)

EX1003 (WO2010/11762) at Claim 1
Parse 121

- **Slide 122:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Explanation For Claim 1



John Quackenbush
10X's Expert

Q. So did you review **claim 1** when you reviewed Linnarsson?

A. **I reviewed it**, but I didn't review it in great enough detail to answer your question, because Dr. Cooper didn't provide any opinions that I was required – that required a response.

Q. Okay. But **you can see in claim 1, there's no reference to fragmentation, correct; there's no fragmenting step?**

A. I haven't read all of claim 1, and I haven't read it in the context of the written description to fully understand what Linnarsson is claiming. And I don't believe Dr. Cooper offered any analysis and so **I'm not prepared to offer an opinion today as to what it encompasses.**

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 149:10-151:2
Parse 122

- **Slide 123:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: No Explanation For Claim 1



John Quackenbush
10X's Expert

Q. In Linnarsson, the cDNA library is generated according to the method of claim 1 without any fragmentation or use of biotin, correct?

A. So I don't believe Dr. Cooper provides an analysis of claim 1 in his report. I haven't included an analysis -- consequently, I have not included an analysis of each step of claim 1 or each step of the claimed invention in my report. And so I haven't performed a sufficient analysis to be able to tell you exactly what is encompassed in the scope of claim 1 as presented in Linnarsson.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 149:10-151:2
Parse 123

- **Slide 124:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Will Not Say Whether Claim 1 Requires Fragmentation



John Quackenbush
10X's Expert

Q. Okay. So you're saying you can't answer the question whether there's a fragmentation step in claim 1 of Linnarsson?

A. I haven't analyzed claim 1 to the extent where I would feel confident offering an informed opinion sitting here today.

Q. All right. And you understand that the claims of the Linnarsson patent are part of the disclosure of the patent application?

A. I believe that's correct, yes.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 149:10-151:2
Parse 124

- **Slide 125:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush Will Not Say Whether Claim 1 Uses Biotin



John
Quackenbush
10X's Expert

Q. And then in terms of – can you see that there's no attachment using biotin in Claim 1?

A. Again, I haven't done that analysis and I believe if Dr. Cooper felt it was important to single out claim 1, he would have done that in his declaration. And I didn't see anything in his declaration making that argument, and so I'm not in a position to render an opinion because I have nothing to respond to.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 149:10-151:2

Parse 125

- **Slide 127:** The slide mischaracterizes Dr. Quackenbush's testimony, and relies on new evidence and argument regarding claim 26, which is unsupported by the citation on the slide, and includes Dr. Quackenbush's

photo, which is not in the record.

Dr. Quackenbush: No Explanation For Claims 26-27



John Quackenbush
10X's Expert

Q. How does – what does claim 26 – excuse me, claim 27, which states – for Linnarsson claim 27 where it adds fragmenting the cDNA library. Do you see that?

A. Yes, I do.

Q. What does that add to the claim 1?

A. Dr. Cooper didn't present an analysis of the claims of Linnarsson in the context of representing invalidating prior art, and so I haven't done that analysis because I didn't have to do it to respond to Dr. Cooper.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2, 7)

EX1057 (Quackenbush Depo) at 164:15-165:9
Parse 127

- **Slide 128:** This slide reflects new Ground 1 argument, which is not supported by the citation on the slide.

Law: Bodily Incorporation Not Required For Obviousness

The “test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.”

In re Keller, 642 F.2d 413, 425 (C.C.P.A. 1981)

Parse 128

- **Slide 129:** This slide reflects new Ground 1 argument, which is not supported by the citation on the slide, and includes Dr. Cooper's photo, which is not in the record.

Dr. Cooper: A POSA Would Be Able To Modify Figure 11



Gregory Cooper
Parse's Expert

110. Even if a biotin molecule is deemed an essential aspect of the CDS, the claims would still be obvious. I understand that a person of ordinary skill is also a person of ordinary creativity, not an automaton. A skilled artisan seeking to introduce an additional tag to the CDS of Linnarsson by ligation would understand that the biotin would need to be added to the additional tag sequence rather than the CDS to ensure capture of the desired polynucleotide and allow ligation of the second tag. Such modifications would have been routine and obvious to a skilled artisan.

Dr. Quackenbush acknowledges in his testimony that a POSA would have known that the biotin would block ligation:

Q. And would a person of ordinary skill in the art in 2009 know that you couldn't ligate a barcode to the biotin on the five prime end of the CDS?

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 23)

EX1059 (Cooper Decl.) ¶¶ 109-12
Parse 129

- **Slide 130:** This slide reflects new Ground 1 arguments, which is not supported by the citation on the slide, and includes Dr. Cooper's photo,

which is not in the record.

Dr. Cooper: A POSA Would Be Able To Modify Figure 11	
	111. Given that a POSA would have known about the effects of biotinylation, it is my opinion that a POSA would have known how to work around it. Specifically, a POSA would have used routine and well-known methods that do not require biotinylation and/or associate the biotin with the second tag to ensure capture of the desired polynucleotide. Dr. Quackenbush's assertions to the contrary require that POSAs lack even basic skill in the art.
Gregory Cooper Parse's Expert	
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE (Petitioner's Resp to POR at 23)	EX1059 (Cooper Decl.) ¶¶ 109-112 Parse 130

- **Slide 139:** The slide fails to include the context of Dr. Quackenbush's testimony by omitting the entirety of the question and answer, and includes

Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Ligation Was Known And Conventional



"I told you earlier ligation was a conventional technique."

John Quackenbush
10X's Expert

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 19)

EX1057 (Quackenbush Depo) at 188:17-18
Parse 139

- **Slide 140:** The slide fails to include the context of Dr. Quackenbush's testimony by omitting the entirety of the question and answer, and includes

Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Ligation Was Known And Conventional



John Quackenbush
10X's Expert

"So I'm not contesting that ligation was a well-known method of attaching oligonucleotides."

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 19)

EX1057 (Quackenbush Depo) at 187:23-25
Parse 140

- **Slide 143:** The slide fails to include the context of Dr. Quackenbush's testimony by omitting the entirety of the question and answer, and includes Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Ligation Was Known And Conventional



John Quackenbush
10X's Expert

"So ligation is used. Ligation is a method that was known in the art just like PCR was known in the art. But it's a way of carrying out claim 1."

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 18)

EX1057 (Quackenbush Depo) at 186:6-9
Parse 143

- **Slide 161:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr. Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Fails To Justify PO's Incompatibility Theory



John Quackenbush
10X's Expert

Q. Do you have an opinion whether or not a person skilled in the art would be able to do that? And by "that," I mean ligate a tag to the CDS before placing biotin on the five prime end?

A. So biotin isn't placed on the five prime end. Biotin is incorporated into the five prime end in the PCR step between Step B and Step C in Figure 11. Dr. Cooper doesn't offer any alternative which would allow such ligation. And so while I can speculate about different ways in which it could possibly be carried out, I wouldn't know all the ramifications unless I thought about that more deeply, and so I'm not prepared to speculate today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 175:7-176:21
Parse 161

- **Slide 162:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Fails To Justify PO's Incompatibility Theory



John Quackenbush
10X's Expert

Q. We'll address that case as well. But right now I'm just asking you, would a person of skill in the art know how to adjust the process of Linnarsson, such that the tag could be ligated to the CDS before biotin is introduced to the molecule at the five prime end? Just whether it's within the scope of the skilled level in the art, whether you have an opinion on that.

A. So it's a complex question that doesn't have a "yes" or "no" answer. Dr. Cooper doesn't provide an explanation for how that would be done. While one could speculate about different ways that it could be done, potentially be done, one would have to think about whether or not it would actually be compatible with the rest of what's disclosed in Linnarsson or actually prevent Linnarsson from carrying out the method that's proposed here. So I haven't done that analysis because Dr. Cooper hasn't presented a scenario in which it would have.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 177:10-179:16

Parse 162

- **Slide 163:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Fails To Justify PO's Incompatibility Theory



John Quackenbush
10X's Expert

Q. Leaving aside how it would be done, do you have an opinion, sitting here now, as to whether it would be within the scope of the competency of a skilled artisan in 2009 to modify the Linnarsson process so that the tag is ligated before biotin is added?

A. You're asking a question which doesn't have a simple answer and I wish I could give you a simple answer, right. You're saying biotin is added. It's not physically added to a double-stranded molecule. It's a part of the synthesis of the double-stranded molecule the way Linnarsson describes it. So that's the first place where I'm having a trouble giving a simple "yes" or "no" answer.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 177:10-179:16
Parse 163

- **Slide 164:** The heading reflects new unbriefed argument regarding the opinions Dr. Quackenbush provided, which is unsupported by the citation on the slide (cited only in unexplained string cite), and includes Dr.

Quackenbush's photo, which is not in the record.

Dr. Quackenbush: Fails To Justify PO's Incompatibility Theory



John Quackenbush
10X's Expert

Q. Would a person of skill in the art have the competency to do it? Do you have an opinion on that?

A. It would depend on a lot of factors, and I'm happy to reiterate those as I did previously. I haven't done an analysis to understand whether or not it would actually completely disrupt the process in Linnarsson such that it would not carry out its stated goals.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2)

EX1057 (Quackenbush Depo) at 180:19-181:5
Parse 164

- **Slide 166:** This slide reflects reliance on new evidence regarding McCloskey's status as prior art based on "Received" and "Accepted" date,

which is unsupported by the citation on the slide.

McCloskey: Published In 2007

Molecular Genes (2007) 267:301–307
DOI 10.1007/s00438-007-0200-0

Encoding PCR Products with Batch-stamps and Barcodes

Megan L. McCloskey · Reinhard Stöger ·
R. Scott Hansen · Charles D. Laird

Received: 11 January 2007 / Accepted: 29 May 2007 / Published online: 23 October 2007
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Abstract Polymerase chain reaction (PCR) has become the backbone of DNA sequence analysis. Yet there is always uncertainty concerning the source of the template DNA that goes into a particular PCR product. The risks of cross-contamination, mislabeling, and product redundancy are especially high when limited amounts of template DNA are used. We have developed and applied molecular encoding principles to create this source-uncertainty problem for DNA sequences generated by standard PCR. Batch-stamps encode the date and sample identity, and barcodes detect template redundancy. Our approach thus enables identification of each PCR-derived sequence as valid, contaminated, or redundant, and provides a measure of sequence diversity. We recommend that batch stamps and barcodes be used when amplifying template DNA and cDNA available for forensic, clinical, single cell, and ancient DNA analyses.

Keywords PCR · Contamination · Redundancy · Batch-stamp · Barcode · Source DNA · Population of molecules

Introduction

One essential condition of DNA-based technologies is that sequence information be reliable (Lewontin 1982). Sequence information obtained by PCR, however, always

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Encoding PCR Products with Batch-stamps and Barcodes

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R. Scott Hansen · Charles D. Laird

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DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 3)

Parse 166

- **Slide 167:** This slide reflects reliance on new evidence, including the photo of Ms. Hall-Ellis, which is not in the record.

Dr. Hall-Ellis: McCloskey is Prior Art



Sylvia Hall-Ellis
Petitioner's Expert

A. McCloskey Is Prior Art

Patent Owner claims that Petitioner did not show that McCloskey is prior art. POR at 18. The Petition, however, states that McCloskey was published online in October 2007 and is hence prior art under § 102(a) and (b). Petition at 29. Patent Owner never disputes this publication date, which appears on the face of McCloskey. EX1004.001. Nonetheless, supplied here is an authenticating declaration from Sylvia Hall-Ellis, further confirming McCloskey's prior art status.² See EX1065 ¶¶ 44-45, 50. This 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).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 3)

Petitioner's Resp to PO's Resp at 3
Parse 167

- **Slide 168:** This slide reflects reliance on new evidence regarding McCloskey's prior art status that was not discussed in the briefing, including the photo of Ms. Hall-Ellis, which is not in the record.

Dr. Hall-Ellis: McCloskey is Prior Art



Sylvia Hall-Ellis
Petitioner's Expert

45. Based on finding a print copy of Exhibit A in the Linda Hall Library of Science, Engineering & Technology and MARC record in its online library catalog attached as Attachment 1A, it is my opinion that the McCloskey article published in the journal *Biochemical Genetics* was publicly available on or shortly after January 3, 2008, as shown on the cover. Attachment 1A also shows that Exhibit A was catalogued with a descriptor term reading "Biochemical genetics \$v Periodicals" (see Attachment 1B, Library of Congress subject heading sh85014121 and Attachment 1C, Library of Congress subject heading sh85099890) in the 650 field.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 3)

EX1065 (Hall-Ellis Decl) ¶ 45
Parse 168

- **Slide 170:** This slide reflects reliance on new argument regarding McCloskey's status as prior art, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Opposition

to Patent Owner's Motion to Exclude.

Law: Evidence To Confirm Publication Date May Be Submitted On Reply

"The Board denied VidStream's Motion to Exclude, holding that it was appropriate to permit Twitter to respond to VidStream's challenge by providing additional evidence to establish the Bradford publication date. We conclude that the Board acted appropriately...."

Vidstream v. Twitter, 981 F.3d 1060, 1065-67 (Fed. Cir. 2020)

Parse 170

- **Slide 171:** This slide reflects reliance on new argument regarding McCloskey's status as prior art, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Opposition

to Patent Owner's Motion to Exclude.

Law: Evidence To Confirm Publication Date May Be Submitted On Reply

The Board does "not agree with Patent Owner that Petitioner's new evidence, submitted in the Reply, was improper as untimely" to support a showing that a reference is a printed publication because "it was filed in response to arguments raised in Patent Owner's Response" and "did not amount to, or result in, a change in Petitioner's theory in the case."

Cooler Masters Co., Ltd. v. Aavid Thermalloy LLC, IPR2019-00146, Pap.55, 22-23 (June 4, 2020)

Parse 171

- **Slide 172:** This slide reflects reliance on new argument regarding McCloskey's status as prior art, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Opposition

to Patent Owner's Motion to Exclude.

Law: Evidence To Confirm Publication Date May Be Submitted On Reply

"Patent Owner argues that Petitioner was required to submit any evidence of the printed-publication status of its asserted references with the Petition rather than with the Reply. That argument is unpersuasive in view of the decision in *Hulu, LLC v. Sound View Innovations, LLC*."

Grunenthal GMBH v. Antecip Bioventures II LLC, PGR2019-00026, Pap.24, 19 (July 28, 2020)

Parse 172

- **Slide 173:** This slide reflects reliance on new evidence regarding McCloskey's status as prior art based on "Received" and "Accepted" date ,

which is unsupported by the citation on the slide.

McCloskey: Published In 2007

Received: 31 January 2007 / Accepted: 29 May 2007 / Published online: 23 October 2007
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Encoding PCR Products with Batch-stamps and Barcodes

Megan L. McCloskey • Reinhard Stöger •
R. Scott Hansen • Charles D. Laird

Abstract Polymerase chain reaction (PCR) has become the standard of DNA sequence analysis. Yet there is always uncertainty concerning the source of the template DNA that gave rise to a particular PCR product. The risks of contamination, mislabel, misinterpretation, and product misanalysis are especially high when limited amounts of template DNA are used. We have developed and applied molecular encoding principles to solve this source uncertainty problem for DNA sequences generated by standard PCR. Batch-stamps specify the date and sample identity, and barcodes detect sample redundancy. Our approach thus enables identification of each PCR-derived sequence as valid, contaminated, or redundant, and provides a measure of sequence identity. We recommend that batch stamps and barcodes be used when amplifying template DNA and cDNAs available for forensic, clinical, single cell, and ancient DNA analyses.

Keywords PCR • Contamination • Redundancy • Batch-stamp • Barcode • Source DNA • Population of molecules

Introduction

One essential condition of DNA-based technologies is that sequence information be reliable (Levinthal 1994). Sequence information obtained by PCR, however, carries

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PARSE EX.1004.001

Encoding PCR Products with Batch-stamps and Barcodes

Megan L. McCloskey • Reinhard Stöger •
R. Scott Hansen • Charles D. Laird

Received: 31 January 2007 / Accepted: 29 May 2007 / Published online: 23 October 2007
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DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 3)

Parse 173

- **Slide 174:** This slide reflects reliance on new argument regarding McCloskey's status as prior art, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Opposition

to Patent Owner's Motion to Exclude.

Law: Totality Of Indicia Considered For Publication Date

"Especially when dealing with documents from recognized sources, such as these, and following the lead of the Federal Circuit" the Board considers "external indicia of publication as proof" on the issues of publication date and accessibility.

Trend Micro Inc. v. Cupp Computing AS, IPR2019-00803, Pap.29, 9 (Sept. 15, 2020)

Parse 174

- **Slide 175:** This slide reflects reliance on new argument regarding McCloskey's status as prior art, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Opposition

to Patent Owner's Motion to Exclude.

McCloskey: Indicia Confirming Publication	
▪ Date publication was received ▪ Date publication was accepted for publication ▪ Date of online publishing ▪ Copyright date ▪ Peer-reviewed journal ▪ Edition identifier ▪ Citations in the literature ▪ Reputable publisher ▪ Conventional attributes of peer-reviewed publication	
	Parse 175

- **Slide 176:** This slide reflects reliance on new argument regarding McCloskey's status as prior art, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Opposition

to Patent Owner's Motion to Exclude.

Law: Conventional Indicia Are Sufficient

A date appearing on a reference is sufficient “when dealing with documents from recognized sources” with conventional markers.”

Trend Micro Inc. v. Cupp Computing AS, IPR2019-00803, Pap.29, 9 (Sept. 15, 2020)

Parse 176

- **Slide 177:** This slide reflects reliance on new argument regarding McCloskey's status as prior art, which is unsupported by citations to merits briefing and is included only in briefing in support of Petitioner's Opposition

to Patent Owner's Motion to Exclude.

Law: Conventional Indicia Are Sufficient

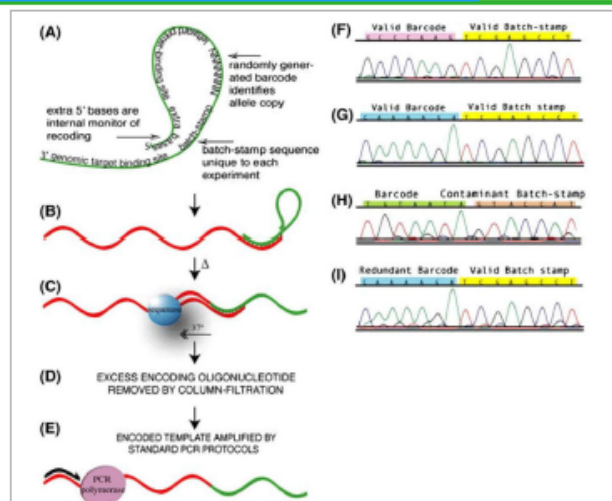
"Twitter responds that the Board correctly found that the collective evidence, including: the Copyright Office evidence of Bradford's 2011 copyright registration, the 2011 copyright date in every copy of Bradford, the presence of an established publisher, the listing for sale on Amazon web pages in 2011, and the book's existence in the MARC records dated August 25, 2011, all uniformly support publication and public accessibility before the '997 patent's priority date of May 9, 2012."

Vidstream v. Twitter, 981 F.3d 1060, 1066 (Fed. Cir. 2020)

Parse 177

- **Slide 184:** The heading reflects new unbriefed argument regarding the disclosures of McCloskey and what Petitioner has defined as "Dual Tagging," which is unsupported by the citation on the slide.

McCloskey: Directed To Dual Tagging



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(‘981 Petition at 31)

EX1004 (McCloskey et al.) at 2, Fig. 1

Parse 184

Respectfully submitted,

Dated: July 23, 2024

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S SUBMISSION OF UNRESOLVED OBJECTIONS TO PETITIONER'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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