Petitioner's Oral Argument Presentation

Parse Biosciences Inc. v. 10X Genomics Inc.
IPR2023-00876

July 24, 2024

’981 Patent: Claim 1

1. A method of analyzing nucleic acids from a plurality of single cells, the method comprising:

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

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

(i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and

(ii) a multiplex identifier (MID) sequence comprising:

I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and

II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;

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

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

(e) using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’981 Petition at 6)

EX1001 (’981 Patent) at Claim 1

Parse 2

’981 Patent: Claim 1

1. A method of analyzing nucleic acids from a plurality of single cells, the method comprising:

(ii) a multiplex identifier (MID) sequence comprising:

I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and

II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;

nucleotide from which the identified polynucleotide sequence is derived.

EX1001 (’981 Patent) at Claim 1

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

Specification: Alleged Invention Is "Reflex Method"

> The invention is drawn to compositions and methods for intramolecular nucleic acid rearrangement that find use in various applications of genetic analysis, including sequencing, as well as general molecular biological manipulations of polynucleotide structures.

EX1001 ('981 Patent) at 12:52-56

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

Specification: Alleged Invention Is "Reflex Method"

SUMMARY OF THE INVENTION

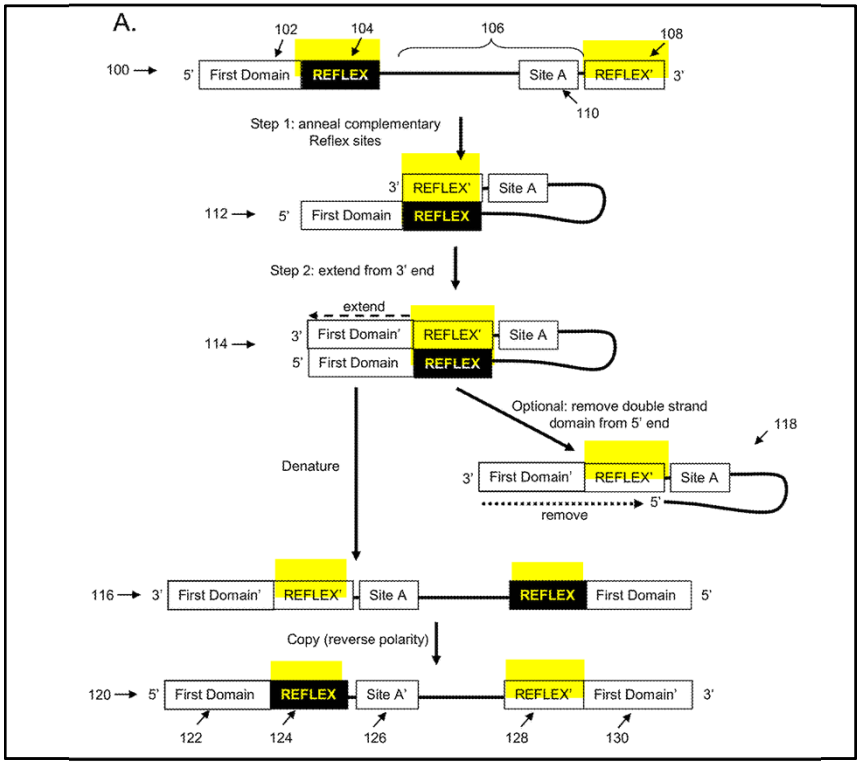
Aspects of the present invention are drawn to processes for moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide, also referred to as a "reflex method" (or reflex process, reflex sequence process, reflex reaction, and the like). In certain embodiments, the reflex method results in moving a region of interest into functional proximity to specific domain elements present in the polynucleotide (e.g., primer sites and/or MID). Compositions, kits and systems that find use in carrying out the reflex processes described herein are also provided.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 1)

EX1001 ('981 Patent) at 1:49-61

Parse 5

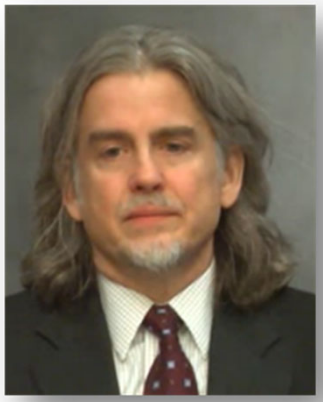
“Reflex” Method: Mentioned Over 250 Times



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

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

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.

Specification: Tagging Is Not The Invention

We have previously described methods that enable tagging each of a population of fragmented genomes and then combining them together to create a 'population library' that can be processed and eventually sequenced as a mixture.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 2)

EX1001 ('981 Patent) at 1:26-29

Parse 8

Specification: Tagging Is Prior Art

nucleic acid sequence of the MID. Any type of MID can be used, including but not limited to those described in co-pending U.S. patent application Ser. No. 11/656,746, filed on Jan. 22, 2007, and titled "Nucleic Acid Analysis Using Sequence Tokens", as well as U.S. Pat. No. 7,393,665, issued on Jul. 1, 2008, and titled "Methods and Compositions for Tagging and Identifying Polynucleotides", both of which are incorporated herein by reference in their entirety for their description of nucleic acid tags and their use in identifying polynucleotides. In certain embodiments, a set of

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 15)

EX1001 ('981 Patent) 15:20-29

Specification: Tagging Is Prior Art

and/or order of subunits. Exemplary nucleic acid tags that find use as MIDs are described in U.S. Pat. No. 7,544,473, issued on Jun. 6, 2009, and titled "Nucleic Acid Analysis Using Sequence Tokens", as well as U.S. Pat. No. 7,393,665, issued on Jul. 1, 2008, and titled "Methods and Compositions for Tagging and Identifying Polynucleotides", both of which are incorporated herein by reference in their entirety for their description of nucleic acid tags and their use in identifying polynucleotides. In certain embodiments, a set of

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

PO's Position: Tagging Is "Conventional"

10x's Brief From Becton-Dickinson Case

Because the asserted claims of the Fodor patents are directed to an abstract idea under step 1, they can satisfy § 101 only if they can survive *Mayo* step 2 by reciting sufficient additional inventive elements such that the invention is "significantly more" than the ineligible abstract idea. *Alice*, 134 S. Ct. at 2357. They cannot, because they do not recite ***any*** additional inventive elements. Instead, the claims recite only the abstract labeling idea together with generic, routine, well-known laboratory techniques for working with DNA and other nucleic acid molecules (like attaching, hybridizing, amplifying, detecting, and sequencing). The specification repeatedly admits that these techniques were known and conventional before the Fodor patents.

EX1016 (BD v. 10X MTD) at 17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 2)

PO's Position: Tagging Is "As Old As The Scientific Method"

10x's Brief From Becton-Dickinson Case

with different labels. This concept is as old as the scientific method and is familiar to every student in any introductory science class—when performing an experiment, one needs a control and an experiment and will label them accordingly (whether that means written labels of "control" and "experiment" or "test 1" and "test 2" or "sample A" and "sample B" or some other form of labeling such as placing one in a green cup and one in a blue cup). Even outside of the context of scientific experiments, using different labels to differentiate and distinguish between different instances of similar objects is commonplace. For example, different instances of the same model of a television

PO's Position: Tagging Is "Long-Practiced"

10x's Brief From Becton-Dickinson Case

The claims of the Fodor patents similarly fail under step 1 because they are directed to the long-practiced idea of labeling different objects with different labels applied in the particular technological environment of DNA (and other nucleic acid molecules). Merely applying this "old solution" of different labels in the particular technological environment of DNA is insufficient to produce patent-eligible claims. *Alice*, 134 S. Ct. at 2358 ("the prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of [the idea] to a particular technological environment"); *Intellectual Ventures I LLC v. Erie Indem. Co.*, 850 F.3d 1315, 1330

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 2)

EX1016 (BD v. 10X MTD) at 16

Parse 14

PO's Position: Attaching, Amplifying, Detection Were "Well-Known" And "Conventional"

10x's Brief From Becton-Dickinson Case

Standard Book Numbers (ISBNs) (by the Library of Congress). The Fodor patents did not invent this idea—they simply take this abstract idea and attempt to limit the use of the idea to the particular technological environment of DNA (and other nucleic acids) by adding "attaching", "amplifying", and "detecting" steps and other similarly generic techniques that were well-known and conventional before 2009 (the earliest provisional application). The claim language and intrinsic record confirm this. BD's conclusory attorney argument to the contrary in its Complaint is legally insufficient to defeat 10X's Motion and is also contrary to the specification itself.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 16)

EX1016 (BD v. 10X MTD) at 10

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

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

19. The system of claim **13**, wherein the common sequence for the plurality of oligonucleotides attached to a given bead is different from that for the pluralities of oligonucleotides attached to other beads in the plurality of beads.

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

EX1053 ('659 Patent) at Claim 19

PO's Position: Becton-Dickinson Claims Not "Inventive"

10x's Brief From Becton-Dickinson Case

Because the asserted claims of the Fodor patents are directed to an abstract idea under step 1, they can satisfy § 101 only if they can survive *Mayo* step 2 by reciting sufficient additional inventive elements such that the invention is "significantly more" than the ineligible abstract idea. *Alice*, 134 S. Ct. at 2357. They cannot, because they do not recite ***any*** additional inventive elements. Instead, the claims recite only the abstract labeling idea together with generic, routine, well-known laboratory techniques for working with DNA and other nucleic acid molecules (like attaching, hybridizing, amplifying, detecting, and sequencing). The specification repeatedly admits that these techniques were known and conventional before the Fodor patents.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 2)

EX1016 (BD v. 10X MTD) at 17

PO's Position: Two Tags Was Conventional

10x's Brief From Becton-Dickinson Case

358 patent Claim 6	Summary
6. A method comprising:	Preamble
(a) combining a mixture comprising at least two distinct target nucleic acid molecules with a pool of nucleic acid label-tags, wherein the pool of nucleic acid label-tags comprises a plurality of nucleic acid label-tags with different sequences;	Different molecules ("two distinct target nucleic acid molecules") and Different labels ("a pool of nucleic acid label-tags")
(b) attaching at least two nucleic acid label-tags from the pool of nucleic acid label-tags to the at least two distinct target nucleic acid molecules to obtain at least two label-tag-target nucleic acid molecules, wherein the distinct target nucleic acid molecules have different sequences from one another;	Generic, conventional attaching techniques
(c) amplifying at least a portion of the label-tag-target nucleic acid molecules, wherein an amplified portion of the label-tag-target nucleic acid molecules comprises at least a portion of said target nucleic acid molecule; and	Generic, conventional amplifying techniques
(d) detecting an amplified product of step (c).	Generic, conventional detecting techniques

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 14)

EX1016 (BD v. 10X MTD) at 11

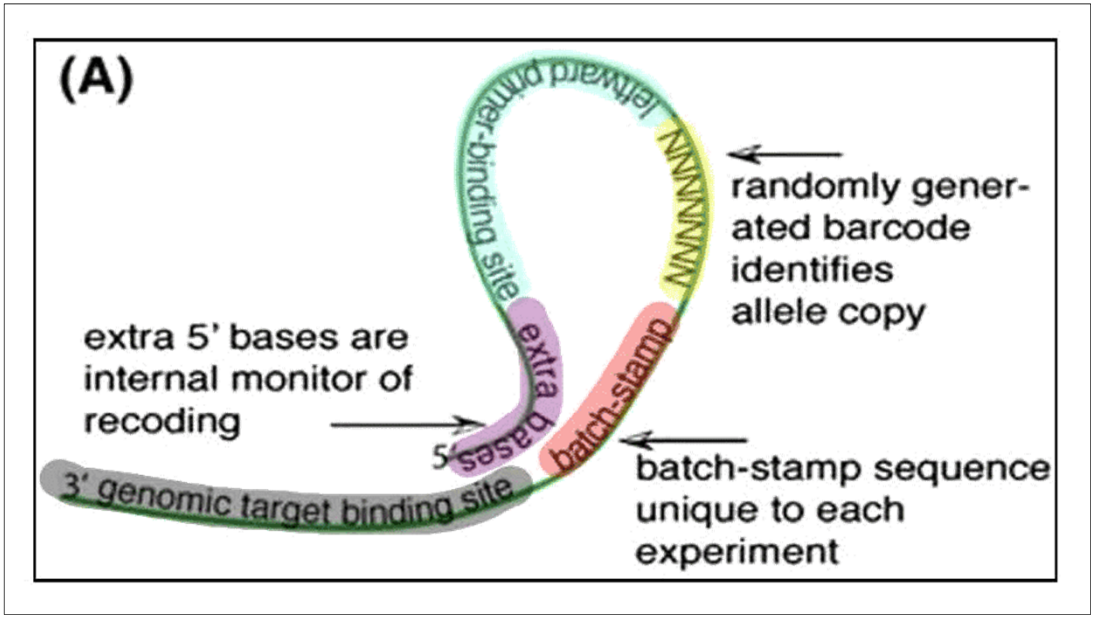
File History: Linnarsson Teaches Everything But Dual Tag

The following is an examiner's statement of reasons for allowance:

The 35 USC 102 rejection is hereby withdrawn. The closest prior art, Linnarsson (WO 2010/117620), does not teach or suggest generating a plurality of tagged polynucleotides comprising an identifier sequence of instant claim 1(ii). The claimed identifier sequence comprises a first tag sequence, which distinguishes each single cell in a sample of a plurality of cells, and a second tag sequence, which distinguishes a sample polynucleotide from other sample polynucleotides derived from a single cell, which is not taught by Linnarsson.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 18)

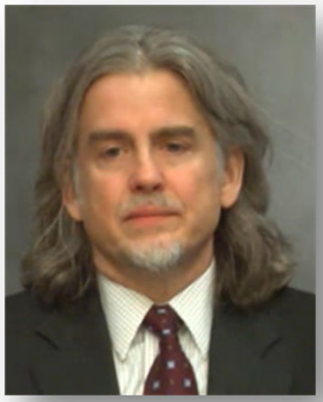
McCloskey: Teaches Dual Tagging



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

EX1004 (McCloskey et al.) at Fig. 1

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?

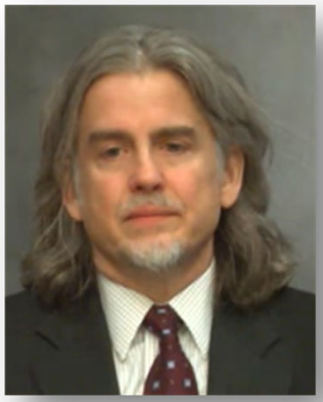
A. So to the best of my recollection, I didn't offer any opinions on objective indicia. I don't believe Dr. Cooper provided any arguments regarding that.

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

EX1057 (Quackenbush Depo) at 15:10-25

Parse 22

Dr. Quackenbush: No Objective Indicia Evidence

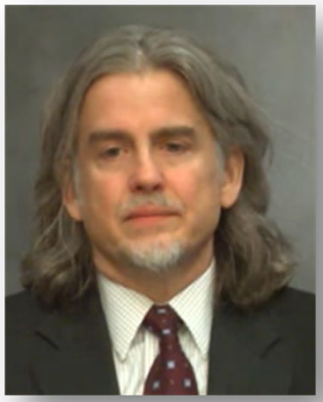


John Quackenbush
10X's Expert

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.

Dr. Quackenbush: No Objective Indicia Evidence

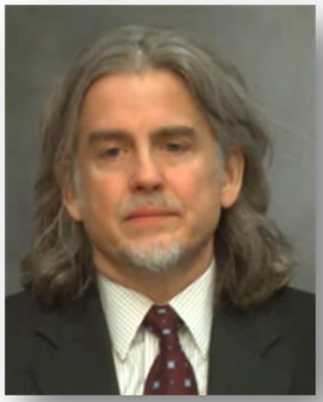


John Quackenbush
10X's Expert

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.

Dr. Quackenbush: No Opinion On Commercial Success



John Quackenbush
10X's Expert

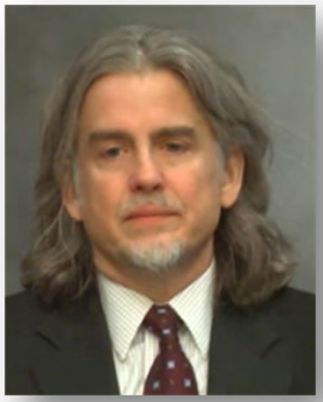
Q. Are the claimed inventions of the '981 patent commercially successful?

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

Dr. Quackenbush: No Opinion On Unexpected Results



John Quackenbush
10X's Expert

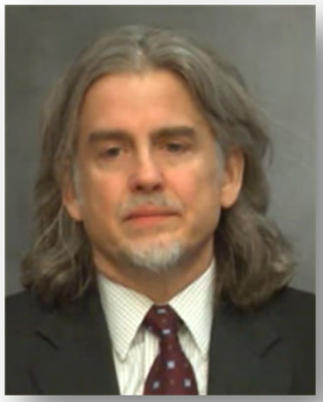
Q. Do the claimed inventions of the patents-in-suit – can you identify any unexpected results offered by the claimed inventions of the patent – – of the '981 patent?

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

Dr. Quackenbush: No Opinion On Copying



John Quackenbush
10X's Expert

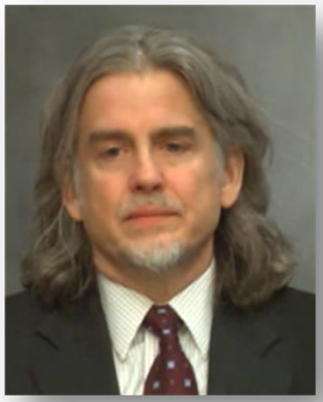
Q. Are you aware of any – can you identify any copying of the claimed inventions of the patents-in-suit?

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

Dr. Quackenbush: No Opinion On Praise



John Quackenbush
10X's Expert

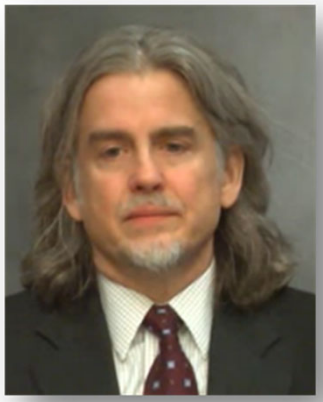
Q. Can you identify any praise by those in the field for the claimed inventions?

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

Dr. Quackenbush: No Opinion On Long-Felt Need

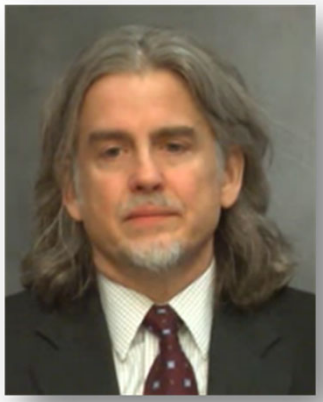


John Quackenbush
10X's Expert

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.

Dr. Quackenbush: No Opinion On Teaching Away



John Quackenbush
10X's Expert

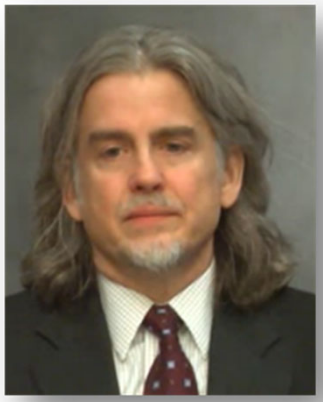
Q. Do you have an opinion here one way or the other whether there is teaching away as an objective indicia of nonobviousness?

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

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



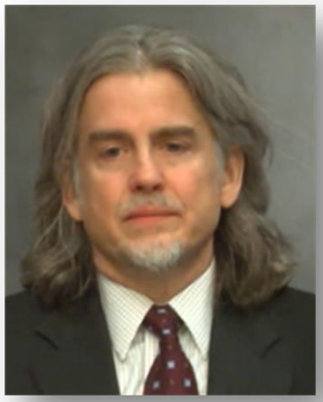
John Quackenbush
10X’s Expert

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

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

EX1057 (Quackenbush Depo) at 190:3-4

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.

Topics For Argument

Ground 1

- Construction of “sequencing the tagged polynucleotides”
- Linnarsson and McCloskey combination
  - Patent Owner’s numerosity of tags argument fails
  - Patent Owner’s fragmentation and capture argument fails

Ground 2: Ligation

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Topics For Argument

Ground 1

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Ground 2: Ligation

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DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

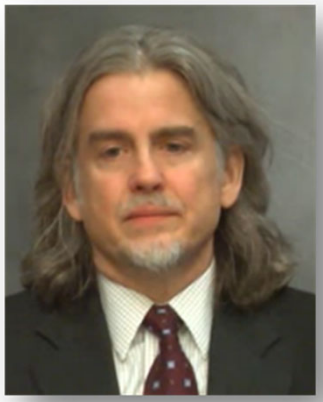
PO's IPR Position: Claims Require Sequencing "Entirety" Of Tagged Polynucleotides

PO's Response

> Moreover, Petitioner's own citations fail to show Linnarsson discloses sequencing the entirety of the "tagged polynucleotide." Pet.57 (citing EX1003, 4:8-13, 19:28-32, 21:13-25). Petitioner's first citation is to a description of Linnarsson's Figure 1, which is an "overview of a method" that simply says "sequencing is performed," but does not provide details or specify what is sequenced. EX1003, 4:8-13; EX2013, ¶58. Petitioner's second citation explains

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

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

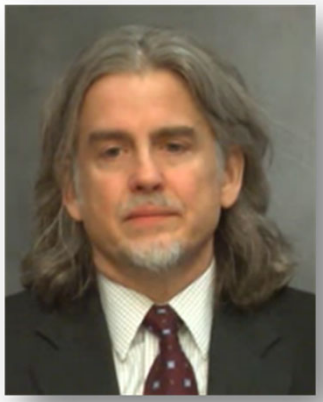
Specification: Negates PO's Interpretation

For example, we might want to sequence one thousand viral genomes (or a specific genomic region) or one thousand copies of a gene present in somatic cells. After tagging each polynucleotide in the sample with a sequencing primer site, MID and reflex sequence (as shown in the figures and described above), we use the reflex process to break each polynucleotide into lengths appropriate to the sequencing procedure being used, transferring the sequencing primer site and MID to each fragment (as described above). Obtain-

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 4)

EX1001 ('981 Patent) at 23:3-8

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



John Quackenbush
10X's Expert

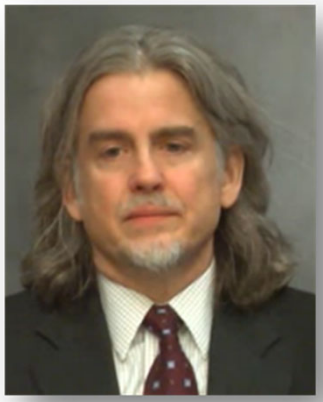
Q. Answering as directly as you can, is the sequence in the tagged polynucleotide in Step 1D, does that have to be the entire sequence of the sample polynucleotide from 1B?

A. So I'm not sure about the context of your use of the word "sequence." I haven't performed that analysis, and I'm not prepared to offer an opinion today.

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

EX1057 (Quackenbush Depo) at 78:15-24

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



John Quackenbush
10X's Expert

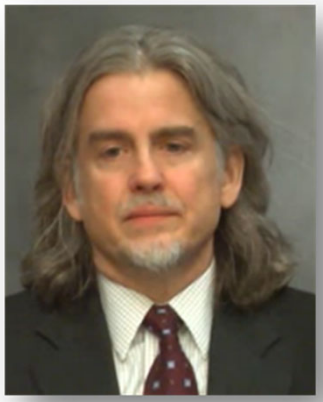
Q. [D]o you have an opinion one way or the other whether that has to be the entire sequence of the sample polynucleotide from Step 1B? If you're using PCR?

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

Dr. Quackenbush: No Analysis Of Claim Scope



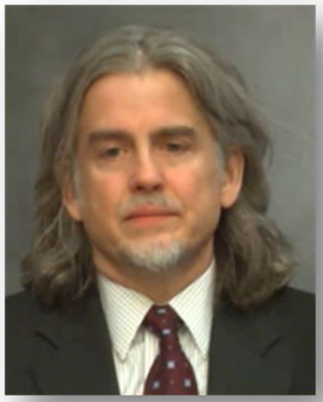
John Quackenbush
10X's Expert

"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

Dr. Quackenbush: No Analysis Of Claim Scope

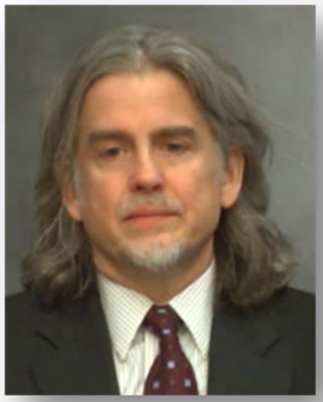


John Quackenbush
10X's Expert

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.

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



John Quackenbush
10X’s Expert

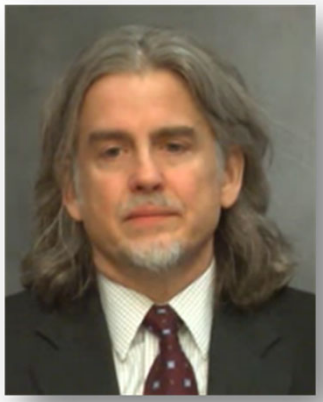
Q. When the tag nucleotides are being generated in Step 1C, can that be done using PCR?

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

Dr. Quackenbush's New District Court Opinion: Claims Do Not Require Sequencing Entire Tagged Polynucleotides



John Quackenbush
10X's Expert

Dr. Quackenbush's District Court Report

161. To the extent Parse argues it does not infringe because it sequences fragments of the tagged polynucleotides, this is incorrect. The claims do not require sequencing the entirety of the tagged polynucleotides.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Paper 36 at 1)

EX1067 (Quackenbush D. Ct Report) ¶ 161

PO's Allegation: Petitioner Relied On Sequencing "Entire" Polynucleotide

PO's Sur-Reply

The Petition argued Linnarsson disclosed "sequencing" based on its sequencing of the "tagged polynucleotide," which Petitioner equated to ***the full-length cDNA molecules generated by reverse transcription***. Pet.44, 56-57. Far from "constru[ing]" the claims to require "sequencing the ***entirety*** of the 'tagged polynucleotide[s]'" (*cf.* Rep.3), the POR responded to ***Petitioner's affirmative mapping of sequencing the entire polynucleotide***:[4] "Linnarsson teaches that after generating ***the tagged polynucleotides***, ***'sequencing is performed' thereon***." *Compare* Pet.57 *with* POR.22-23. Petitioner's Reply now asserts Linnarsson discloses sequencing the entire "tagged polynucleotide" based on an improper new argument that Linnarssons's fragmentation approach is *optional*. Rep.5. Petitioner's new reply theory should be rejected. *Juniper*, IPR2021-01445, Pap.62, 28-29; *Wasica*, 853 F.3d at 1286; *Intelligent Bio-Sys.*, 821 F.3d at 1370. Even if considered, it fails.

PO Sur-reply at 8-9

Parse 44

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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.

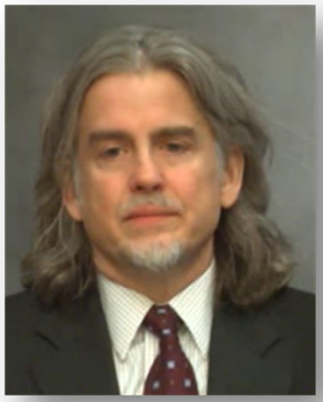
PO's IPR Position: Cited Evidence Does Not "Provide Details" Or "Specify What Is Sequenced"

PO's Response

> Moreover, Petitioner's own citations fail to show Linnarsson discloses sequencing the entirety of the "tagged polynucleotide." Pet.57 (citing EX1003, 4:8-13, 19:28-32, 21:13-25). Petitioner's first citation is to a description of Linnarsson's Figure 1, which is an "overview of a method" that simply says "sequencing is performed," but does not provide details or specify what is sequenced. EX1003, 4:8-13; EX2013, ¶58. Petitioner's second citation explains

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

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

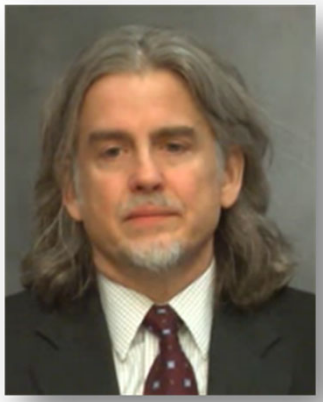


John Quackenbush
10X's Expert

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.

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

Topics For Argument

Ground 1

- Construction of “sequencing the tagged polynucleotides”
- Linnarsson and McCloskey combination
  - Patent Owner’s numerosity of tags argument fails
  - Patent Owner’s fragmentation and capture argument fails

Ground 2: Ligation

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

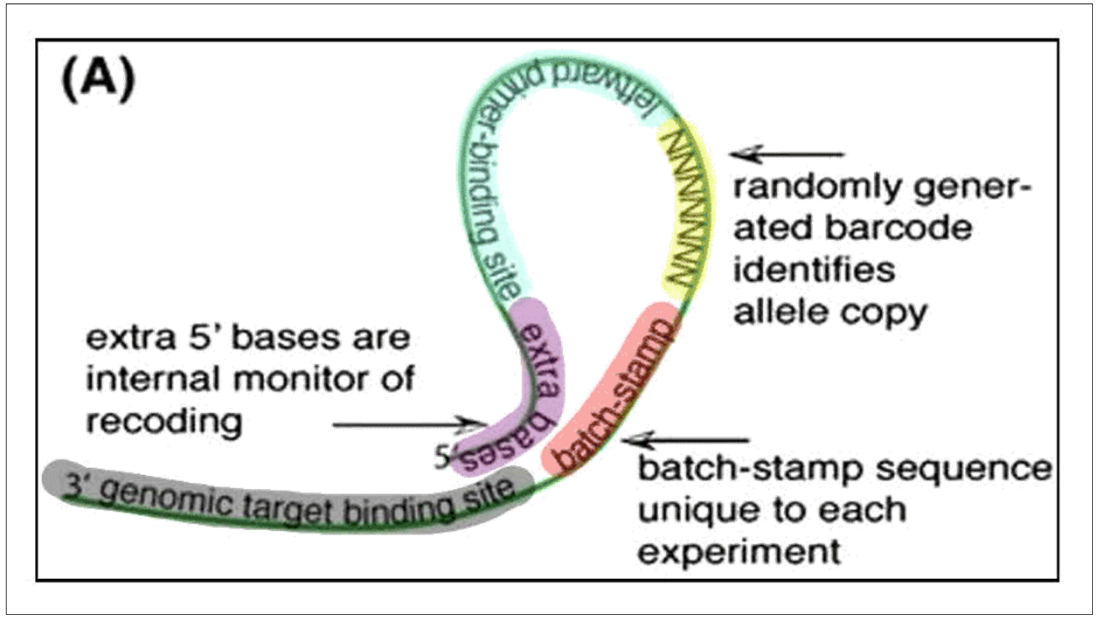
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

McCloskey: Teaches Dual Tagging



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

EX1004 (McCloskey et al.) at Fig. 1

The Theory Of The Petition Is Clear

The Petition

In fact, such prior art exists. McCloskey—which was not expressly considered by the Examiner—discloses such a second tag for single cell experiments like those described in Linnarsson. As documented herein and in the accompanying expert report of Dr. Gregory Cooper, the combination of Linnarsson with McCloskey renders obvious each and every claim of the '981 Patent.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 8)

'981 Petition at 4

Parse 52

The Theory Of The Petition Is Clear

The Petition

A POSA would have understood that McCloskey's reference to "different cell or allele copies" encompasses cDNA (*i.e.*, sample polynucleotides) from single cell experiments. *See* EX1002 ¶¶ 65, 184. Indeed, McCloskey teaches that the "batch-stamps and barcodes [should] be used when amplifying irreplaceable DNAs ***and cDNAs*** for…***single cell***…analyses," and that its method of tagging applies "to single-stranded cDNA templates." EX1004.001, .005. Thus, McCloskey teaches a second tag sequence (*i.e.*, the barcode) distinguishing a sample polynucleotide (*e.g.*, cDNA) from other sample polynucleotides derived from the same single cell.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 9)

'981 Petition at 51

McCloskey: Barcode Is Used To Distinguish "Redundant Sequences"

Redundancy is frequent when template quantities are limited, or when large numbers of product sequences are analyzed. Redundant sequences recovered from the same PCR reaction are readily identified because they are identical in both barcode and batch-stamp. Identifying redundant sequences and removing them from

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 33)

McCloskey: Barcodes Enable Counting

et al. 1997). An additional benefit of our method for mosaic samples is that counting sequences with nonredundant barcodes provides a quantitative measure of template diversity.

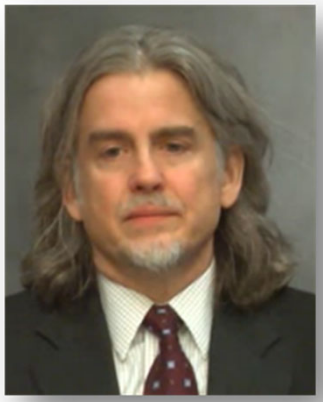
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 33)

McCloskey: Barcodes Useful For "Single Cell" Analysis

identity, and barcodes detect template redundancy. Our approach thus enables classification of each PCR-derived sequence as valid, contaminant, or redundant, and provides a measure of sequence diversity. We recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs available for forensic, clinical, single cell, and ancient DNA analyses.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 9)

Dr. Quackenbush: Batch Stamp Distinguishes Polynucleotides From Different Cell Samples



John Quackenbush
10X's Expert

traced back to its cell of origin. McCloskey's encoding oligonucleotide's batch-stamp allows one, instead, to distinguish between nucleic acids arising from a cell *in the sample* and contaminant nucleic acids arising from cells *from prior samples*. EX1004, 3-4. Similarly, McCloskey's encoding oligonucleotide's barcode allows one to distinguish *between nucleic acids arising from the same sample*, but provides no information as to which allele sequences originate from the same cell, or whether the different sequences originate from different cells. EX1004, 4. Indeed,

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 10)

EX2013 (Quackenbush Decl.) ¶ 66

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

EX1002 (Cooper Decl.) ¶ 188

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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



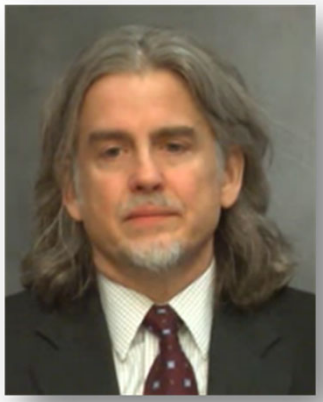
Gregory Cooper
Parse's Expert

191. As mentioned, the risks of amplification bias are "especially high when limited amounts of template DNA are used," such as for single cell genomics or gene expression analysis in single cells. Linnarsson (Ex. 1003) at 2:3-15, 11:6-10, Linnarsson Provisional (Ex. 1015) at 2:6-21, 3:14-20. Because McCloskey provides a direct solution to the problem discussed in Linnarsson, a POSA would have been motivated to incorporate McCloskey's teachings into Linnarsson's methods to remove amplification bias by introducing barcodes to measure true sample complexity/template diversity. By tagging each sample polynucleotide uniquely, true sample complexity can be analyzed because each unique sample sequence can be identified by the tag and amplification bias can be accounted for and corrected.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1002 (Cooper Decl.) ¶ 191

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

Topics For Argument

Ground 1

- Construction of “sequencing the tagged polynucleotides”
- Linnarsson and McCloskey combination
  - Patent Owner’s numerosity of tags argument fails
  - Patent Owner’s fragmentation and capture argument fails

Ground 2: Ligation

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Position: McCloskey Does Not Have Enough Barcodes

PO's Response

> Petitioner's citations to McCloskey show that ***McCloskey does not have enough barcodes to tag each mRNA molecule of Linnarsson***. This is no surprise as there is much less DNA than mRNA in a cell, and McCloskey only tags DNA for alleles of a specific gene to analyze. EX1004, 3-5. Indeed, McCloskey tags

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 11)

Patent Owner's Response at 33

Parse 62

’981 Patent, Claim 1: Requires Tagging “Sample Polynucleotides”

1. A method of analyzing nucleic acids from a plurality of single cells, the method comprising:

(ii) a multiplex identifier (MID) sequence comprising:

I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and

II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;

nucleotide from which the identified polynucleotide sequence is derived.

EX1001 (’981 Patent) at Claim 1

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

PO's District Court Position: Not All Molecules In A Cell Must Be Tagged

PO's District Court Brief

construction. *Id.* To argue that "sample polynucleotides" means every polynucleotide of the cell would rewrite the claim and replace "sample" with "all." This is contrary to the parties' agreed-upon construction and the law. *See Omega Eng'g, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003) ("[W]e presume, unless otherwise compelled, that the same claim term in the same patent or related patents carries the same construed meaning.").

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 12)

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.")

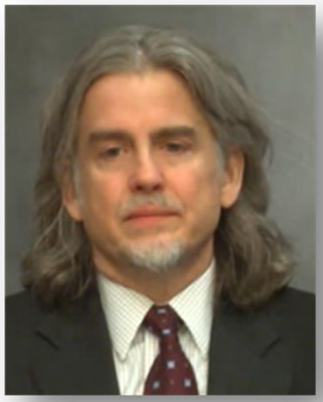
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Argument: Based On Mammalian Cells

PO's Response

16,384 barcodes would not be enough to tag each mRNA molecule in Linnarsson. It would be impossible, using McCloskey's 7-nucleotide barcode (amounting to only 16,348 unique barcodes), to distinguish the 50,000 – 300,000 mRNA molecules Petitioner admits POSITA would have expected to be present in the cell. EX1004, 4; EX2012, Abstract. Indeed, as Petitioner argued and POSITA

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

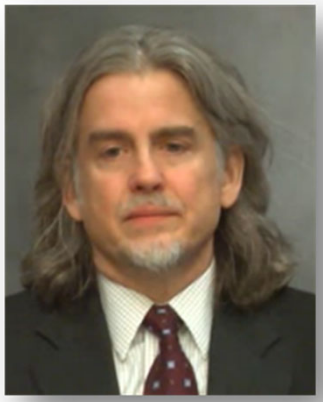
Linnarsson: Not Limited Mammalian Cells

and used in the methods described herein. Furthermore, in general, cells from any population can be used in the methods, such as a population of prokaryotic or eukaryotic single celled organisms including bacteria or yeast. In some aspects of the invention, the method of preparing the cDNA library can include the step of obtaining single cells. A single cell

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 11)

EX1003 (WO2010/11762) at 13:14-16

Dr. Quackenbush: Linnarsson Could Be Applied To Yeast Cells



John Quackenbush
10X's Expert

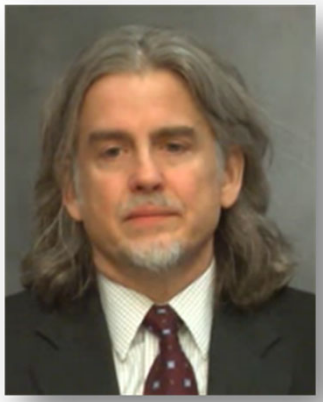
Q. In terms of Linnarsson, is it your understanding that Linnarsson can only be used with mammalian sources?

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

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

Dr. Cooper: Bacteria Have Only About 1,380 mRNA Molecules



Gregory Cooper
Parse's Expert

87. Just like Linnarsson, the '981 Patent notes that "any organism, organic material or nucleic acid-containing substance can be used as a source of nucleic acids …including, but not limited to, plants, animals (e.g., reptiles, mammals, insects, worms, fish, etc.), tissue samples, ***bacteria***, fungi (e.g., ***yeast***), phage, ***viruses***, cadaveric tissue, archaeological/ancient samples, etc." EX1001 at 14:14-21; *see also id.* at 14:61-63 ("In certain embodiments, the nucleic acid sample being analyzed is derived from a single source (e.g., a single organism, virus, tissue, cell, subject, etc.), …"). For example, bacteria such as E. Coli have a little over 4,000 genes and ~1,380 mRNA molecules in each cell. EX1061.001. Furthermore, there are even simpler bacteria such as *Carsonella ruddii* that have only 182 genes and will thus have even fewer mRNA molecules. *See* EX1062.001. The total

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1059 (Cooper Decl. ISO Petitioners Reply) at ¶ 87

The Literature: Bacteria Use PolyA Tails

POLYADENYLATION OF mRNA IN PROKARYOTES

Nilima Sarkar
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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′-ends of primary transcripts, the sites of endonucleolytic processing in the 3′ untranslated and intercistronic 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

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

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

Dr. Cooper: Bacteria Use Poly A Tails



Gregory Cooper
Parse's Expert

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?

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

PO's Position: Petitioner And Its Expert Rely Upon Mammalian Cells

from the mRNA ***in each individual mRNA sample***…"). According to Petitioner and its expert, there are between 50,000 and 360,000 mRNA molecules in any given mammalian cell. EX2008, 61-62; EX2011, ¶257; EX2012, 1; EX2013, ¶74. EX2008, 61-62. And, while McCloskey is directed to analyzing a very small

McCloskey: Provides General Disclosure Regarding Number Of Nucleotides Needed

The barcode is a random sequence of the four deoxyribonucleotides. The number of distinguishable barcodes in a population of oligonucleotides used in a reaction is determined by the number of random bases, n. This enables one to distinguish among 4^n allele copies per reaction. We currently use seven nucleotides for the barcode, giving 16,384 possible barcodes for each encoding oligonucleotide.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner Reply at 13)

Dr. Cooper: McCloskey's Disclosure Is General



Gregory Cooper
Parse's Expert

84. First, McCloskey does not cap its method to the use of *only* a 7-nucleotide long barcode. Dr. Quackenbush's opinion is restricting in the face of McCloskey's clear disclosures that no such restriction exists. For example, McCloskey teaches that any number of random bases "n," can be used to create the random barcode. EX1004.004. McCloskey also clearly states that the 7-nucleotide barcode is exemplary and used for a specific experiment.

> The barcode is a random sequence of the four deoxyribonucleotides. The number of distinguishable barcodes in a population of oligonucleotides used in a reaction is determined by the number of random bases, ***n***. This enables one to distinguish among 4^n allele copies per reaction. ***We currently use*** seven nucleotides for the barcode, giving 16,384 possible barcodes for each encoding oligonucleotide.

Id.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner Reply at 13)

EX1059 (Cooper Decl. ISO Petitioner's Reply) ¶ 84

Dr. Cooper: Using More Nucleotides Would Have Been Obvious



Gregory Cooper
Parse's Expert

85. In fact, the McCloskey patent application US2007002640[2], further notes that much longer barcodes, comprising 20-30 random nucleotide bases, can be designed, that would allow distinguishing among 1,099,511,627,776 - 1,152,921,504,606,846,976 polynucleotides.

> The length of the second sequence is sufficient to provide, with high probability, a unique identity to each target nucleic acid molecule in the sample prior to amplification. For example, a second sequence of 7 random nucleotides N selected from A, G, C, and T will provide a maximum of 4^7 or 16,384 unique barcodes. In some embodiments, the length of the second sequence is between 3 and ***30 nucleotides***, such as between 5 and ***25 nucleotides*** or between 7 and 13 nucleotides.

EX2001 ¶ 21. Thus, a POSA would find it obvious from McCloskey's method to expand barcodes to different lengths depending on the size of a sample and needs of the experiment. This is something I explained in a related IPR proceeding that I understand Patent Owner has cited in these proceedings. *See* EX2011 ¶¶ 256-57.

EX1059 (Cooper Decl. ISO Petitioner's Reply) ¶ 85

Dr. Cooper: Using More Nucleotides Would Have Been Obvious



Gregory Cooper
Parse's Expert

257. For instance, a POSA would have easily designed tag sequences comprising 20-30 random nucleotide bases, which would allow the creation of 4^{20}-4^{30} unique barcodes distinguishing among 1,099,511,627,776-1,152,921,504,606,846,976 polynucleotides. For example, McCloskey II teaches using second tag sequences each comprising up to 30 base pairs. As disclosed in McCloskey II, "the length of the second sequence is between 3 and 30 nucleotides". McCloskey II at ¶ 21 (Ex. 1055). Linnarsson also discloses tag sequences comprising at least 20 nucleotides. Ex. 1001 at 18:31-19:2. A POSA would have understood that using second tag sequences comprising 20-30 nucleotides would provide significantly more unique tag sequences than would be necessary to ensure that each sample polynucleotide from any single cell receives a unique second tag sequence. *See* Ex. 1054.001 (estimating between 50,000 and 300,000 mRNA per mammalian cell).

EX2011 ¶ 257

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(POR at 34)

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.

Topics For Argument

Ground 1

- Construction of “sequencing the tagged polynucleotides”
- Linnarsson and McCloskey combination
  - Patent Owner’s numerosity of tags argument fails
  - Patent Owner’s fragmentation and capture argument fails

Ground 2: Ligation

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Position: Figure 11 Is Incompatible With McCloskey

> Once a biotin molecule is covalently bound to the end of these nucleic acids, it prevents any other molecule, including a nucleic acid tag, from being covalently bound to the end of the nucleic acid to which the biotin is already bound. EX2013, ¶89. Thus, Petitioner's tag(s) cannot be ligated to the "CDS" because a biotin is already bound to the CDS's 5' end's phosphoryl group, blocking the necessary covalent bond from being formed between the 5' end of the nucleic acid and any tag(s)..[21] EX2013, ¶89. Petitioner's CDS theory fails. EX2013, ¶88-93.

Linnarsson Figure 11: Uses Biotin And Restriction Enzyme

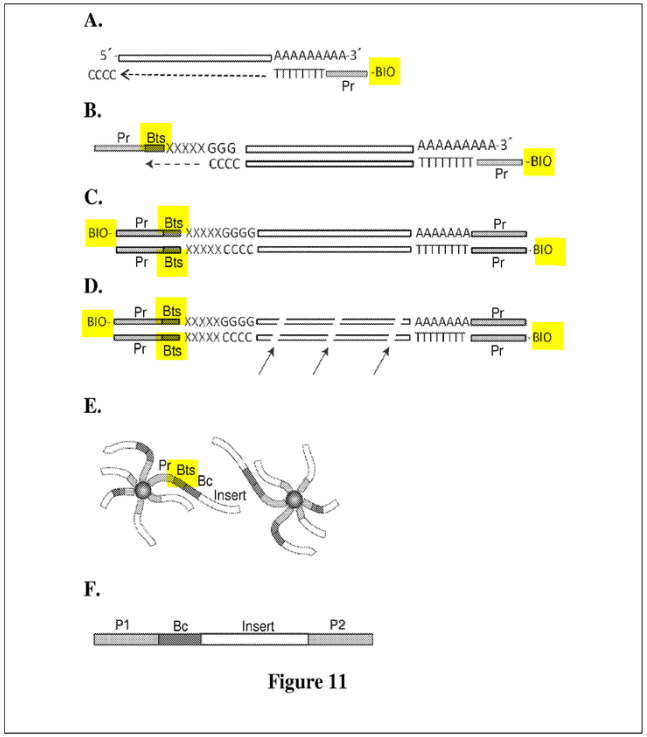
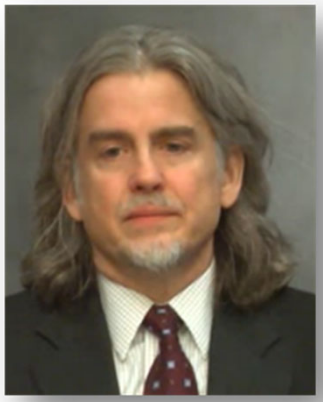


Figure 11

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

EX1003 (WO2010/11762) at Fig. 11

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.

Linnarsson: Steps of Figure 11 Are "Optionally Used"

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),

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

EX1003 (WO2010/11762) at 5:28-29

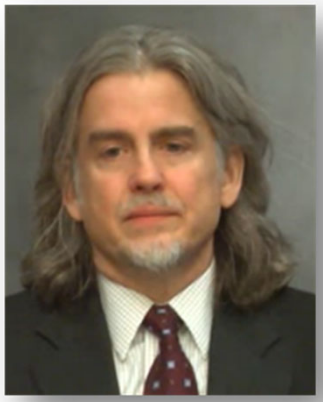
Linnarsson: Disclosure Is General

As the tag is present in the CDS and/or the TSO it will be incorporated into the cDNA during its synthesis and can therefore act as a "barcode" to identify the cDNA. Both the CDS and the TSO can include a tag. The CDS and the TSO can each include a different tag, such that the tagged cDNA sample comprises a combination of tags. Each cDNA sample generated by the above method can have a distinct tag, or a distinct combination of tags, such that once the tagged cDNA samples have been pooled, the tag can be used to identify which single cell from each cDNA sample originated. Thus, each cDNA sample can be linked to a single cell, even after the tagged cDNA samples have been pooled in the methods described herein.

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

EX1003 (WO2010/11762) at 19:4-11

Dr. Quackenbush: No Explanation For Why CDS Is Tagged



John Quackenbush
10X's Expert

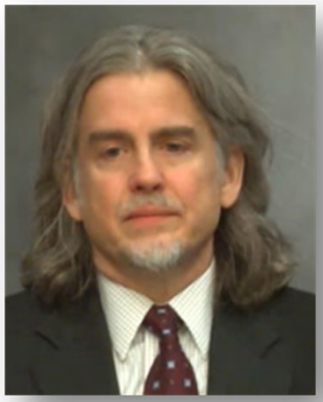
Q. So why would the CDS be tagged if it was never – if it was attached to a streptavidin and it never cut for sequencing?

A. So I haven't done that analysis. Dr. Cooper makes statements about either the CDS or TSO including a tag, but Dr. Cooper doesn't provide an analysis as to how the TSO tag would be read given his description of Linnarsson And his assertion that Linnarsson, as he describes it, represents invalidating prior art.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 2, 8)

EX1057 (Quackenbush Depo) at 151:18-152:2

Dr. Quackenbush: No Explanation For Why CDS Is Tagged



John Quackenbush
10X's Expert

Q. And why would there be a cell tag if it was never going to be sequenced?

A. So Dr. Cooper doesn't provide any arguments as to how one would modify what's presented in Linnarsson to sequence that. I can speculate about ways in which it might be done. But to the extent that Dr. Cooper doesn't provide such an argument, I don't have anything to respond to.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 8)

EX1057 (Quackenbush Depo) at 152:22-153:5

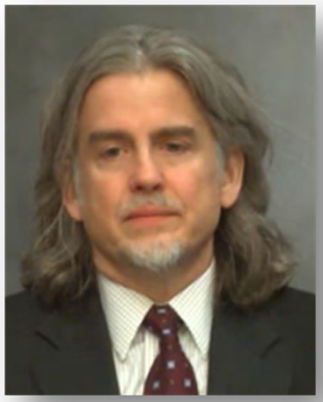
Linnarsson: Disclosure Is General

The invention provides method for preparing a cDNA library from a plurality of single cells. In one aspect, the method includes the steps of releasing mRNA from each single cell to provide a plurality of individual mRNA samples, 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, pooling the tagged cDNA samples and amplifying the pooled cDNA samples to generate a cDNA library having double-stranded cDNA. The invention also provides a cDNA library produced by the methods described herein. The invention further provides methods for analyzing gene expression in a plurality of cells by preparing a cDNA library as described herein and sequencing the library.

EX1003 (WO2010/11762) at 3:25-4:2

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

Dr. Quackenbush: Did Not Analyze Full Breadth Of Linnarsson's Disclosure



John Quackenbush
10X's Expert

Q. And did you – when you reviewed Linnarsson, did you have any reaction at all to the fact that he described his method for generating a cDNA library not to include fragmenting or the use of biotin?

A. I didn't do that kind of detailed analysis because it wasn't required to respond to Dr. Cooper's arguments about obviousness.

Linnarsson Figure 3: No Biotin Or Restriction Enzyme

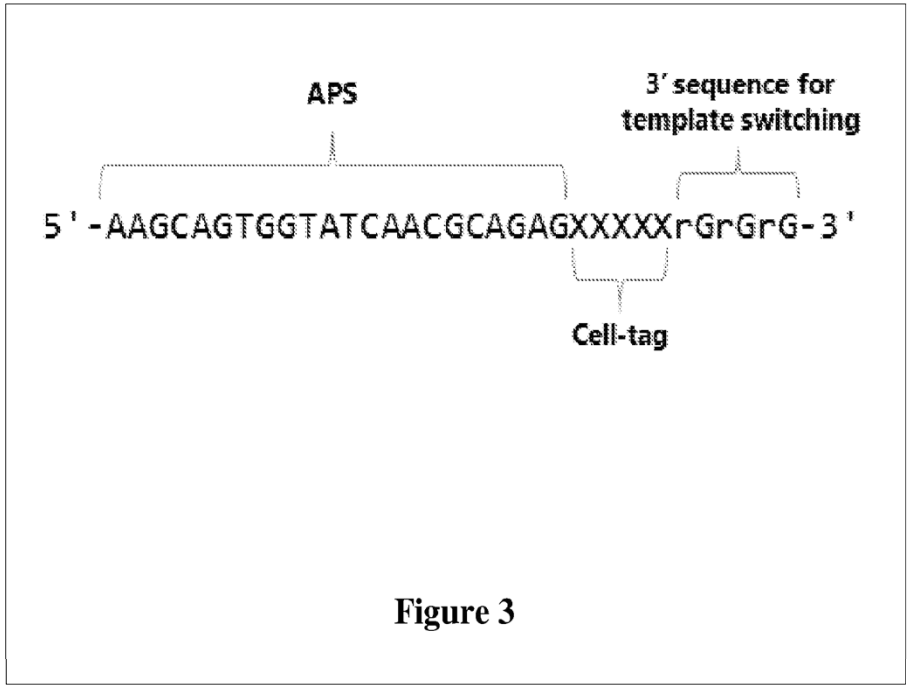


Figure 3

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

EX1003 (WO2010/11762) at Fig. 3

Linnarsson Figure 4: No Biotin Or Restriction Enzyme

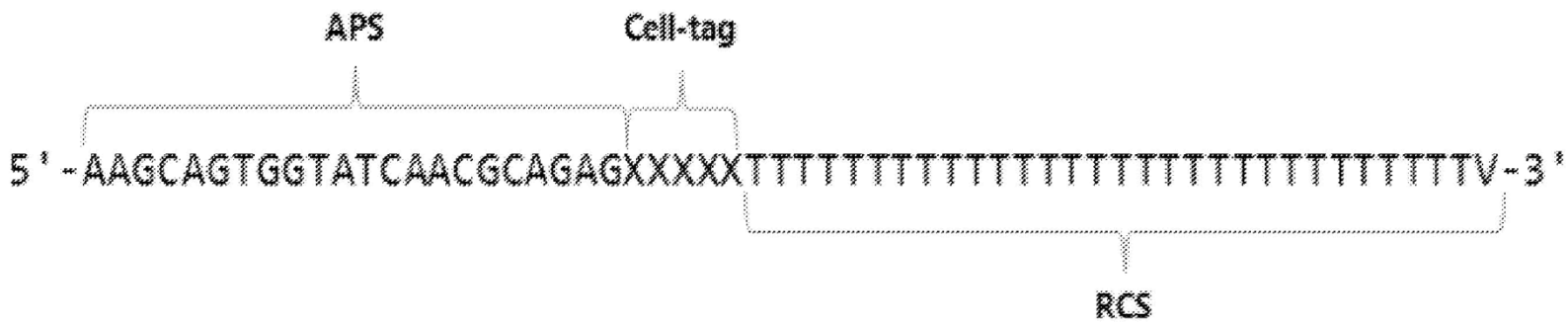


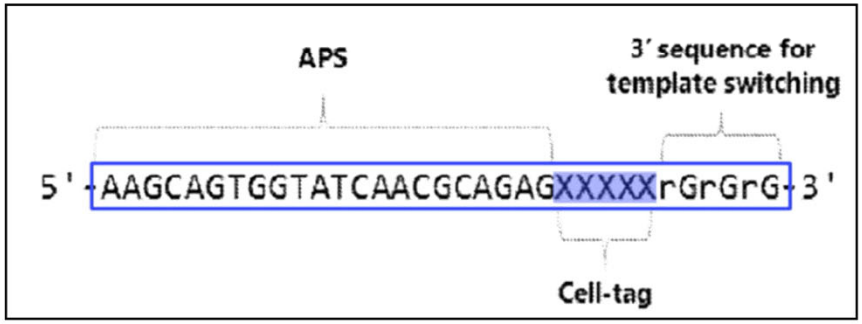
Figure 4

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 6, 7)

EX1003 (WO2010/11762) at Fig. 4

Dr. Cooper: Repeatedly Cited Figure 3

114. Linnarsson discloses that the TSO cell-tag "can be incorporated into the cDNA" and can "be used to identify which single cell from each cDNA sample originated." Ex. 1003 at 18:31, 19:9-10. Figure 3 depicts an example of a TSO (boxed in blue, below) with a cell-tag (highlighted in blue, below):



Ex. 1003 at Fig. 3.

EX1002 (Cooper Decl) ¶ 114

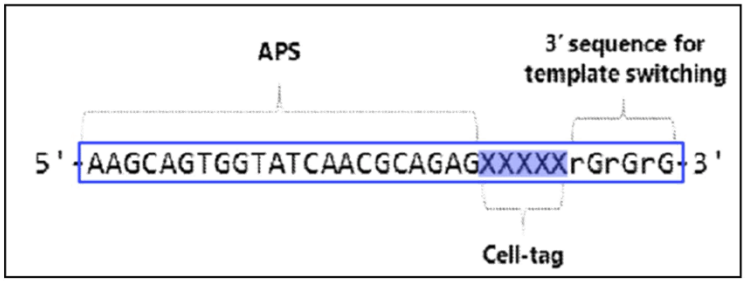
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 6)

Dr. Cooper: POSA Would Know To Use More Barcodes If Needed



Gregory Cooper
Parse's Expert

114. Linnarsson discloses that the TSO cell-tag "can be incorporated into the cDNA" and can "be used to identify which single cell from each cDNA sample originated." Ex. 1003 at 18:31, 19:9-10. Figure 3 depicts an example of a TSO (boxed in blue, below) with a cell-tag (highlighted in blue, below):



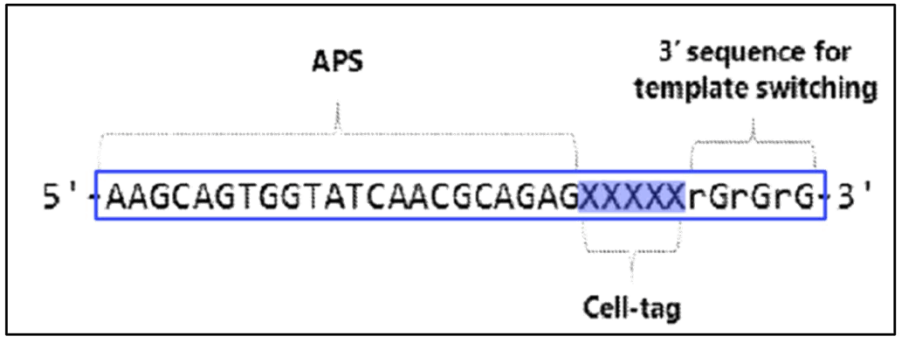
Ex. 1003 at Fig. 3.

EX1002 (Cooper Decl) ¶ 114

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

Dr. Cooper: Repeatedly Cited Figure 3

144. Figure 3 depicts an example of a TSO (boxed in blue, below) with a cell-tag (highlighted in blue, below):



Ex. 1003 at Fig. 3; Ex. 1015 at Fig. 3.

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

Dr. Cooper: Repeatedly Cited Figure 3



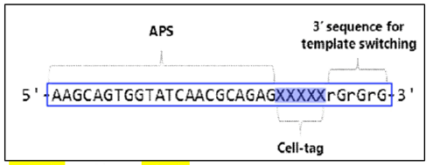
Gregory Cooper
Parse's Expert

114. Linnarsson discloses that the TSO cell-tag "can be incorporated into the cDNA" and can "be use originated." Ex. 1003 a (boxed in blue, below) w

5' AAGCA

Ex. 1003 at Fig. 3.

144. Figure 3 depicts an example of a TSO (boxed in blue, below) with a cell-tag (highlighted in blue, below):



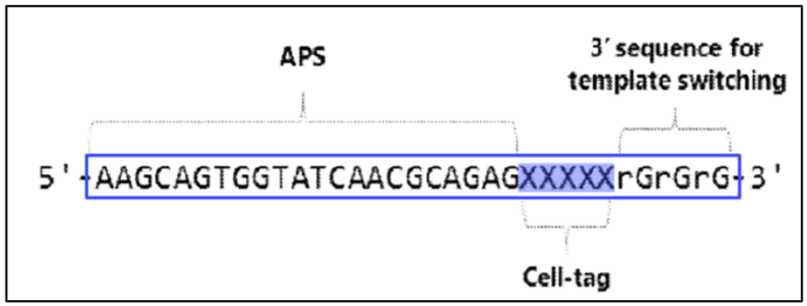
Ex. 1003 at Fig. 3; Ex. 1015 at Fig. 3.

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

EX1002 (Cooper Decl) ¶ 114, 114

Dr. Cooper: Repeatedly Cited Figure 3

163. As depicted below in Figure 3, Linnarsson discloses a MID, sequence comprising a first tag sequence. Linnarsson's Figure 3, as shown below, depicts using a TSO comprising a "cell tag" (highlighted in blue below), an amplification primer sequence ("APS"), and a sequence for template switching

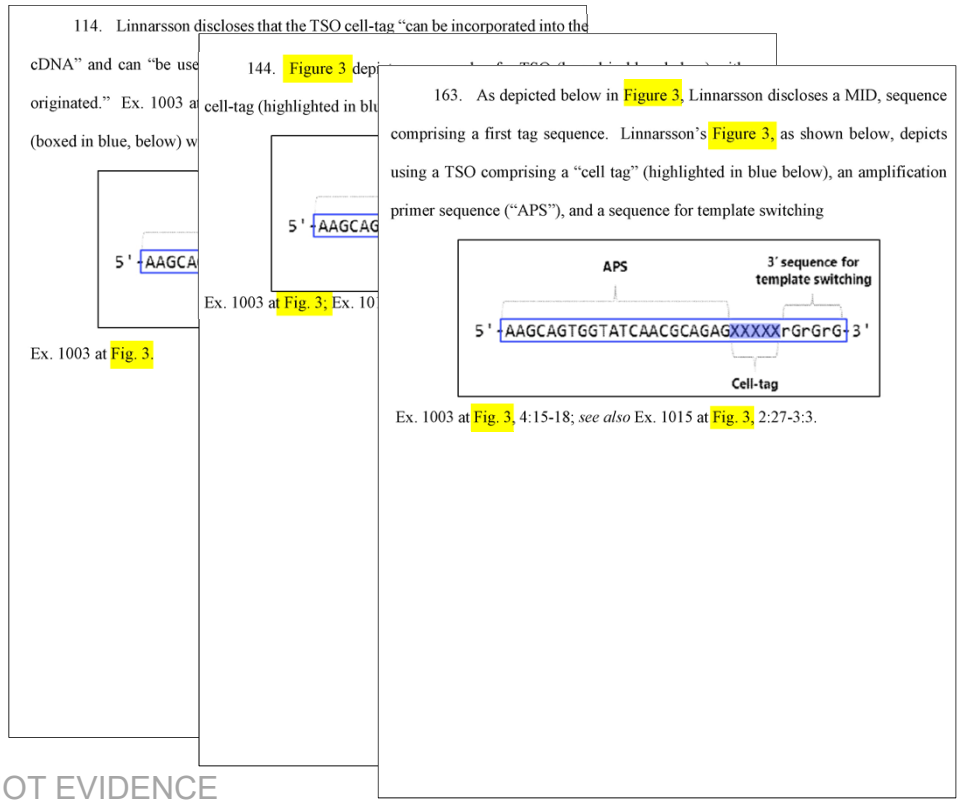


Ex. 1003 at Fig. 3, 4:15-18; *see also* Ex. 1015 at Fig. 3, 2:27-3:3.

Dr. Cooper: Repeatedly Cited Figure 3



Gregory Cooper
Parse's Expert



EX1002 (Cooper Decl) ¶¶
114, 144, 163
Parse 99

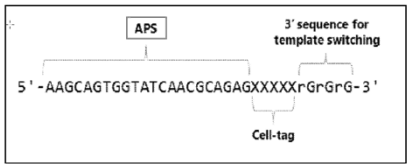
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 6)

Dr. Cooper: Repeatedly Cited Figure 3

232. Further, Linnarsson teaches generating the plurality of tagged polynucleotides using an amplification primer molecule. Specifically, Linnarsson teaches that each of the CDS and/or TSO comprises an "amplification primer sequence" ("APS"):

> The CDS can comprise a 5′ amplification primer sequence (APS), which subsequently allows the first strand of cDNA to be amplified by PCR using a primer that is complementary to the 5′APS. The TSO can also comprise a 5′ APS . . .

Ex. 1003 at 19:18-23; Ex. 1015 at 8:9-12. The APS in the TSO is depicted in Linnarsson Figure 3:



Ex. 1003 at Fig. 3. Figure 4 similarly depicts the APS for the CDS:



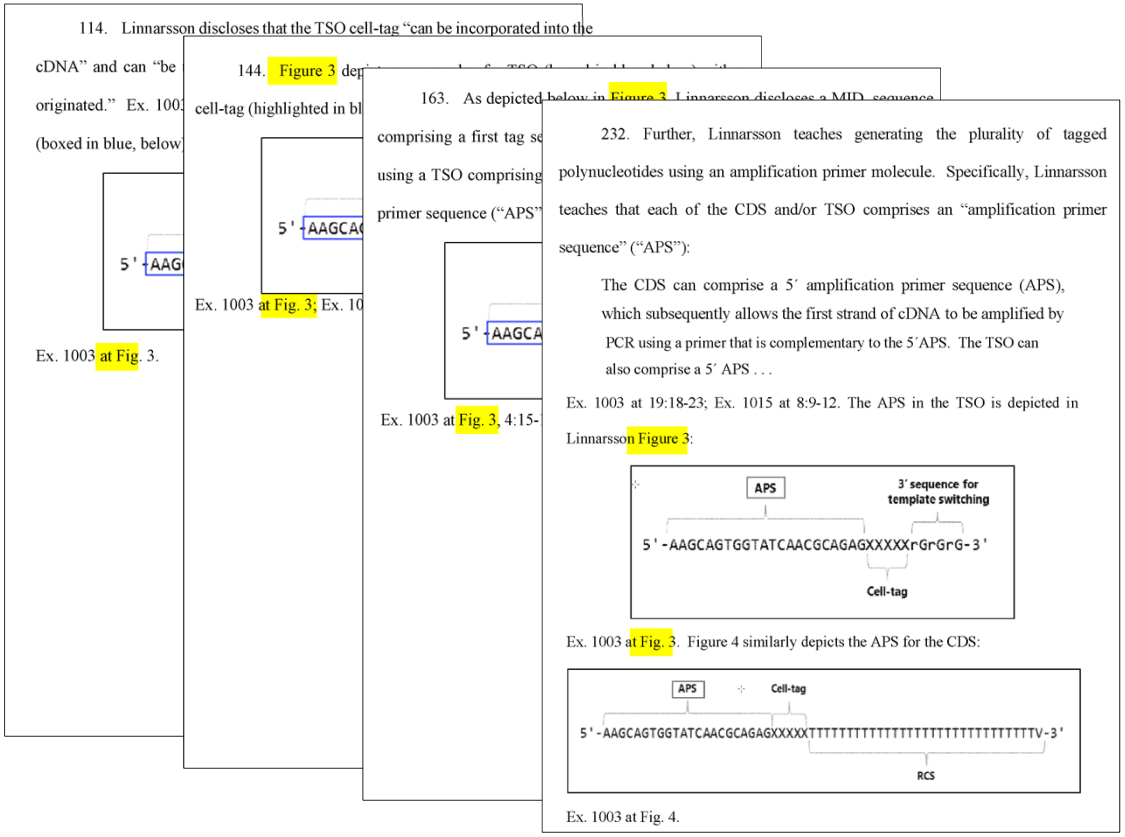
Ex. 1003 at Fig. 4.

EX1002 (Cooper Decl) ¶ 232

Parse 100

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

Dr. Cooper: Repeatedly Cited Figure 3



114. Linnarsson discloses that the TSO cell-tag "can be incorporated into the cDNA" and can "be originated." Ex. 1003 (boxed in blue, below

Ex. 1003 at Fig. 3.

144. Figure 3 dep

cell-tag (highlighted in bl

Ex. 1003 at Fig. 3; Ex. 10

163. As depicted below in Figure 3, Linnarsson discloses a MID sequence comprising a first tag se using a TSO comprising primer sequence ("APS"

Ex. 1003 at Fig. 3, 4:15-

232. Further, Linnarsson teaches generating the plurality of tagged polynucleotides using an amplification primer molecule. Specifically, Linnarsson teaches that each of the CDS and/or TSO comprises an "amplification primer sequence" ("APS"):

> The CDS can comprise a 5′ amplification primer sequence (APS), which subsequently allows the first strand of cDNA to be amplified by PCR using a primer that is complementary to the 5′APS. The TSO can also comprise a 5′ APS . . .

Ex. 1003 at 19:18-23; Ex. 1015 at 8:9-12. The APS in the TSO is depicted in Linnarsson Figure 3:

Ex. 1003 at Fig. 3. Figure 4 similarly depicts the APS for the CDS:

Ex. 1003 at Fig. 4.

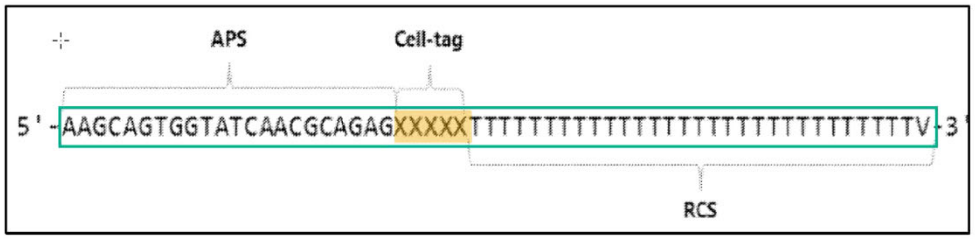


Gregory Cooper
Parse's Expert

EX1002 (Cooper Decl) ¶¶ 114, 144, 163, 232

Dr. Cooper: Repeatedly Cited Figure 4

112. Linnarsson discloses that the CDS cell-tag "can be incorporated into the cDNA" and can "be used to identify which single cell from each cDNA sample originated." Ex. 1003 at 18:31, 19:9-10. Figure 4 of Linnarsson depicts an example of a CDS (boxed in green, below) with a cell-tag (highlighted in yellow, below):



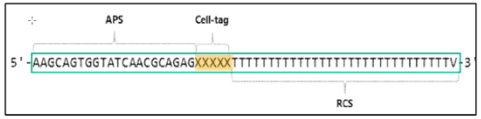
Ex. 1003 at Fig. 4.

Dr. Cooper: Repeatedly Cited Figure 4



Gregory Cooper
Parse's Expert

112. Linnarsson discloses that the CDS cell-tag "can be incorporated into the cDNA" and can "be used to identify which single cell from each cDNA sample originated." Ex. 1003 at 18:31, 19:9-10. Figure 4 of Linnarsson depicts an example of a CDS (boxed in green, below) with a cell-tag (highlighted in yellow, below):



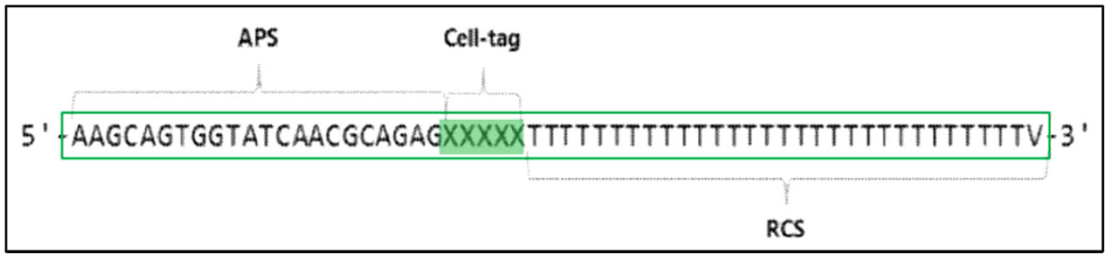
Ex. 1003 at Fig. 4.

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

EX1002 (Cooper Decl) ¶ 112

Dr. Cooper: Repeatedly Cited Figure 4

141. For example, Figure 4 depicts an example of a CDS (boxed in green, below) with a cell-tag (highlighted in green, below):

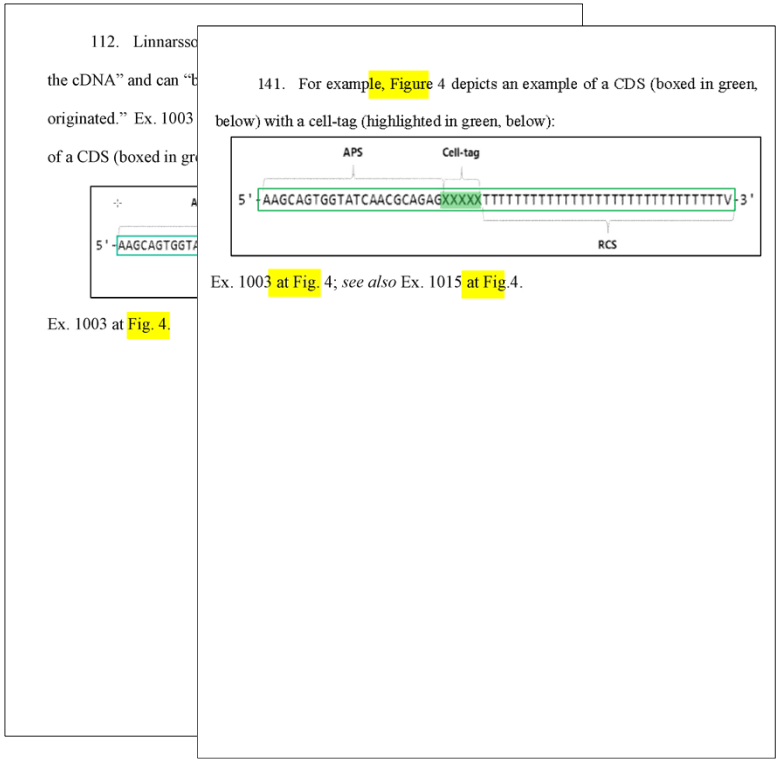


Ex. 1003 at Fig. 4; *see also* Ex. 1015 at Fig.4.

Dr. Cooper: Repeatedly Cited Figure 4



Gregory Cooper
Parse's Expert



112. Linnarsso
the cDNA" and can "b
originated." Ex. 1003
of a CDS (boxed in gr
5' -AAGCAGTGGTA
Ex. 1003 at Fig. 4.

141. For example, Figure 4 depicts an example of a CDS (boxed in green, below) with a cell-tag (highlighted in green, below):

APS Cell-tag
5' -AAGCAGTGGTATCAACGCAGAGXXXXXTTTTTTTTTTTTTTTTTTTTTTTTTTTTV-3'
RCS

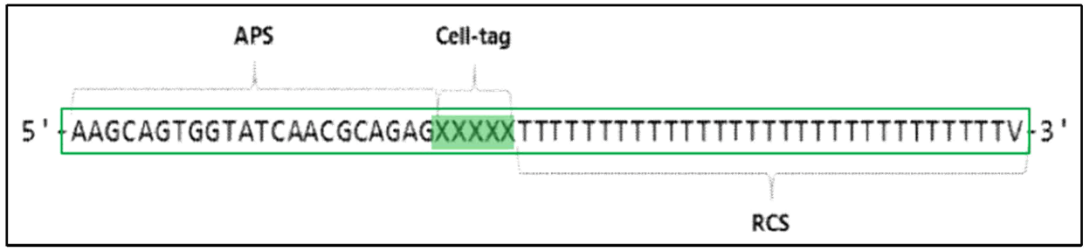
Ex. 1003 at Fig. 4; *see also* Ex. 1015 at Fig.4.

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

EX1002 (Cooper Decl) ¶ 112

Dr. Cooper: Repeatedly Cited Figure 4

165. Alternatively, Linnarsson discloses a CDS as the MID sequence comprising a first tag. Figure 4, as shown below, depicts a CDS comprising a "cell tag" (highlighted in green below), an amplification primer sequence ("APS"), and a RNA complementary sequence ("RCS"):



Ex. 1003 at Fig. 4, 4:17-18; *see also* Ex. 1015 at Fig. 4, 10:14-16.

Dr. Cooper: Repeatedly Cited Figure 4



Gregory Cooper
Parse's Expert

112. Linnarsson discloses that the CDS cell-tag "can be incorporated into the cDNA" and car originated." Ex. 10 of a CDS (boxed in

5' -AAGCAGTG

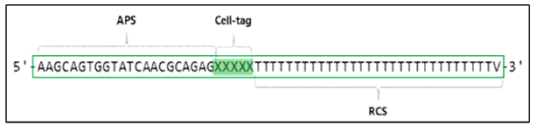
Ex. 1003 at Fig. 4.

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5' -AAGCAGTG

Ex. 1003 at Fig.

165. Alternatively, Linnarsson discloses a CDS as the MID sequence comprising a first tag. Figure 4, as shown below, depicts a CDS comprising a "cell tag" (highlighted in green below), an amplification primer sequence ("APS"), and a RNA complementary sequence ("RCS"):



Ex. 1003 at Fig. 4, 4:17-18; *see also* Ex. 1015 at Fig. 4, 10:14-16.

EX1002
(Cooper Decl) ¶¶ 112, 141, 165, 232
Parse 107

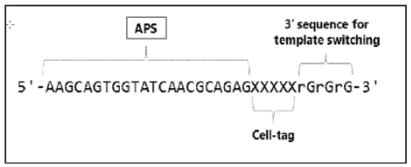
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 6)

Dr. Cooper: Repeatedly Cited Figure 4

232. Further, Linnarsson teaches generating the plurality of tagged polynucleotides using an amplification primer molecule. Specifically, Linnarsson teaches that each of the CDS and/or TSO comprises an "amplification primer sequence" ("APS"):

> The CDS can comprise a 5′ amplification primer sequence (APS), which subsequently allows the first strand of cDNA to be amplified by PCR using a primer that is complementary to the 5′APS. The TSO can also comprise a 5′ APS . . .

Ex. 1003 at 19:18-23; Ex. 1015 at 8:9-12. The APS in the TSO is depicted in Linnarsson Figure 3:



Ex. 1003 at Fig. 3. Figure 4 similarly depicts the APS for the CDS:



Ex. 1003 at Fig. 4.

EX1002 (Cooper Decl) ¶ 232

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

Dr. Cooper: Repeatedly Cited Figure 4

112. Linnarsson discloses that the CDS cell-tag "can be incorporated into the cDNA" and ca... originated." Ex. 10... of a CDS (boxed in...

5'-AAGCAGTG...

Ex. 1003 at Fig. 4.

141. For example, Figure 4 depicts an example of a CDS (boxed in green, below) with a cel...

5'-AAGCAGTG...

Ex. 1003 at Fig. ...

165. Alternatively, Linnarsson discloses a CDS as the MID sequence comprising a first tag. ... tag" (highlighted in gre... RNA complementary s...

APS

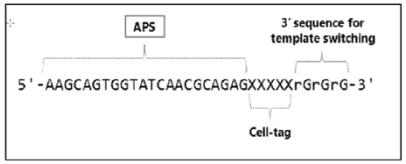
5'-AAGCAGTGGTATC...

Ex. 1003 at Fig. 4, 4:17...

232. Further, Linnarsson teaches generating the plurality of tagged polynucleotides using an amplification primer molecule. Specifically, Linnarsson teaches that each of the CDS and/or TSO comprises an "amplification primer sequence" ("APS"):

> The CDS can comprise a 5′ amplification primer sequence (APS), which subsequently allows the first strand of cDNA to be amplified by PCR using a primer that is complementary to the 5′APS. The TSO can also comprise a 5′ APS . . .

Ex. 1003 at 19:18-23; Ex. 1015 at 8:9-12. The APS in the TSO is depicted in Linnarsson Figure 3:



Ex. 1003 at Fig. 3. Figure 4 similarly depicts the APS for the CDS:



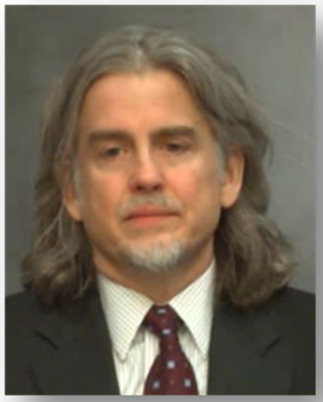
Ex. 1003 at Fig. 4.



Gregory Cooper
Parse's Expert

EX1002 (Cooper Decl) ¶¶ 112, 141, 165, 232

Dr. Quackenbush: Ignores Dr. Cooper's Opinions And Full Scope Of Linnarsson



John Quackenbush
10X's Expert

Q. I'm just asking, did you understand that Figure 11 is just one embodiment of the inventions of the Linnarsson patent document?

A. Dr. Cooper doesn't discuss any other embodiments and so I had nothing else to respond to.

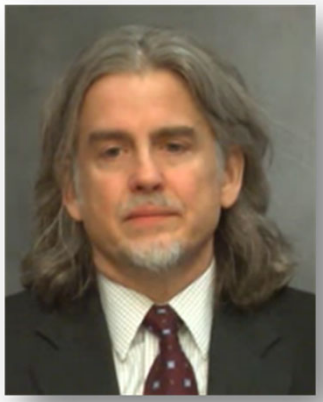
Q. But you do understand that it's one embodiment?

A. I haven't done an analysis of all of the patent to the extent that I've looked at all the possible embodiments. Linnarsson may or may not describe it that way.

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

EX1057 (Quackenbush Depo) at 166:17-167:3

Dr. Quackenbush: Ignored Figure 4



John Quackenbush
10X's Expert

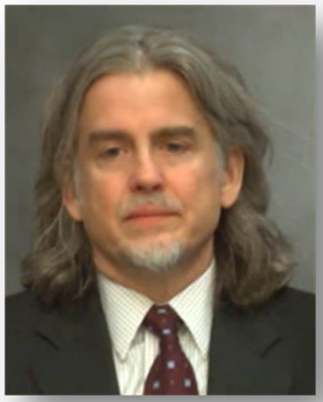
"So you are absolutely correct, I didn't cite to Figure 4."

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

EX1057 (Quackenbush Depo) at 170:17-18

Parse 112

Dr. Quackenbush: Ignored Figure 4

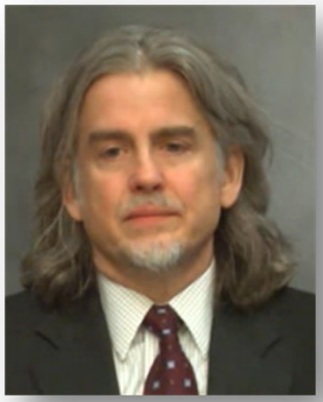


John Quackenbush
10X's Expert

Q. How come you never addressed Figure 4?

A. So I don't explicitly call out Figure 4 in my analysis, but I do talk about some of Dr. Cooper's suggestions that Linnarsson's method as presented in Figure 11 in the examples could be modified.

Dr. Quackenbush: No Biotin In Figures 3 and 4



John Quackenbush
10X's Expert

Q. Do you have any understanding why there's no identification of biotin in Figures 3 and 4?

A. Again, I can't comment on why Dr. Linnarsson made certain choices in preparing his figures. I have no way of knowing.

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

EX1057 (Quackenbush Depo) at 139:24-140:14

PO's Position: Figures 3 and 4 Include A Restriction Enzyme Sequence

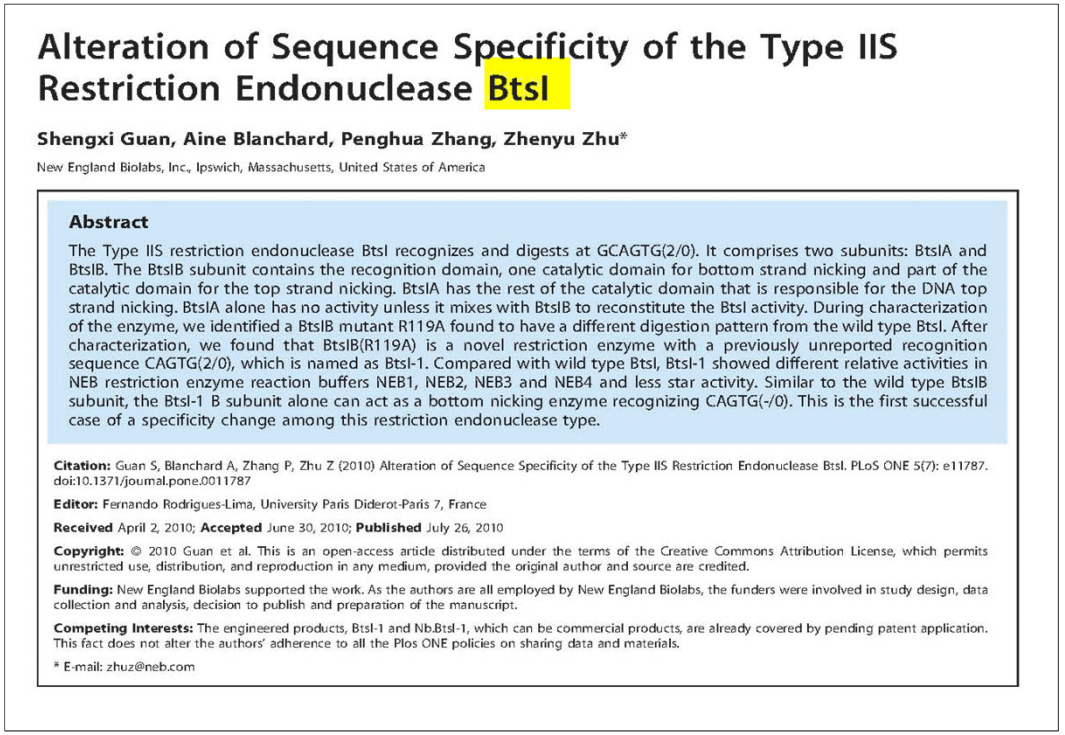
PO's Sur-Reply

> Indeed, according to Linnarsson, Figs.3-4 show nucleotide sequences for a "typical" TSO and CDS and, consistent with Example I's STRT disclosures, include, *inter alia*, a primer (APS), cell-tag, and Bts restriction site. EX1003, Figs.3-4; EX2101, 1. Cooper testified Figs.3-4 "do not contain ***any*** restriction

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Sur-reply at 10

PO Points To BtsI Enzyme



Alteration of Sequence Specificity of the Type IIS Restriction Endonuclease BtsI

Shengxi Guan, Aine Blanchard, Penghua Zhang, Zhenyu Zhu*

New England Biolabs, Inc., Ipswich, Massachusetts, United States of America

Abstract

The Type IIS restriction endonuclease BtsI recognizes and digests at GCAGTG(2/0). It comprises two subunits: BtsIA and BtsIB. The BtsIB subunit contains the recognition domain, one catalytic domain for bottom strand nicking and part of the catalytic domain for the top strand nicking. BtsIA has the rest of the catalytic domain that is responsible for the DNA top strand nicking. BtsIA alone has no activity unless it mixes with BtsIB to reconstitute the BtsI activity. During characterization of the enzyme, we identified a BtsIB mutant R119A found to have a different digestion pattern from the wild type BtsI. After characterization, we found that BtsIB(R119A) is a novel restriction enzyme with a previously unreported recognition sequence CAGTG(2/0), which is named as BtsI-1. Compared with wild type BtsI, BtsI-1 showed different relative activities in NEB restriction enzyme reaction buffers NEB1, NEB2, NEB3 and NEB4 and less star activity. Similar to the wild type BtsIB subunit, the BtsI-1 B subunit alone can act as a bottom nicking enzyme recognizing CAGTG(-/0). This is the first successful case of a specificity change among this restriction endonuclease type.

Citation: Guan S, Blanchard A, Zhang P, Zhu Z (2010) Alteration of Sequence Specificity of the Type IIS Restriction Endonuclease BtsI. PLoS ONE 5(7): e11787. doi:10.1371/journal.pone.0011787

Editor: Fernando Rodrigues-Lima, University Paris Diderot-Paris 7, France

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Funding: New England Biolabs supported the work. As the authors are all employed by New England Biolabs, the funders were involved in study design, data collection and analysis, decision to publish and preparation of the manuscript.

Competing Interests: The engineered products, BtsI-1 and Nb.BtsI-1, which can be commercial products, are already covered by pending patent application. This fact does not alter the authors' adherence to all the Plos ONE policies on sharing data and materials.

* E-mail: zhuz@neb.com

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Mtn to Exc at 5)

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

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

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 µL of 1 mM ATP, 1 µM SOLEXA-ADP1 adapter

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

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

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

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;

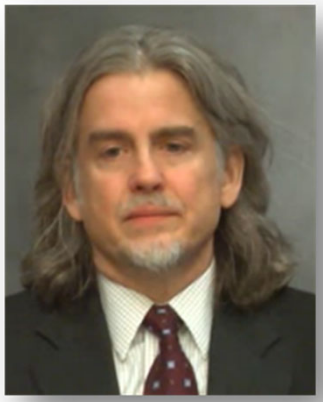
(iii) pooling the tagged cDNA samples; and

(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

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.

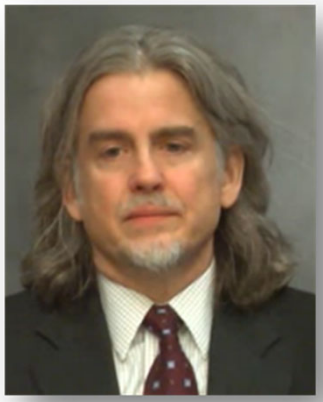
Q. Okay. But you can see in claim 1, there's no reference to fragmentation, correct; there's no fragmenting step?

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

Dr. Quackenbush: No Explanation For Claim 1



John Quackenbush
10X's Expert

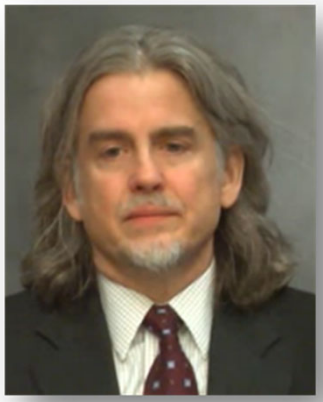
Q. In Linnarsson, the cDNA library is generated according to the method of claim 1 without any fragmentation or use of biotin, correct?

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

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.

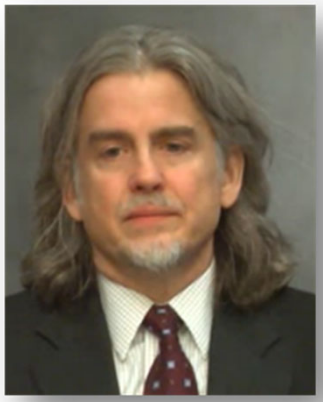
Q. All right. And you understand that the claims of the Linnarsson patent are part of the disclosure of the patent application?

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

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.

Linnarsson Claims 26-27: Methods Not Limited To Fragmentation

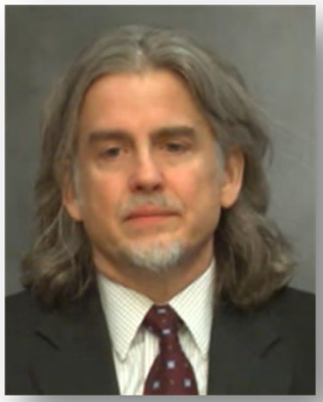
26. The method according to claim 1, wherein the method further comprises processing the cDNA library to obtain a library suitable for sequencing.

27. The method according to claim 26, wherein the processing comprises fragmenting the cDNA library.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE (Petitioner's Resp to POR at 6; Petitioner's Resp to POR at 25)

EX1003 (WO2010/11762) at Claim 26

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

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)

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

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



Gregory Cooper
Parse's Expert

> 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.

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

EX1059 (Cooper Decl.) ¶¶ 109-112

Topics For Argument

Ground 1

- Construction of “sequencing the tagged polynucleotides”
- Linnarsson and McCloskey combination
  - Patent Owner’s numerosity of tags argument fails
  - Patent Owner’s fragmentation and capture argument fails

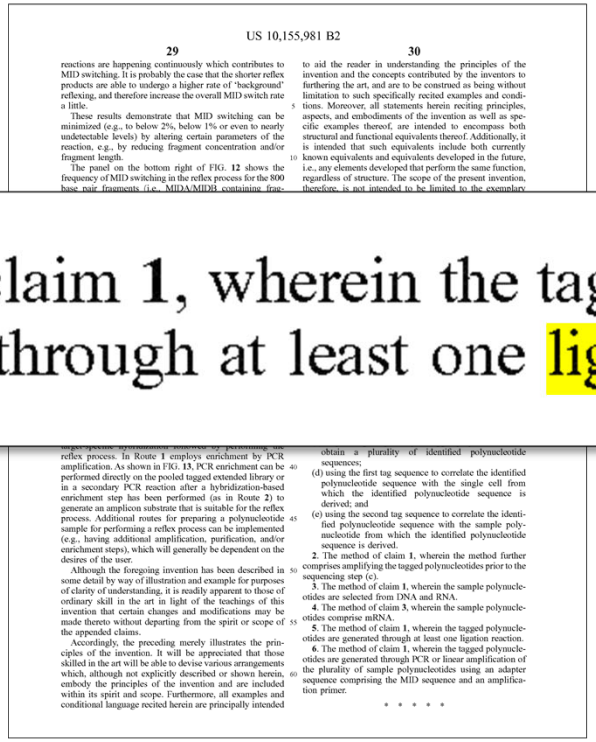
Ground 2: Ligation

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

’981 Patent: Claim 5


US 10,155,981 B2

29

reactions are happening continuously which contributes to MID switching. It is probably the case that the shorter reflex products are able to undergo a higher rate of 'background' reflexing, and therefore increase the overall MID switch rate a little.

These results demonstrate that MID switching can be minimized (e.g., to below 2%, below 1% or even to nearly undetectable levels) by altering certain parameters of the reaction, e.g., by reducing fragment concentration and/or fragment length.

The panel on the bottom right of FIG. **12** shows the frequency of MID switching in the reflex process for the 800

30

to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary

5. The method of claim **1**, wherein the tagged polynucleotides are generated through at least one ligation reaction.

reflex process. In Route **1** employs enrichment by PCR amplification. As shown in FIG. **13**, PCR enrichment can be performed directly on the pooled tagged extended library or in a secondary PCR reaction after a hybridization-based enrichment step has been performed (as in Route **2**) to generate an amplicon substrate that is suitable for the reflex process. Additional routes for preparing a polynucleotide sample for performing a reflex process can be implemented (e.g., having additional amplification, purification, and/or enrichment steps), which will generally be dependent on the desires of the user.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended

obtain a plurality of identified polynucleotide sequences;

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

(e) using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.

2. The method of claim **1**, wherein the method further comprises amplifying the tagged polynucleotides prior to the sequencing step (e).

3. The method of claim **1**, wherein the sample polynucleotides are selected from DNA and RNA.

4. The method of claim **3**, wherein the sample polynucleotides comprise mRNA.

5. The method of claim **1**, wherein the tagged polynucleotides are generated through at least one ligation reaction.

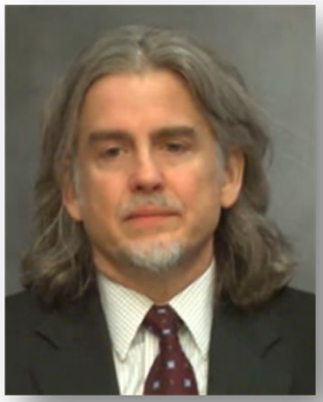
6. The method of claim **1**, wherein the tagged polynucleotides are generated through PCR or linear amplification of the plurality of sample polynucleotides using an adapter sequence comprising the MID sequence and an amplification primer.

* * * * *

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1001 (981’ Patent) at Claim 5

Dr. Quackenbush: No Opinion As To Whether Claim 5 Is Inventive



John Quackenbush
10X's Expert

Q. Now, with respect to the dependent claim 5, do you contend that dependent claim 5 of the '981 patent, which adds using ligation to generate the tag polynucleotides, do you contend that that's inventive?

A. So I haven't done a thorough analysis of the inventiveness of the '981 patent. My assumption is because the patent issued, that the patent examiner found it to be inventive.

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

EX1057 (Quackenbush Depo) at 189:21-190:18

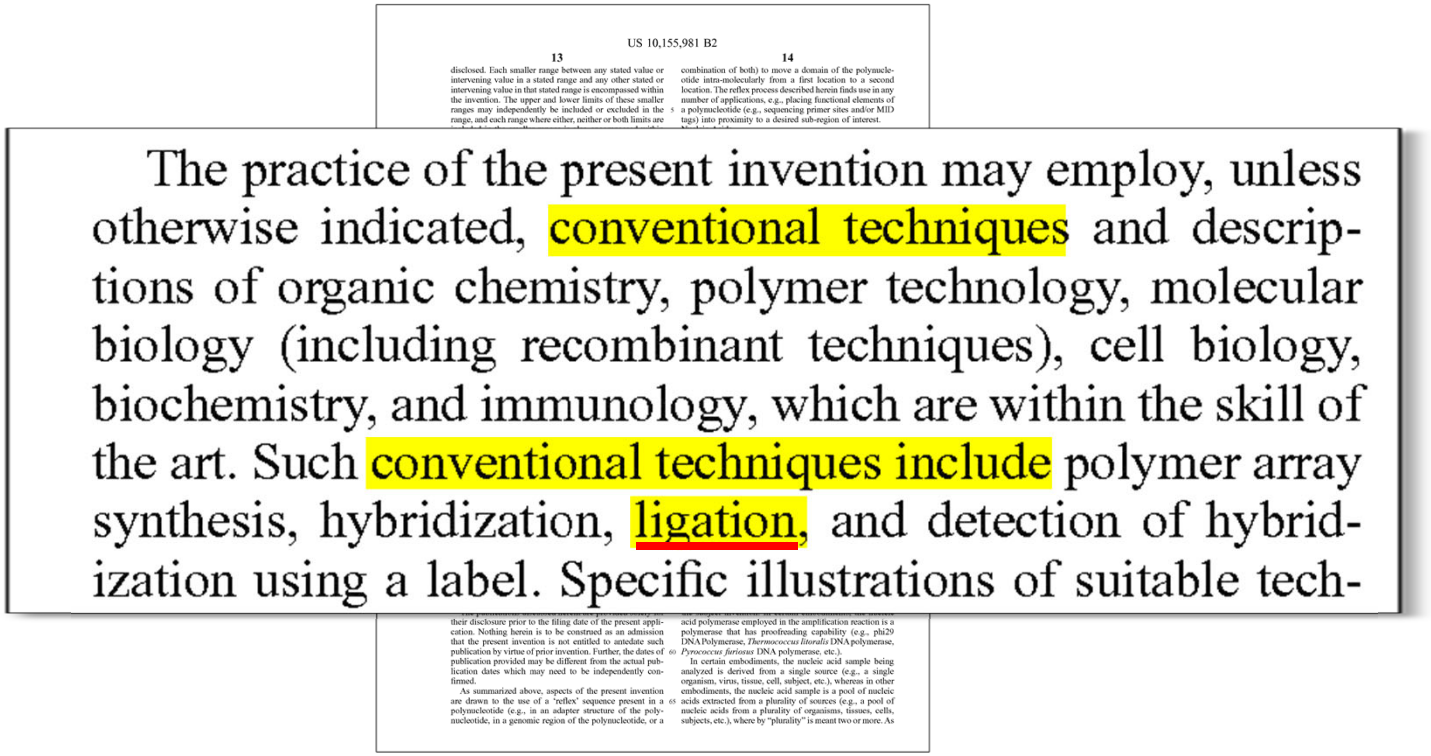
Specification: Ligation Is Prior Art

3' carbon of another oligonucleotide. A variety of template-driven ligation reactions are described in the following references, which are incorporated by reference: Whiteley et al, U.S. Pat. No. 4,883,750; Letsinger et al, U.S. Pat. No. 5,476,930; Fung et al, U.S. Pat. No. 5,593,826; Kool, U.S. Pat. No. 5,426,180; Landegren et al, U.S. Pat. No. 5,871, 921; Xu and Kool, Nucleic Acids Research, 27: 875-881 (1999); Higgins et al, Methods in Enzymology, 68: 50-71 (1979); Engler et al, The Enzymes, 15: 3-29 (1982); and Namsaraev, U.S. patent publication 2004/0110213.

EX1001 ('981 Patent) at 3:42-56

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Reply at 2; Petition at 67 (citing EX1002 ¶ 238))

Specification: Ligation Is "Conventional" Prior Art



US 10,155,981 B2

13 14

disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are

combination of both) to move a domain of the polynucleotide intra-molecularly from a first location to a second location. The reflex process described herein finds use in any number of applications, e.g., placing functional elements of a polynucleotide (e.g., sequencing primer sites and/or MID tags) into proximity to a desired sub-region of interest.

The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include polymer array synthesis, hybridization, ligation, and detection of hybridization using a label. Specific illustrations of suitable tech-

their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

As summarized above, aspects of the present invention are drawn to the use of a "reflex" sequence present in a polynucleotide (e.g., in an adapter structure of the polynucleotide, in a genomic region of the polynucleotide, or a

acid polymerase employed in the amplification reaction is a polymerase that has proofreading capability (e.g., phi29 DNA Polymerase, *Thermococcus litoralis* DNA polymerase, *Pyrococcus furiosus* DNA polymerase, etc.).

In certain embodiments, the nucleic acid sample being analyzed is derived from a single source (e.g., a single organism, virus, tissue, cell, subject, etc.), whereas in other embodiments, the nucleic acid sample is a pool of nucleic acids extracted from a plurality of sources (e.g., a pool of nucleic acids from a plurality of organisms, tissues, cells, subjects, etc.), where by "plurality" is meant two or more. As

EX1001 (981' Patent) at 13:32-39

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Reply at 2; Petition at 67 (citing EX1002 ¶ 238))

Law: Cannot Evade Obviousness Through Admittedly Conventional Technique

"Given that its own patents acknowledge that using the original search query for filtering was a 'conventional' technique, I/P Engine cannot now evade invalidity by arguing that integrating the query into the filtering process was a non-obvious departure from the prior art."

I/P Engine, Inc. v. AOL Inc., 576 Fed.Appx. 982, 987 (Fed. Cir. 2014)

Law: Cannot Evade Obviousness Through Admittedly Conventional Technique

"The Board did not err by accepting the specification's own assertions of what is well known in the art."

McCoy v. Heal Sys., LLC, 850 Fed.Appx. 785, 789 (Fed. Cir. 2021)

PO's Position: Ligation Was Conventional

10x's Brief From Becton-Dickinson Case

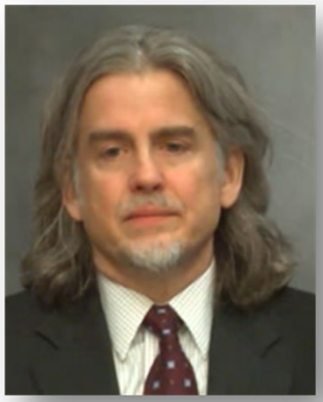
techniques that were required to attach "diverse" (*i.e.* different) labels. To the contrary, the specification admits that "in one embodiment" of the invention "the label-tag is attached by ligation" and that "methods of ligation will be known to those of skill in the art." Br. at 13.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petition at 67)

EX1017 at 1017.012

Parse 138

Dr. Quackenbush: Ligation Was Known And Conventional



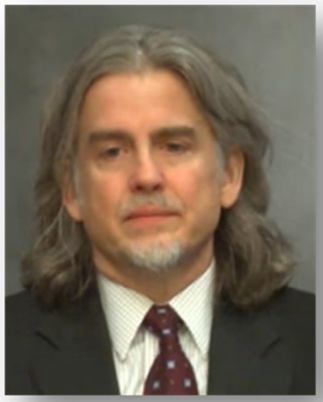
John Quackenbush
10X's Expert

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

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

EX1057 (Quackenbush Depo) at 188:17-18

Dr. Quackenbush: Ligation Was Known And Conventional



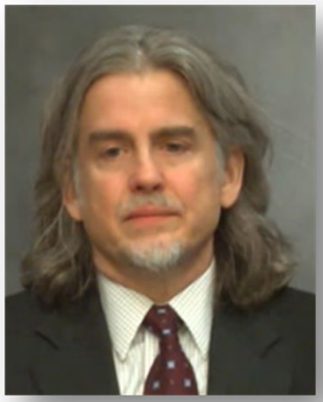
John Quackenbush
10X's Expert

"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

Dr. Quackenbush: Ligation Was Known And Conventional



John Quackenbush
10X's Expert

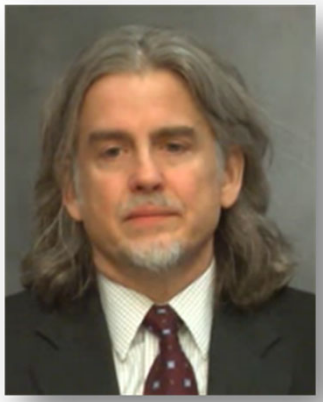
Q. And you'll agree that ligation is described in column 6 of the '981 patent is described as a conventional prior art technique?

A. So I don't think they use the term – I don't see the term "conventional" here. But ligation was a method that was well known in the art before the priority date of the '981 patent.

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

EX1057 (Quackenbush Depo) at 185:9-15

Dr. Quackenbush: Ligation Was Known And Conventional



John Quackenbush
10X's Expert

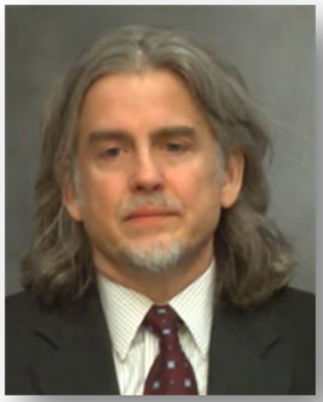
Q. As of August 2009, were you familiar with the use of ligation for polynucleotide tagging?

A. So as of 2009, I personally performed a number of ligation experiments, both what we refer to as sticky-ended and blunt-ended ligation.· A number of those introduced a variety of different tags, including sequencing tags such as sequencing primers. I was also familiar with ligation in the context of sequencing instruments like the Applied Biosystems SOLiD, which performed sequencing by ligation, as well as other applications.

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

EX1057 (Quackenbush Depo) at 57:12-58:1

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

Law: POSA Would Be Motivated To Use Known Options

A person of ordinary skill "has good reason to pursue the known options within his or her technical grasp," such that § 103 bars the patentability of obvious variations.

KSR Intl. Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

Law: POSA Would Be Motivated To Use Known Options

A "person of ordinary skill is also a person of ordinary creativity, not an automaton."

KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 421 (2007)

Law: POSA Would Be Motivated To Use Known Options

Reversing verdict of non-obviousness, explaining that the "fundamental flaw in I/P Engine's argument is that using an individual user's search query for filtering was a technique widely applied in the prior art."

I/P Engine, Inc. v. AOL Inc., 576 Fed.Appx. 982, 987 (Fed. Cir. 2014)

Dr. Cooper: POSA Would Be Motivated To Introduce McCloskey's Second Tag To Overcome Amplification Bias



Gregory Cooper
Parse's Expert

amplification in Linnarsson's method. *Id.* ¶¶ 178-194. As detailed in my original declaration, a POSA would be motivated to make this modification to address the problem of amplification bias, as expressly taught in McCloskey. *Id.* There are only two ways to include this second tag. A POSA would either include the second tag as part of the CDS or TSO when synthesizing the CDS or TSO such that both the first and second tags are synthesized together in one go from the outset. Alternatively, the first and second tag would be prepared separately, in which case one would attach the second tag to the first by ligation. While it ***might*** be possible

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 21)

EX1059 (Cooper Decl.) ¶ 99

Dr. Cooper: Only A Small Number Of Ways Exist To Introduce The Second Tag



Gregory Cooper
Parse's Expert

amplification in Linnarsson's method. *Id.* ¶¶ 178-194. As detailed in my original declaration, a POSA would be motivated to make this modification to address the problem of amplification bias, as expressly taught in McCloskey. *Id.* There are only two ways to include this second tag. A POSA would either include the second tag as part of the CDS or TSO when synthesizing the CDS or TSO such that both the first and second tags are synthesized together in one go from the outset. Alternatively, the first and second tag would be prepared separately, in which case one would attach the second tag to the first by ligation. While it ***might*** be possible

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 21)

EX1059 (Cooper Decl.) ¶ 99

Dr. Cooper: Ligation Offers Clear Flexibility Benefit



Gregory Cooper
Parse's Expert

243. A POSA would have understood that such an approach, using ligation to add the tag sequences to the CDS and/or TSO, would have been entirely equivalent to the method disclosed by the combination of Linnarsson and McCloskey. The only difference is in the timing: with the combination of Linnarsson and McCloskey discussed above, Section XII.A.1, the tag sequence is part of the CDS or TSO prior to extension whereas by using ligation, the tag sequence is added after extension. Using ligation to add the tag after extension would allow for increased flexibility in selecting tag sequences during an experiment. Thus, a POSA would have understood that using ligation was a routine choice and would have been motivated to use ligation because of the increased flexibility in tag choice.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petition at 68)

EX1002 (Cooper Decl.) ¶ 243

Dr. Cooper: Ligation Offers Clear Flexibility Benefit



Gregory Cooper
Parse's Expert

102. It is further my opinion that a POSA would be motivated to use ligation not just because this would have been a routine design choice given the narrow set of options available, but because, as I explain in my original declaration, this would provide increased flexibility in tag choice. EX1002 ¶ 243. Dr. Quackenbush contends that I did not adequately explain the added flexibility that ligation would offer, but the flexibility advantage is clear and straightforward. Because the barcodes that track individual molecules are being synthesized separately and then subsequently linked, one has added flexibility in choosing tags during the experiment. For instance, if one needs to tag only a small number of molecules in a given cell, one can use molecular barcodes of shorter overall length and introduce them during the experimental workflow without the need to synthesize a large batch of composite tags (not all of which may be used and would lead to a waste of reagents) in advance. As I explained during my deposition "that's just sort of a – a design choice that you could optimize your particular needs and goals, and it would just be a matter of flexibility for different kinds of – different kinds of setups that allow you maximize efficiency of your overall process." EX2018 at 57:2-12.

EX1059 (Cooper Decl.) ¶ 102

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(Petitioner's Resp to POR at 20)

Using Ligation With Linnarsson And McCloskey Would Have Been Obvious

- A POSA would have used McCloskey's barcode with Linnarsson to avoid amplification bias
- There are only a small number of ways to introduce the barcode
- Ligation was routine and conventional
- Ligation offered clear flexibility benefit

Law: POSA Would Be Motivated To Use Known Options

"[B]ecause Okubo's terminal-side plotting and Konishi's server-side plotting were both well known in the art, and were the only two identified, predictable solutions…it would have been obvious to substitute server-side plotting for terminal-side plotting in a combination of Okubo and Konishi."

Uber Techs., Inc. v. X One, Inc., 957 F.3d 1334, 1340 (Fed. Cir. 2020)

Law: POSA Would Be Motivated To Use Known Options

Explaining that "clear motivation" to modify exists where modification was "slight variation that produced convenience" and "was common"

Nike, Inc. v. Adidas AG, No. 2021-1903, 2022 WL 4002668, at *8 (Fed. Cir. Sept. 1, 2022)

Law: POSA Would Be Motivated To Use Known Options

Rejecting contention that Board erroneously found motivation to combine where two prior art components could be "interchangeably used" and substitution was "routine and predictable" because agents were "known for use."

Almirall, LLC v. Amneal Pharms. LLC, 28 F.4th 265, 274 (Fed. Cir. 2022)

Law: POSA Would Be Motivated To Use Known Options

Explaining that where an "ordinary artisan would...be left with two design choices ...[e]ach of these two design choices is an obvious combination"

ACCO Brands Corp. v. Fellowes, Inc., 813 F.3d 1361, 1367 (Fed. Cir. 2016)

Law: POSA Would Be Motivated To Use Known Options

Reversing district court finding of non-obviousness based on alleged "conclusory statements in lieu of an explanation of a motivation to combine" where district court failed to take account of "routine steps" an inventor would employ.

Ball Aerosol & Specialty Container, Inc. v. Ltd. Brands, Inc., 555 F.3d 984, 992-93 (Fed. Cir. 2009)

PO's Position: Figure 11 Is Incompatible With McCloskey

> Once a biotin molecule is covalently bound to the end of these nucleic acids, it prevents any other molecule, including a nucleic acid tag, from being covalently bound to the end of the nucleic acid to which the biotin is already bound. EX2013, ¶89. Thus, Petitioner's tag(s) cannot be ligated to the "CDS" because a biotin is already bound to the CDS's 5' end's phosphoryl group, blocking the necessary covalent bond from being formed between the 5' end of the nucleic acid and any tag(s)..[21] EX2013, ¶89. Petitioner's CDS theory fails. EX2013, ¶88-93.

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)

Law: POSA Is Not An "Automaton"

A "person of ordinary skill is also a person of ordinary creativity, not an automaton."

KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 421 (2007)

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



Gregory Cooper
Parse's Expert

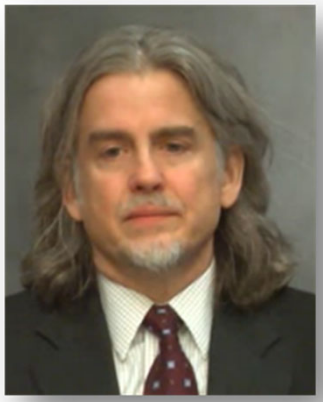
110. Even if a biotin molecule is deemed an essential aspect of the CDS, the claims would still be obvious. I understand that a person of ordinary skill is also a person of ordinary creativity, not an automaton. A skilled artisan seeking to introduce an additional tag to the CDS of Linnarsson by ligation 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

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



John Quackenbush
10X's Expert

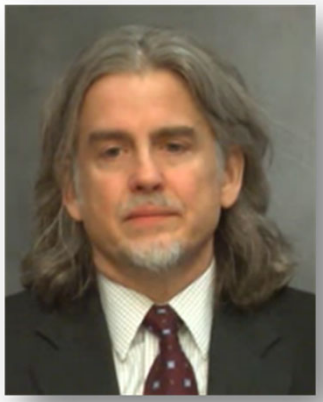
Q. Do you have an opinion whether or not a person skilled in the art would be able to do that? And by "that," I mean ligate a tag to the CDS before placing biotin on the five prime end?

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

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



John Quackenbush
10X's Expert

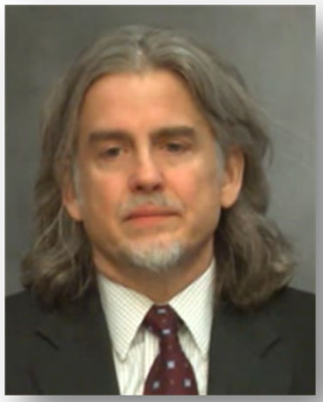
Q. We'll address that case as well. But right now I'm just asking you, would a person of skill in the art know how to adjust the process of Linnarsson, such that the tag could be ligated to the CDS before biotin is introduced to the molecule at the five prime end? Just whether it's within the scope of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

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

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

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



John Quackenbush
10X's Expert

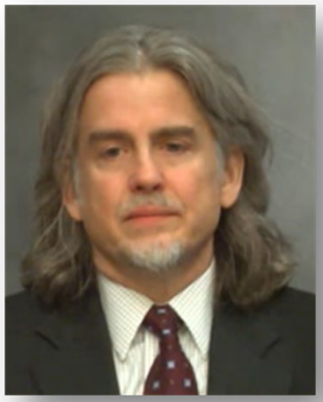
Q. Leaving aside how it would be done, do you have an opinion, sitting here now, as to whether it would be within the scope of the competency of a skilled artisan in 2009 to modify the Linnarsson process so that the tag is ligated before biotin is added?

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

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

Topics For Argument

Ground 1

- Construction of “sequencing the tagged polynucleotides”
- Linnarsson and McCloskey combination
  - Patent Owner’s numerosity of tags argument fails
  - Patent Owner’s fragmentation and capture argument fails

Ground 2: Ligation

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

McCloskey: Published In 2007



Biochem Genet (2007) 45:761–767
DOI 10.1007/s10528-007-9114-x

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
© Springer Science+Business Media, LLC 2007

Abstract Polymerase chain reaction (PCR) has become the mainstay 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, biased amplification, and product redundancy 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 template redundancy. Our approach thus enables classification of each PCR-derived sequence as valid, contaminant, or redundant, and provides a measure of sequence diversity. We recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs available for forensic, clinical, single cell, and ancient DNA analyses.

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

Introduction

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

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Springer

PARSE EX.1004.001

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

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).

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

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

If “a patent owner challenges a reference’s status as a printed publication, a petitioner may submit a supporting declaration with its reply.”

Hulu v. Sound View, IPR2018-01039, Pap.29, 15 (P.T.A.B. Dec. 20, 2019) (precedential).

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)

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)

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)

McCloskey: Published In 2007



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DOI 10.1007/s10528-007-9114-x

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PARSE EX.1004.001

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

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)

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

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)

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)

Topics For Argument

Ground 1

- Construction of “sequencing the tagged polynucleotides”
- Linnarsson and McCloskey combination
  - Patent Owner’s numerosity of tags argument fails
  - Patent Owner’s fragmentation and capture argument fails

Ground 2: Ligation

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Specification: Alleged Invention Pertains To Single Cell Analysis

(57) **ABSTRACT**

Aspects of the present invention include analyzing nucleic acids from single cells using methods that include using tagged polynucleotides containing multiplex identifier sequences.

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

EX1001 ('981 Patent) at Abstract

Specification: Refers To Using Tags For Counting

polynucleotide in a sample. Identification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present in the sample (or from how many original polynucleotides a manipulated polynucleotide sample was derived; see, e.g., U.S. Pat. No. 7,537,897, issued on May 26, 2009, incorporated herein by reference in its entirety). MIDs can range in length from 2 to 100 nucleotide bases or more and may include multiple subunits, where each different MID has a distinct identity and/or order of subunits. Exemplary nucleic acid tags that find use as MIDs are described in U.S. Pat. No. 7,544,473, issued on Jun. 6, 2009, and titled "Nucleic Acid Analysis Using Sequence Tokens", as well as U.S. Pat. No. 7,393,665, issued on Jul. 1, 2008, and titled "Methods and Compositions for Tagging and Identifying Polynucleotides", both of which are incorporated herein by reference in their entirety for their description of nucleic acid tags and their use in identifying polynucleotides. In certain embodiments, a set of

EX1001 ('981 Patent) at 6:33-7:22

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE ('981 Petition at 16; Petitioner's Resp to POR at 25)

Claims: Recite Using Tags For Single Cell Analysis

1. A method of analyzing nucleic acids from a plurality of single cells, the method comprising:

(ii) a multiplex identifier (MID) sequence comprising:

I. a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and

II. a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;

nucleotide from which the identified polynucleotide sequence is derived.

EX1001 ('981 Patent) at Claim 1

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

Linnarsson: Directed To Single-Cell Tagging

(57) Abstract: The present invention provides methods and compositions for the analysis of gene expression in single cells or in a plurality of single cells. The invention provides methods for preparing a cDNA library from individual cells by releasing mRNA from each single cell to provide a plurality of individual mRNA samples, synthesizing cDNA from the individual mRNA samples, tagging the individual cDNA, pooling the tagged cDNA samples and amplifying the pooled cDNA samples to generate a cDNA library. The invention also provides a cDNA library produced by the methods described herein. The invention farther provides methods for analyzing gene expression in a plurality of cells by preparing a cDNA library as described herein and sequencing the library.

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

EX1003 (WO2010/11762) at Abstract

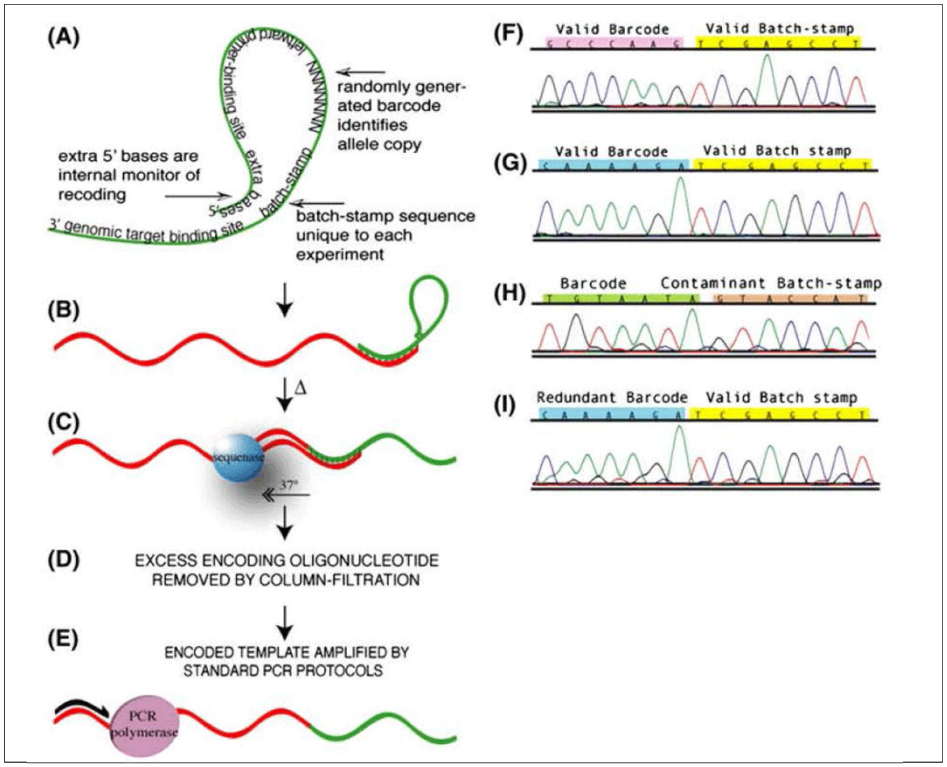
Linnarsson: Directed To Single-Cell Tagging

Embodiments of the invention provide a method of preparing a cDNA library from a plurality of single cells by releasing mRNA from each single cell to provide a plurality of individual samples, wherein the mRNA in each individual mRNA sample is from a single cell, 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 pooling the tagged cDNA samples and amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA. By utilizing the above method, it is feasible to prepare samples for sequencing from several hundred single cells in a short time and with a minimal amount of work. Traditional methods for preparing a fragment library from RNA for sequencing include gel excision steps that are laborious. In the absence of special equipment, it is not convenient to prepare more than a handful of samples in parallel. In some aspects of the methods described herein, a set of 96 cells is prepared as a single sample (after cDNA synthesis), which makes it feasible to prepare several hundred cells for sequencing. Additionally, technical variation is minimized because each set of 96 cells is prepared together (in a single tube).

EX1003 (WO2010/11762) at 10:15-30

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

McCloskey: Directed To Dual Tagging



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

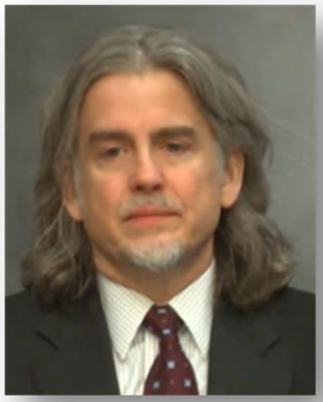
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 31)

McCloskey: Barcodes Useful For "Single Cell" Analysis

identity, and barcodes detect template redundancy. Our approach thus enables classification of each PCR-derived sequence as valid, contaminant, or redundant, and provides a measure of sequence diversity. We recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs available for forensic, clinical, single cell, and ancient DNA analyses.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('981 Petition at 9)

Dr. Quackenbush: No Opinions On Analogous Art Issue



John Quackenbush
10X's Expert

Q. Have you ever given opinions on whether prior art is analogous in your many prior experting efforts?

A. I don't – I don't recall hearing the term "analogous" in the past, so I'm not sure what that means, so I cant – I can't provide an opinion. I don't recall hearing the term "analogous prior art."

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

EX1057 (Quackenbush Depo) at 92:6-12

Thank you.