Petitioner's Oral Argument Presentation

Parse Biosciences Inc. v. 10X Genomics Inc.
IPR2023-00958

November 6, 2024

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

’013 Patent: Claim 1

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

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

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

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

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

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

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

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

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

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

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

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’013 Petition at 8)

EX1001 (’013 Patent) at Claim 1

Parse 2

’013 Patent: Claim 1

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

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

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

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

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

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

(d) sequencing said plurality of amplified polynucleotides to determine sequences of the amplified polynucleotides corresponding to the sample sequence, the first

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’013 Petition at 8)

EX1001 (’013 Patent) at Claim 1

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 ('013 Patent) at 12:60-64

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 7)

Specification: Alleged Invention Is "Reflex Method"

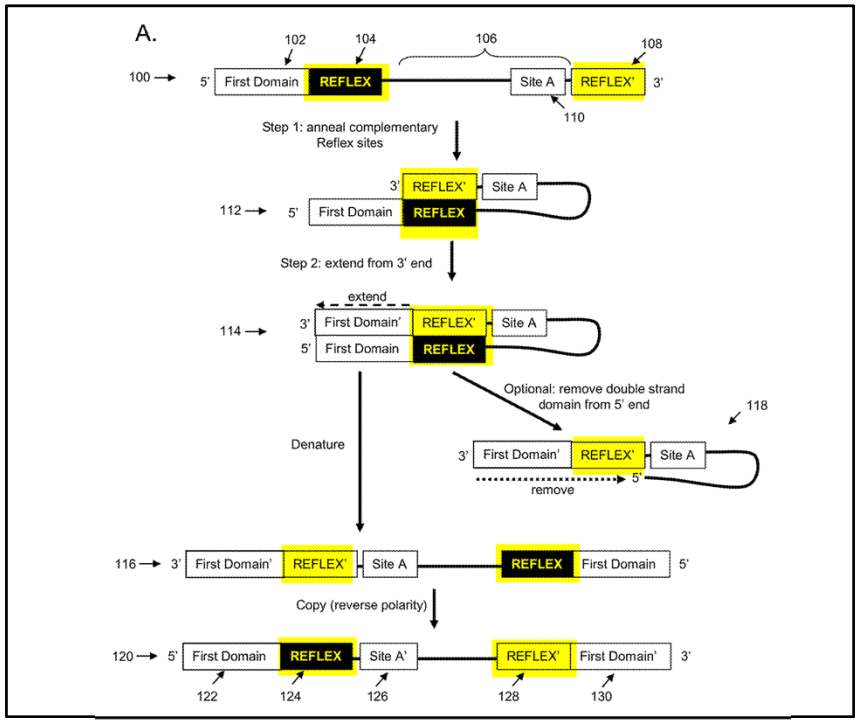
SUMMARY OF THE INVENTION

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
('013 Petition at 7)

EX1001 ('013 Patent) at 1:63-2:6

“Reflex” Method: Mentioned Over 250 Times



EX1001 (’197 Patent & ’013 Patent) at Fig. 1A

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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
('013 Petition at 8)

EX1001 ('013 Patent) at 1:38-41

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
('013 Petition at 8)

EX1001 ('013 Patent) at 15:20-29

Parse 8

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

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.

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
('013 Petition at 2)

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
('013 Petition at 12)

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.

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
('013 Petition at 13)

EX1016 (BD v. 10X MTD) at 17

PO's Position: Two Tags Was Conventional

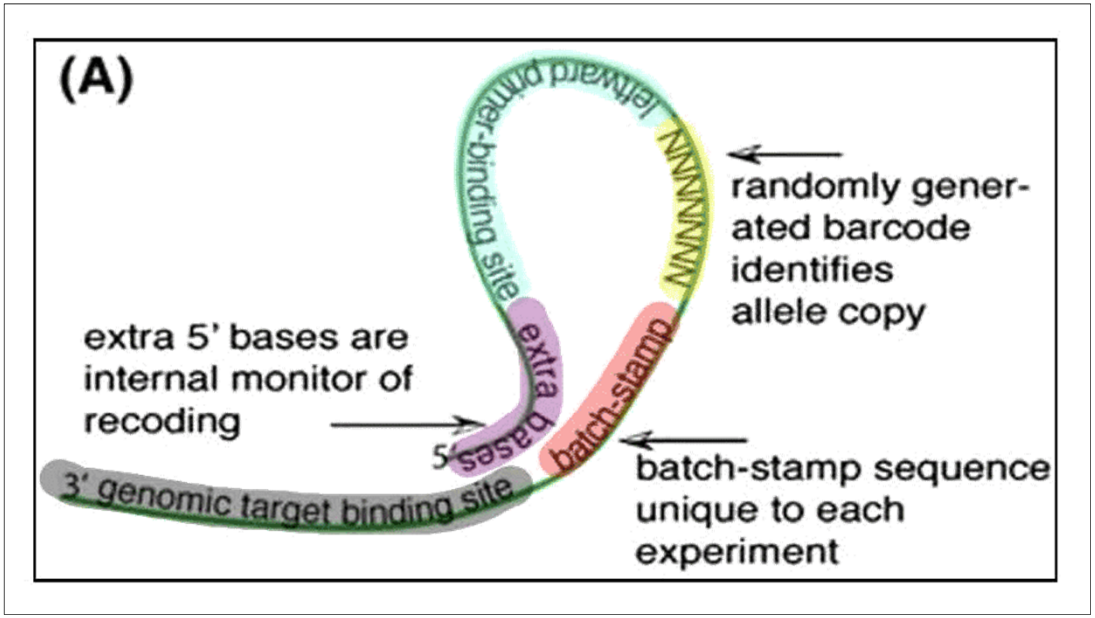
10x's Brief From Becton-Dickinson Case

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
('013 Petition at 13)

EX1016 (BD v. 10X MTD) at 11

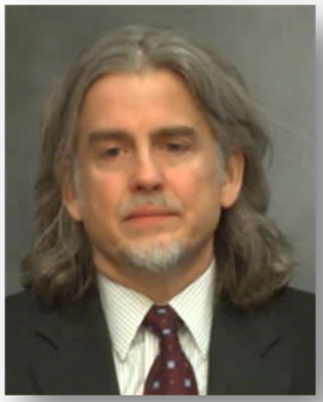
McCloskey: Teaches Dual Tagging



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 23)

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.

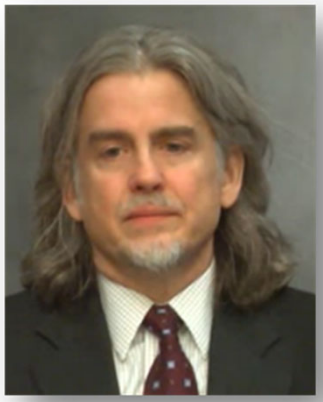
Q. And in terms of the fourth factor, objective indicia, what did you do to investigate whether there was objective indicia supporting your position?

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 15:10-25

Dr. Quackenbush: No Objective Indicia Evidence



John Quackenbush
10X's Expert

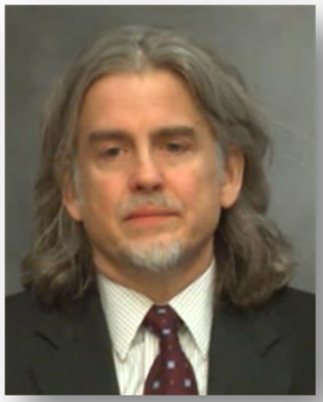
Q. What did you do to investigate whether there were objective indicia supporting your position?

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 16:8-17:3

Dr. Quackenbush: No Objective Indicia Evidence



John Quackenbush
10X's Expert

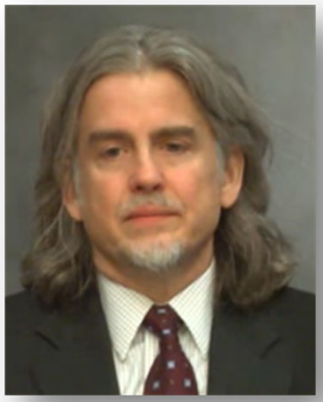
Q. Did you do anything to investigate whether there were objective indicia supporting 10x?

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 16:20-17:3

Dr. Quackenbush: No Opinion On Commercial Success

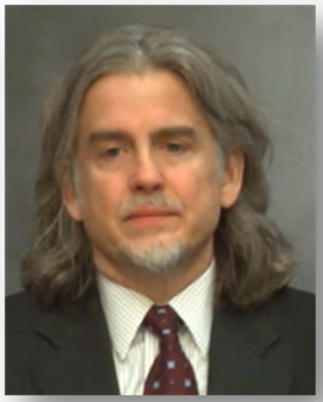


John Quackenbush
10X's Expert

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.

Dr. Quackenbush: No Opinion On Unexpected Results

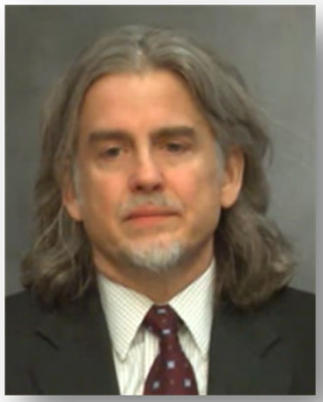


John Quackenbush
10X's Expert

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.

Dr. Quackenbush: No Opinion On Copying



John Quackenbush
10X's Expert

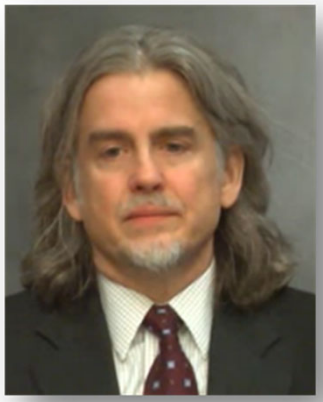
Q. Are you aware of any – can you identify any copying of the claimed inventions of the patents-in-suit?

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 21:25-22:7

Dr. Quackenbush: No Opinion On Praise

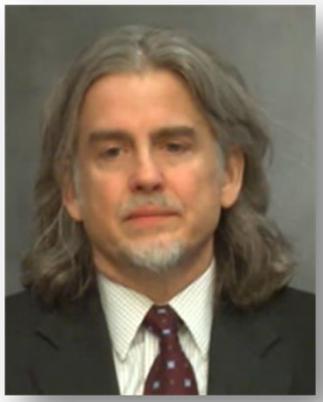


John Quackenbush
10X's Expert

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.

Dr. Quackenbush: No Opinion On Long-Felt Need

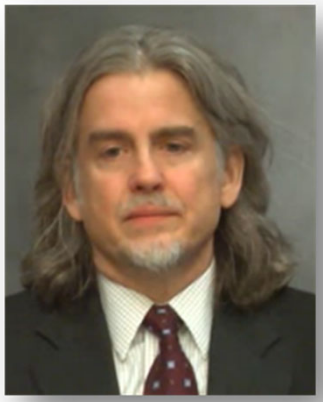


John Quackenbush
10X's Expert

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

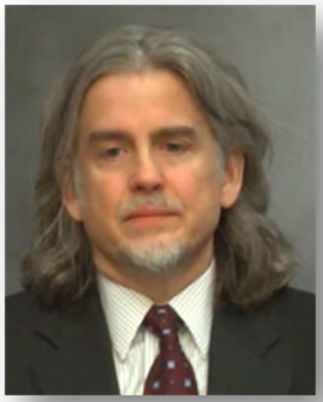
Q. Do you have an opinion here one way or the other whether there is teaching away as an objective indicia of nonobviousness?

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 29:6-13

Dr. Quackenbush: Cannot Say What Is Inventive About Alleged Inventions



John Quackenbush
10X's Expert

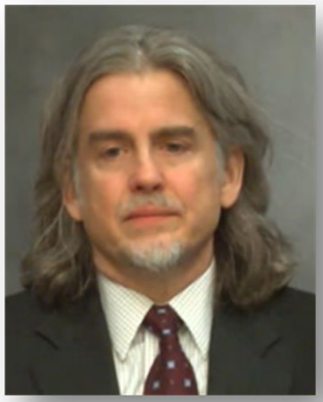
Q. Do you know what the inventive concept is of these claims, if any?

A. So I don't believe Dr. Cooper made arguments in his declarations about what the inventive concept was in these patents. And I don't believe that was something I had to respond to. So I'm not prepared to offer an opinion about that today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 3)

EX1069 (Quackenbush Depo) at 13:1-10 (objection omitted)

Dr. Quackenbush: Cannot Identify Any Challenges For Single-Cell Analysis In 2009

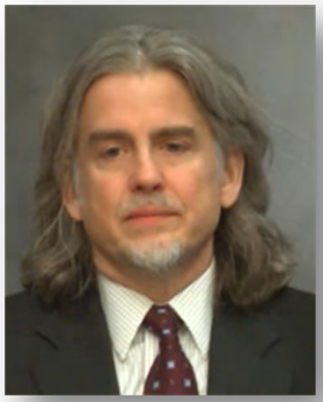


John Quackenbush
10X's Expert

Q. Were there any challenges for single-cell analysis in 2009, of which you are aware?

A. So again, it's not something I could offer an informed opinion about today. I believe if we look at the '013 and '197 patents, Dr. Brenner and his colleagues may have commented on that. I don't believe Dr. Cooper offered opinions about challenges associated with single-cell analysis. And so, that's something I'm not prepared to offer testimony about today.

Dr. Quackenbush: Cannot Say What Is Inventive About Alleged Inventions



John Quackenbush
10X's Expert

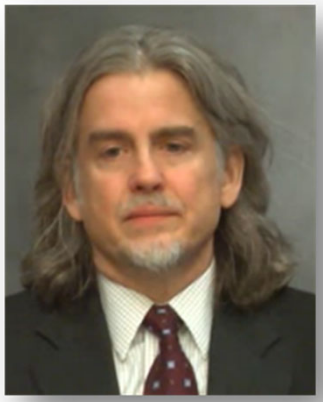
Q. But with respect to the '1 – the claims of the '013 patent or the '197 patent, can you identify what the inventive contribution is at this time, notwithstanding what Dr. Cooper's opinions, were?

A. So it's outside the scope of my reports. If you can point me to places in the reports where I've offered that opinion, I'd be happy to refresh my memory. Otherwise, I'm not really prepared to offer an opinion today.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 2)

EX1069 (Quackenbush Depo) at 14:4-15 (objection omitted)

Dr. Quackenbush: Cannot Say What Is Inventive About Alleged Inventions



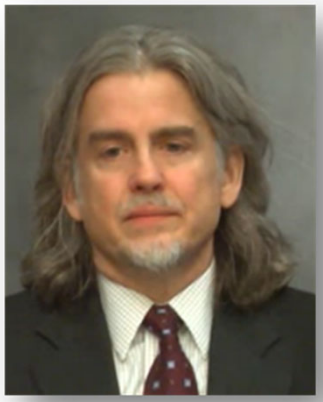
John Quackenbush
10X's Expert

Q. And for Claims 1 through 26 of the '197 patent, what do you understand to be the inventive contribution?

A. Again, Dr. Cooper, I don't believe, in the '197 or the '013 patent made arguments about the inventive concepts that were presented. So I didn't have an opportunity to respond. And my response largely dealt with his arguments about obviousness. So I'm not prepared to offer an opinion about the inventive concepts in the patent today.

EX1069 (Quackenbush Depo) at 13:16-14:3 (objection omitted)

Dr. Quackenbush: Alleged Dual Tagging Invention Was Prior Art



John Quackenbush
10X's Expert

4. Support for Two Tag Sequences

332. Further, as I describe above, the Brenner specification also incorporates various Brenner patents including the '473 Patent and the '665 Patent. These patents, in general, disclose the use of unique tags to identify the origins of a sample polynucleotide and to distinguish it from other polynucleotides from the same cell. Because the method of adding tags is a routine and conventional method, a skilled artisan would have known how to use different first tag sequences for different single cells.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 1)

EX1084 (Quackenbush Rebuttal Rpt) ¶ 332

Topics For Argument

Ground 1

- Ligation would have been obvious
- Linnarsson teaches sequencing the tagged polynucleotides
- A POSA would have been motivated to combine Linnarsson with McCloskey

Ground 2: Tag ratios and numerosity

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Topics For Argument

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Ground 2: Tag ratios and numerosity

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

’013 Patent: Claim 1

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

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

(b) performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucle-

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

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

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

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

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

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

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

(e) using the sequences determined in step (d) to count

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’013 Petition at 8)

EX1001 (’013 Patent) at Claim 1

IPR2023-0876 Decision: Ligation Was A Conventional Design Choice

Final Written Decision

B. Petitioner Articulated Adequate Reasons to Support the Proposed Modification

Patent Owner argues that "Petitioner's sole purported justification for th[e] proposed modification is the conclusory assertion that 'it would allow for added flexibility in selecting tag sequences during an experiment'." PO Resp. 50 (quoting Pet. 68). That is not accurate. Petitioner also argues that ligating a second sequence to Linnarsson's native CDS and/or TSO would have been "a simple and obvious design choice" and involve only "well-known and routine" methods. Pet. 66–7. In fact, as pointed out by Petitioner (*see* Pet. Reply 18), the '981 patent acknowledges that ligation was routine and conventional in the art, stating:

> 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.

Ex. 1001, 13:32–39 (emphasis added); *see also* Ex. 1002 ¶238 (quoting the same).

IPR2023-0876 Decision: Flexibility Would Motivate Ligation

Final Written Decision

Patent Owner argues that this rationale is unclear and conclusory. PO Resp. 50. However, we find this rationale sufficiently clear and not in need of further explanation. It is clear from the Petition that the "flexibility" is the option to add a second tag sequence later in the process and to possibly tailor its length (i.e., number of nucleotides) based on specific needs. Pet. 68 (citing Ex. 1002 ¶243). In the testimony cited by the Petition, Dr. Cooper explains:

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-0876 Decision: Flexibility Would Motivate Ligation

Final Written Decision

> What Patent Owner seems to be arguing is: why would a person of ordinary skill in the art substitute an equivalent technique or step (here, ligation) if it creates more complexity or work? The answer to that question is the flexibility that Petitioner identifies. Petitioner's identification of that benefit renders Patent Owner's reliance on *Schweickert* and *Weber* inapposite.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

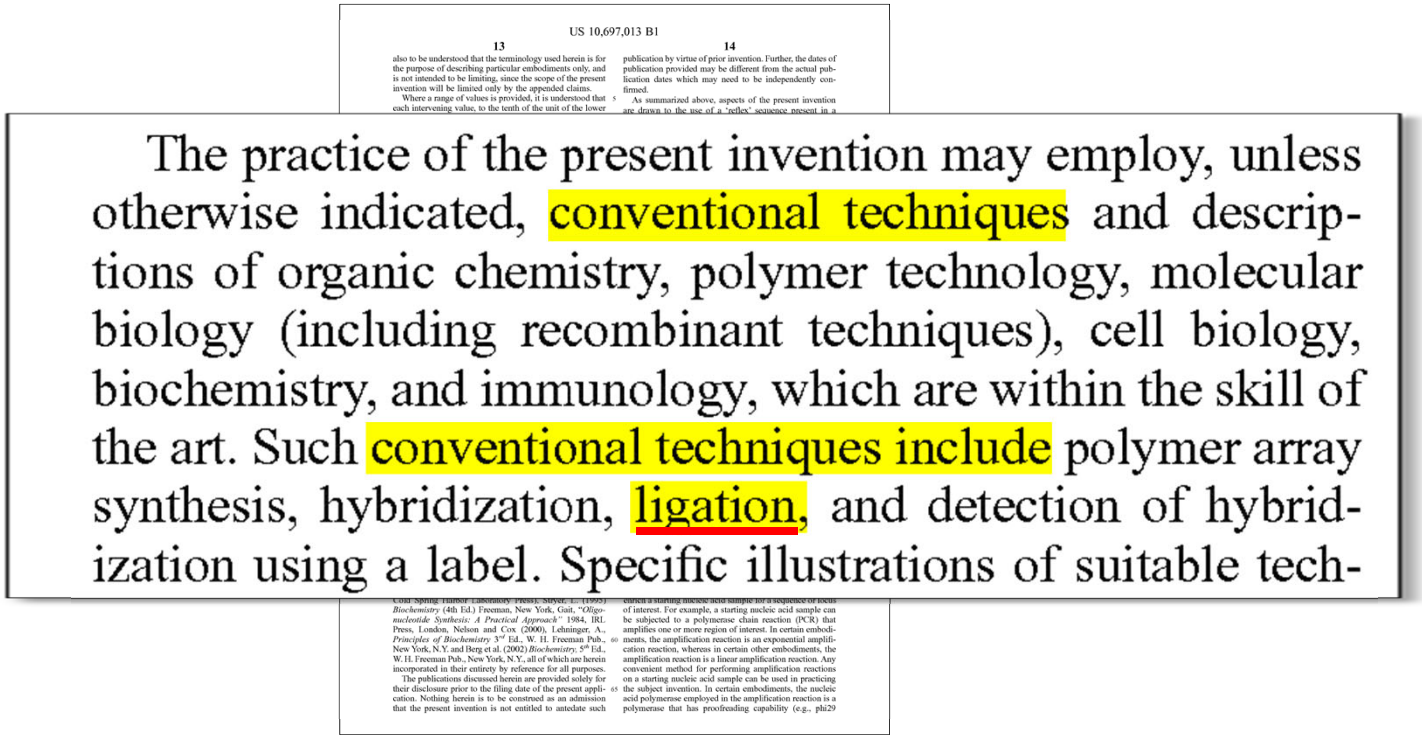
Specification: Ligation Is Prior Art

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 ('013 Patent) at 6:31-40

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 37)

Specification: Ligation Is “Conventional” Prior Art



US 10,697,013 B1

13 14

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-

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’013 Petition at 37)

EX1001 (’013 Patent) at 13:40-47

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Position: Ligation Was Conventional

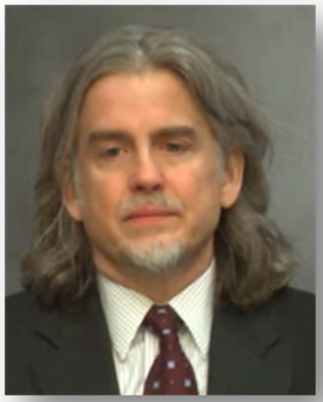
10x's Brief From Becton-Dickinson Case

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
('013 Petition at 38)

EX1017 at 1017.012

Dr. Quackenbush: Acknowledges Patent's Admission That Ligation Was Conventional



John Quackenbush

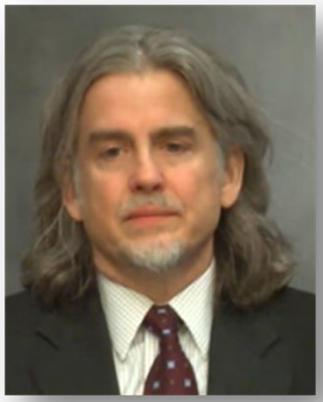
10X's Expert

327. The provisional application which is incorporated to the Brenner Patents describes how to add tag by ligation. "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".

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at at 1)

EX1084 (Quackenbush Rebuttal Rpt) ¶ 327

Dr. Quackenbush: Ligation Was Known And Conventional



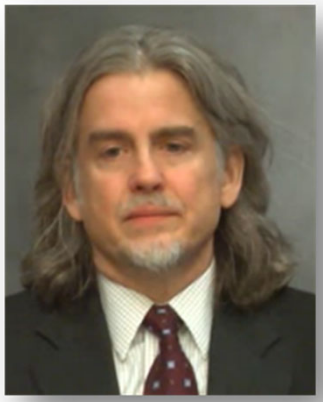
John Quackenbush
10X's Expert

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 6)

EX1071 (Quackenbush Depo) at 188:17-18

Dr. Quackenbush: Ligation Was Known And Conventional



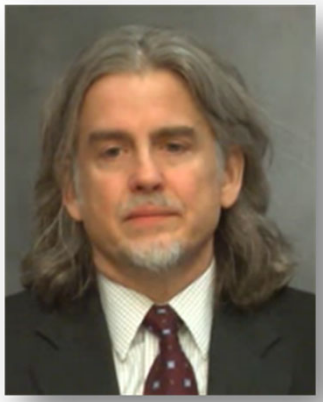
John Quackenbush
10X's Expert

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 6)

EX1071 (Quackenbush Depo) at 187:23-25

Dr. Quackenbush: Ligation Was Known And Conventional



John Quackenbush
10X's Expert

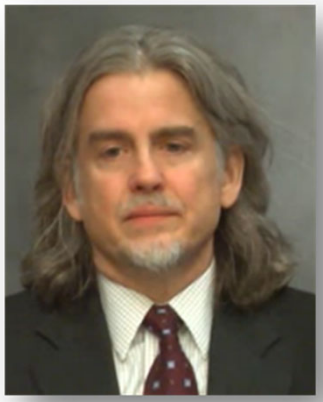
Q. As of August 2009, were you familiar with the use of ligation for polynucleotide tagging?

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
('013 Reply to POR at 6)

EX1071 (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
('013 Reply to POR at 6)

EX1071 (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).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Dr. Cooper: Ligation Offers Clear Flexibility Benefit



Gregory Cooper
Parse's Expert

149. 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
('013 Reply to POR at 8-9)

EX1002 (Cooper Decl.) ¶ 149

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Linnarsson Is Not Limited To Fragmentation And Capture

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Position: Figure 11 Is Incompatible With McCloskey

PO's Response

Once a biotin molecule is covalently bound to the end of these nucleic acids, as it is in Linnarsson, the biotin 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, ¶63. Thus, Petitioner's tag 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. EX2013, ¶63. Petitioner's CDS theory fails.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 5, 8)

PO's Response at 30-31

PO's Position: Linnarsson Is Limited To Fragmentation And Capture

PO's Sur-Reply

(a) **Linnarsson's STRT Method Consistently Discloses Fragmentation and Capture**

Petitioner again asserts, on Reply, that Linnarsson discloses sequencing the entire tagged polynucleotide, but makes the new argument (contradicting its Petition mapping) that "Linnarsson cannot possibly require fragmentation as in Figure 11," and Figs.3-4 "include neither a biotin nor a restriction enzyme cut site." Rep.17-18. But Linnarsson's fragmentation-and-capture STRT method employs ***both*** biotin and a restriction enzyme cut site (EX1003, 23:1-37:32;

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Sur-Reply at 18

Linnarsson Figure 11: Uses Biotin And Restriction Enzyme

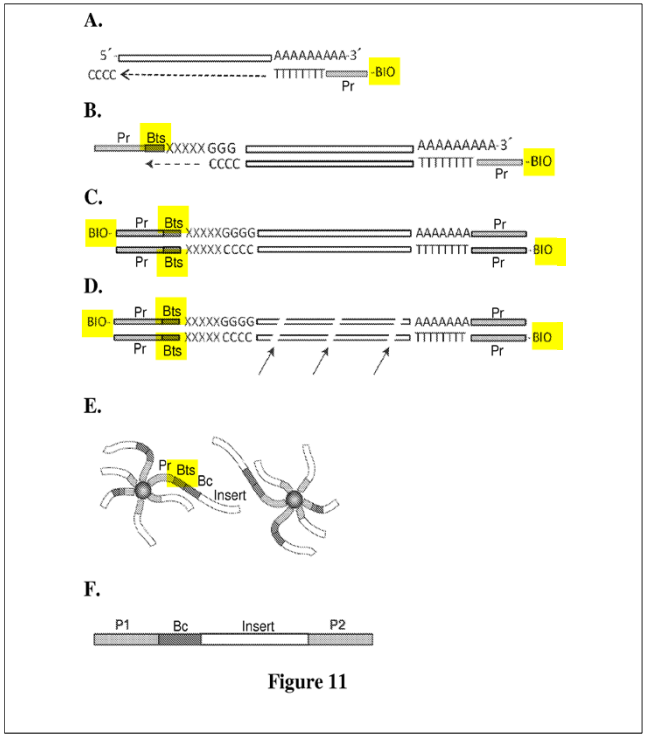


Figure 11

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),

IPR2023-0876 Decision: Biotin Not Required And The Steps Of Figure 11 Are "Optionally Used"

Final Written Decision

Patent Owner argues that Petitioner's argument that Linnarsson does not require biotin is a new and improper argument on reply. PO Sur-Reply 19. We disagree. Petitioner's argument is directly responsive to Patent Owner's argument. *See* 37 C.F.R. § 42.23(b) ("A reply may only respond to arguments raised in the corresponding opposition, patent owner preliminary response, patent owner response, or decision on institution."). Petitioner's argument is not only proper, but also persuasive; Linnarsson does not require biotin. *See* Ex. 1003, 3:25–4:2 ("Summary of the Invention" not mentioning biotin), 5:28–29 ("Figure 11 [which does include biotin], panels A-F, show graphical representation of steps *optionally used* in the STRT method." (emphasis added)), Figs. 3–4 (not including biotin).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 53-54

IPR2023-0876 Decision: POSA Would Know To Use Biotin In Non-Interfering Way

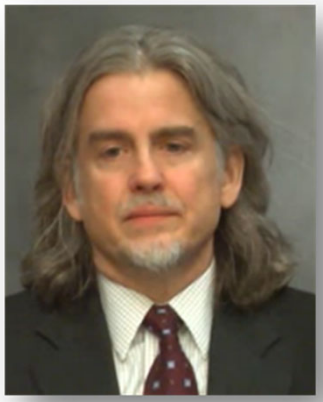
Final Written Decision

> Further, we are persuaded by Petitioner's argument that a person of ordinary skill in the art would have known how to use biotin in a manner that did not interfere with the proposed modification. Pet Reply 24 (citing Ex. 1059 ¶¶109–112); *see also KSR*, 550 U.S. at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."); Ex. 1057, 175:2–6 (Dr. Quackenbush: "So if there's already a biotin attached, you wouldn't be able to create that bond, hence, ligation wouldn't occur. And a person in 2009 would have understood this.").

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 54

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.

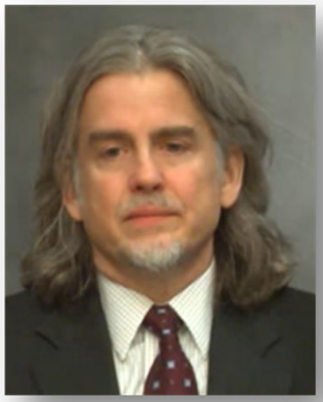
Linnarsson: Disclosure Is General

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
('013 Reply to POR at 20)

EX1003 (WO2010/117620) at 19:4-11

Dr. Quackenbush: No Explanation For Why CDS Is Tagged



John Quackenbush
10X's Expert

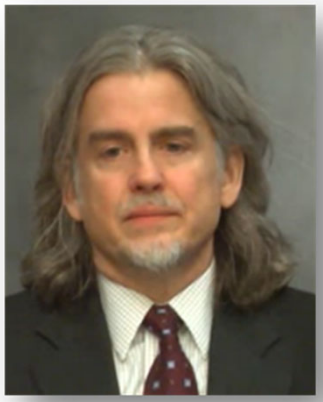
Q. So why would the CDS be tagged if it was never – if it was attached to a streptavidin and it never cut for sequencing?

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
('013 Reply to POR at 3)

EX1071 (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
('013 Reply to POR at 20)

EX1071 (Quackenbush Depo) at 152:22-153:5

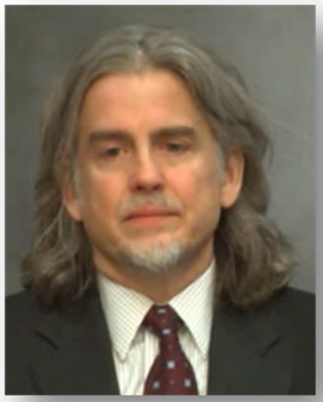
Linnarsson: Disclosure Is General

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.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 27)

EX1003 (WO2010/117620) at 3:25-4:2

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

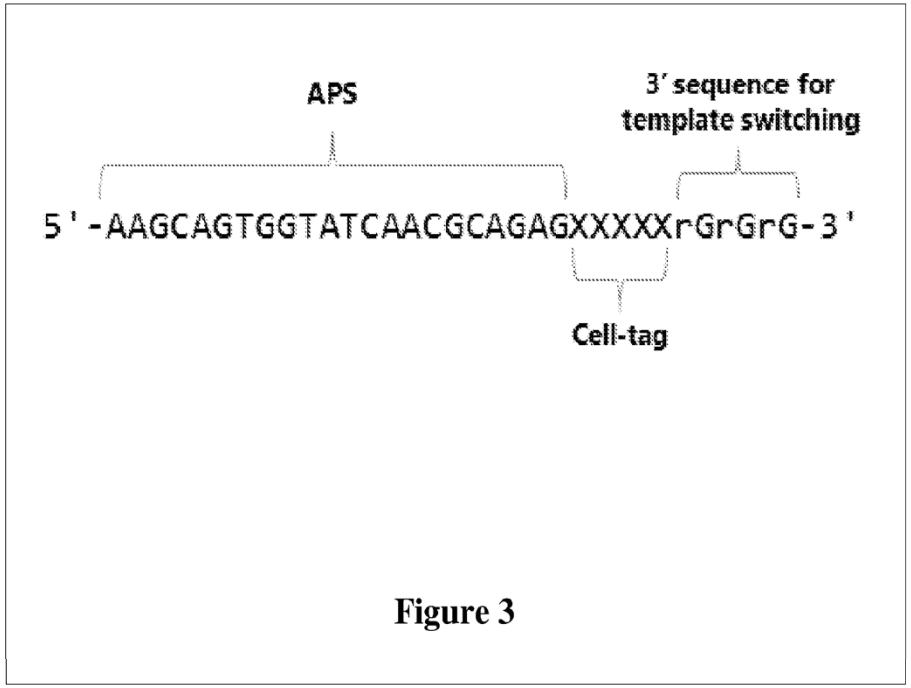


Figure 3

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

EX1003 (WO2010/117620) at Fig. 3

Linnarsson Figure 4: No Biotin Or Restriction Enzyme

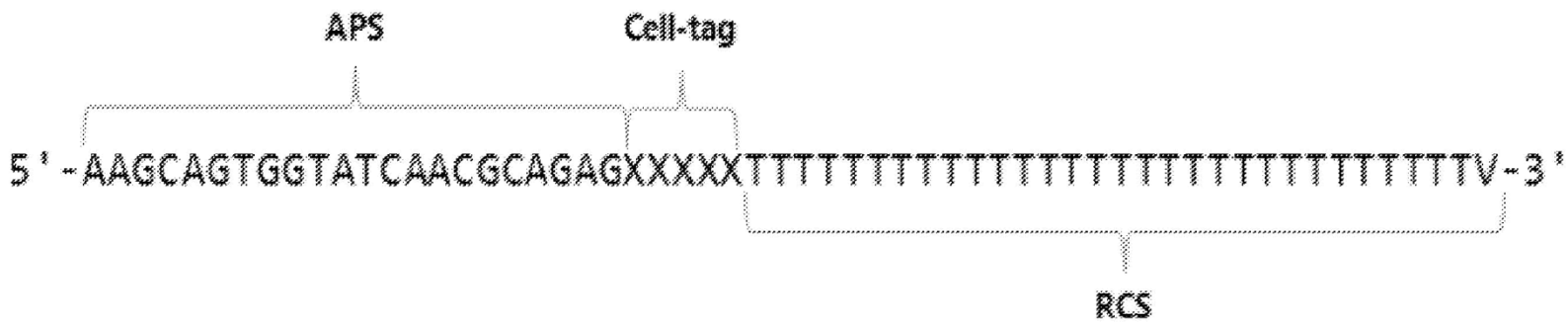


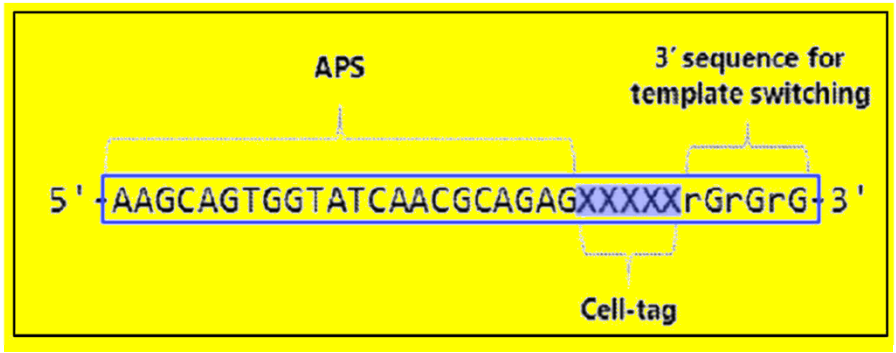
Figure 4

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 32)

EX1003 (WO2010/117620) at Fig. 4

The Petition: Repeatedly Cited Figure 3

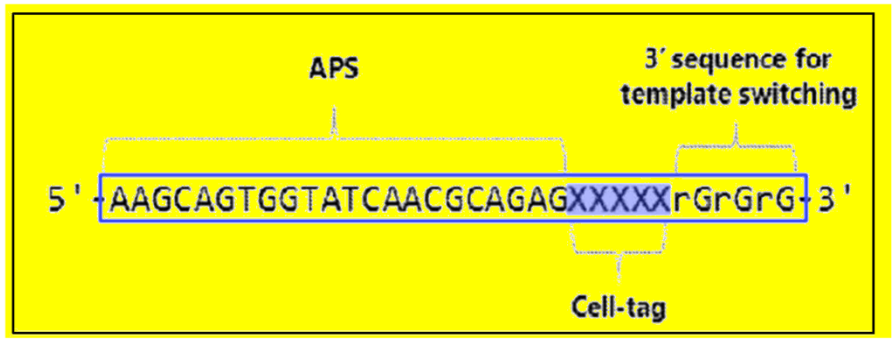
Figure 3 similarly depicts an example of a TSO (boxed in blue) with a cell-tag (highlighted in blue):



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Petition: Repeatedly Cited Figure 3

Figure 3 of Linnarsson similarly discloses a TSO (boxed in blue) comprising a cell-tag (highlighted in blue):



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Petition: Repeatedly Cited Figure 3

Figure 3 similarly depicts an example of a TSO (boxed in blue) with a cell-tag (highlighted in blue):

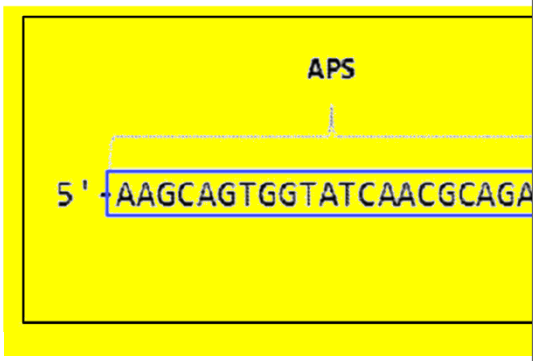
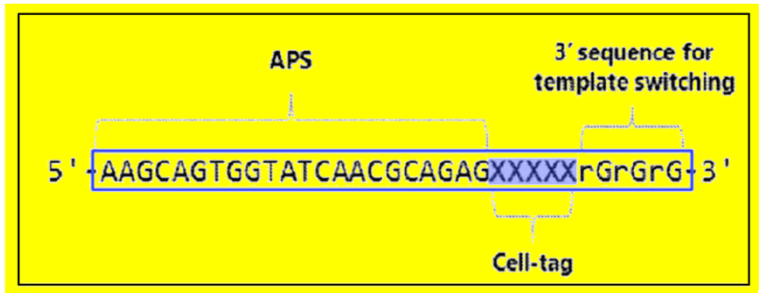


Figure 3 of Linnarsson similarly discloses a TSO (boxed in blue) comprising a cell-tag (highlighted in blue):



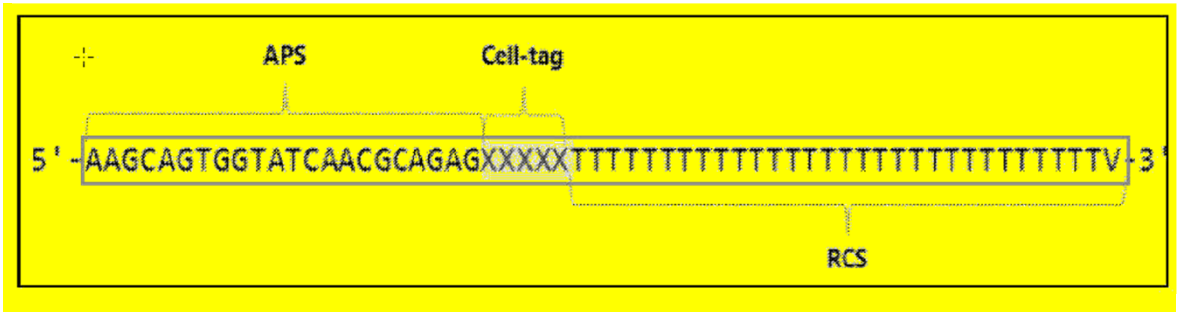
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petition at 20, 33

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The Petition: Repeatedly Cited Figure 4

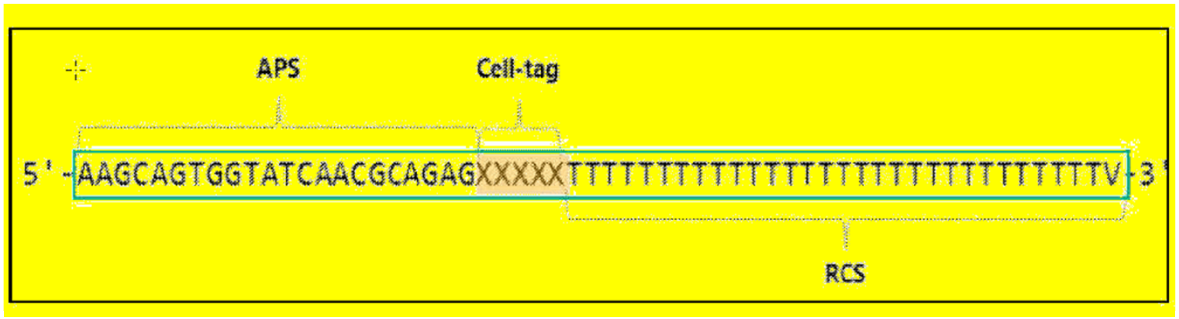
Figure 4 of Linnarsson depicts an example of a CDS (boxed in green) with a cell-tag (highlighted in yellow):



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Petition: Repeatedly Cited Figure 4

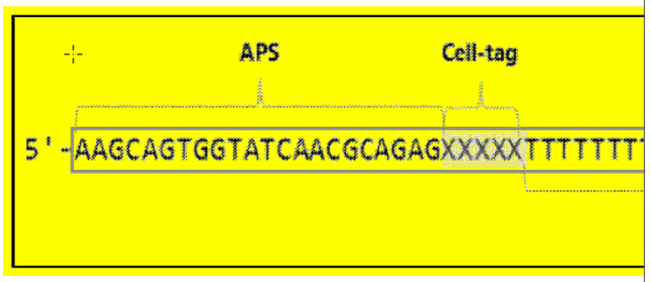
As shown in Figure 4, Linnarsson discloses that the CDS (boxed in green) comprises a cell-tag (highlighted in yellow):



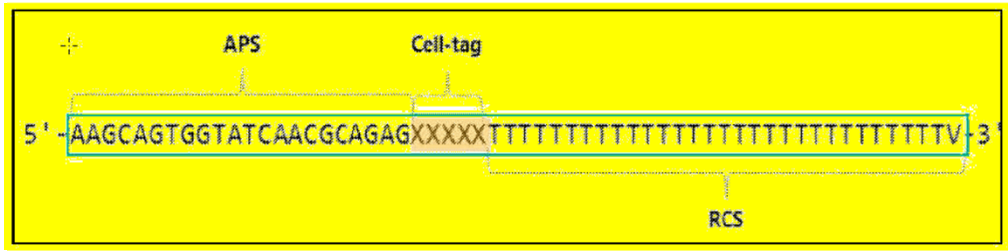
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The Petition: Repeatedly Cited Figure 4

Figure 4 of Linnarsson depicts an example of a CDS (boxed in green) with a cell-tag (highlighted in yellow):



As shown in Figure 4, Linnarsson discloses that the CDS (boxed in green) comprises a cell-tag (highlighted in yellow):



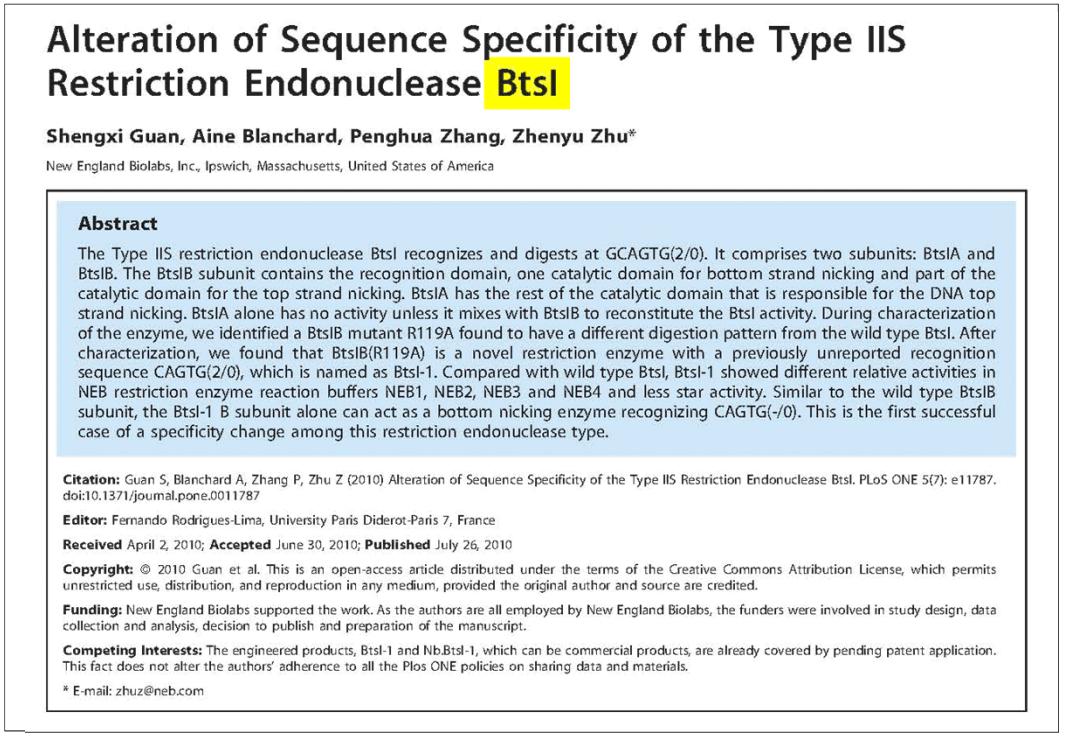
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petition at 19, 32

Figures 3 and 4 Do Not Use Restriction Enzymes

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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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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.

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DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 POR at 17)

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
('013 Petition at 32)

EX1003 (WO2010/117620) 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

EX1003 (WO2010/117620) 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

EX1003 (WO2010/117620) 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.

* * *

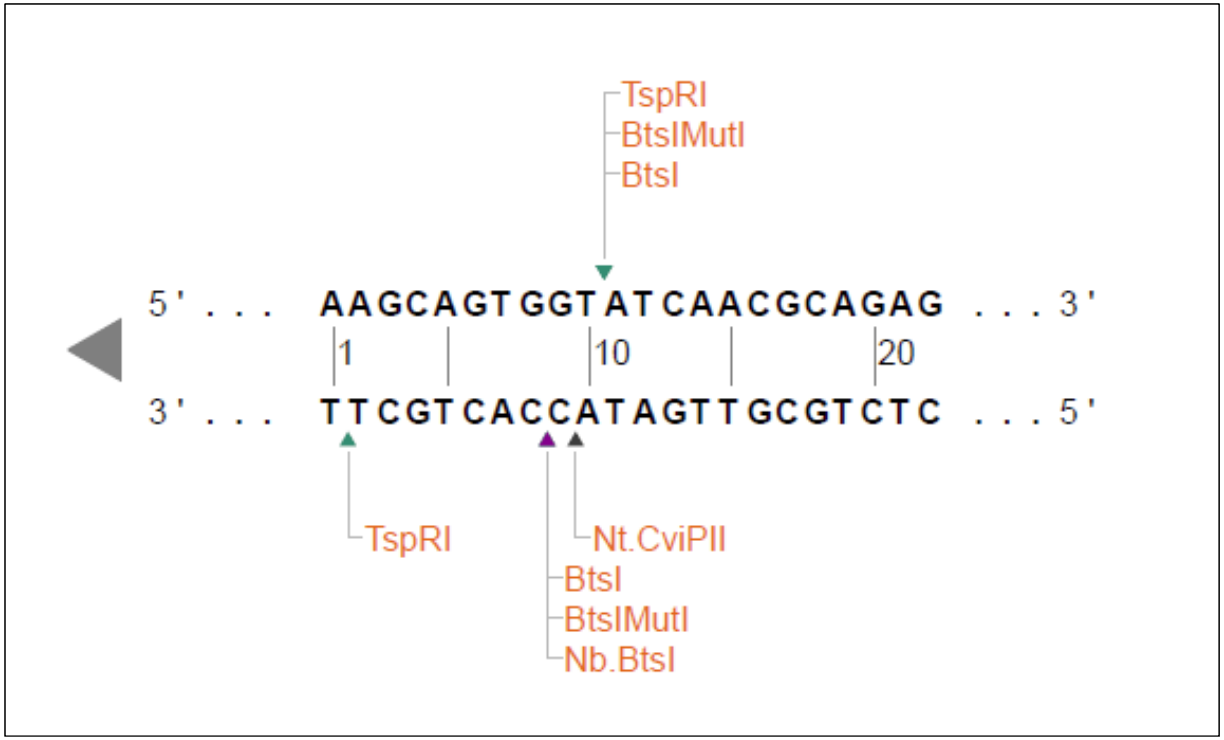
Q. So if that's a restriction enzyme cut site for BtsI, it's in both Figures 3 and 4, correct?

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

EX1081 (Cooper Depo) at 124:10-15; 124:22-125:4

Thousands Of Restriction Enzymes Exist



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply at 18 n.7)

Linnarsson's Claims Are Not Limited To Fragmentation And Capture

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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;

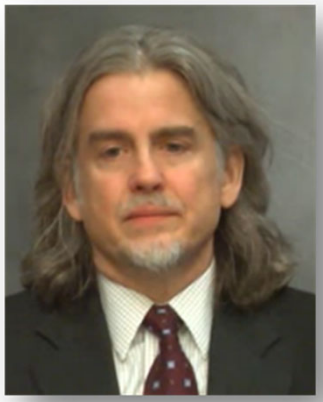
(iii) pooling the tagged cDNA samples; and

(iv) amplifying the pooled cDNA samples to generate a cDNA library comprising double-stranded cDNA.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 26)

EX1003 (WO2010/117620) 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.

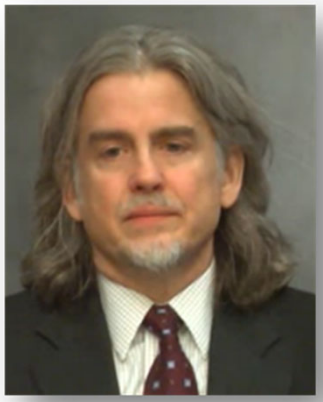
Q. Okay. But you can see in claim 1, there's no reference to fragmentation, correct; there's no fragmenting step?

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 149:24-150:15

Dr. Quackenbush: No Explanation For Claim 1



John Quackenbush
10X's Expert

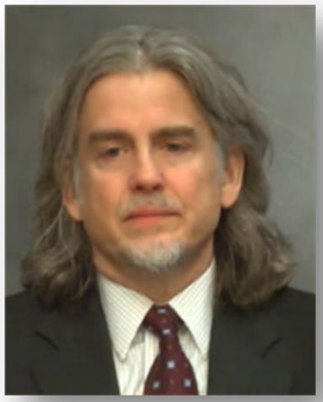
Q. In Linnarsson, the cDNA library is generated according to the method of claim 1 without any fragmentation or use of biotin, correct?

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 149:10-23

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.

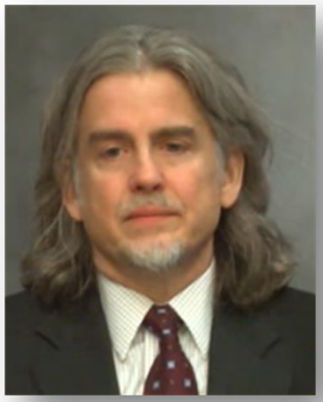
Q. All right. And you understand that the claims of the Linnarsson patent are part of the disclosure of the patent application?

A. I believe that's correct, yes.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 150:16-151:2

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?

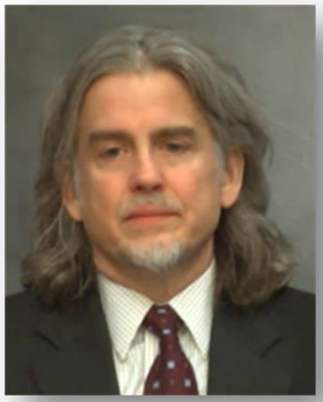
A. Again, I haven't done that analysis and I believe if Dr. Cooper felt it was important to single out claim 1, he would have done that in his declaration. And I didn't see anything in his declaration making that argument, and so I'm not in a position to render an opinion because I have nothing to respond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

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 164:15-165:1

IPR2023-0876 Decision: POSA Would Know To Use Biotin In Non-Interfering Way

Final Written Decision

> Further, we are persuaded by Petitioner's argument that a person of ordinary skill in the art would have known how to use biotin in a manner that did not interfere with the proposed modification. Pet Reply 24 (citing Ex. 1059 ¶¶109–112); *see also KSR*, 550 U.S. at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."); Ex. 1057, 175:2–6 (Dr. Quackenbush: "So if there's already a biotin attached, you wouldn't be able to create that bond, hence, ligation wouldn't occur. And a person in 2009 would have understood this.").

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 54

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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



Gregory Cooper
Parse's Expert

82. 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.

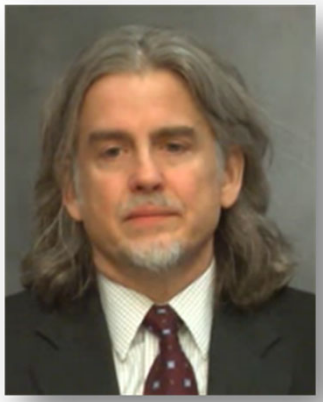
Dr. Quackenbush acknowledges that a POSA would have known that the biotin would block ligation:

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
('013 Reply to POR at 12-13)

EX1070 (Cooper Decl. ISO Petitioner's Reply) ¶ 82

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

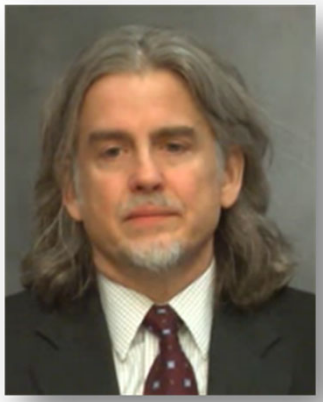


John Quackenbush
10X's Expert

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.

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



John Quackenbush
10X's Expert

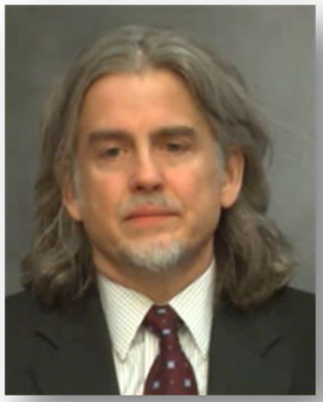
Q. We'll address that case as well. But right now I'm just asking you, would a person of skill in the art know how to adjust the process of Linnarsson, such that the tag could be ligated to the CDS before biotin is introduced to the molecule at the five prime end? Just whether it's within the scope of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

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 177:10-178:9

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



John Quackenbush
10X's Expert

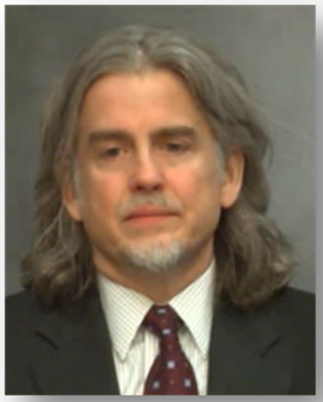
Q. Leaving aside how it would be done, do you have an opinion, sitting here now, as to whether it would be within the scope of the competency of a skilled artisan in 2009 to modify the Linnarsson process so that the tag is ligated before biotin is added?

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 178:15-179:6

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.

IPR2023-0876 Decision: Petitioner's Use Of Hug Was Not Improper

Final Written Decision

Petitioner's reliance on Hug and other references is not improper. Petitioner's Ground 2 asserts that claim 5 would have been obvious over "Linnarsson in View of McCloskey, and *Further in View of the Knowledge of a POSA*." Pet. 66 (emphasis added). Petitioner cited four references to support its argument that a person of ordinary skill in the art would have found ligating a sequence to a polynucleotide well-known and routine. Pet. 67–68 (citing Ex. 1007, 7–8; Ex. 1024, 5; Ex. 1039, 1–2, Fig. 1; Ex. 1040 ¶¶71–75, 235–239, Fig. 2); *see also* Ex. 1002 ¶¶240–243 (Dr. Cooper testifying that ligation was "well-known, conventional, and routine" in the art); Ex. 1057, 187:23–25, 188:17–8 (Dr. Quackenbush agreeing that ligation was "well-known" and "conventional" in the art).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 52

Topics For Argument

Ground 1

- Ligation would have been obvious
- Linnarsson teaches sequencing the tagged polynucleotides
- A POSA would have been motivated to combine Linnarsson with McCloskey

Ground 2: Tag ratios and numerosity

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Position: Petitioner Did Not Show That "Entirety" Of Tagged Polynucleotide Is Sequenced

PO's Response

Petitioner's own citations fail to show Linnarsson discloses sequencing the entirety of the "tagged polynucleotide" as Petitioner argues. Pet.43 (citing EX1003, 4:8-13). 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 or how much is sequenced. EX1003, 4:8-13; EX2013, ¶84. Petitioner's second and third citations confirm Linnarsson does ***not*** sequence the entirety of the "tagged polynucleotide" as Petitioner's theory requires. Petitioner's second citation explains that the "5'

Petition: Did Not Rely On Sequencing "Entire" Polynucleotides

Page 44 Of The Petition

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

'013 Petition at 44

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

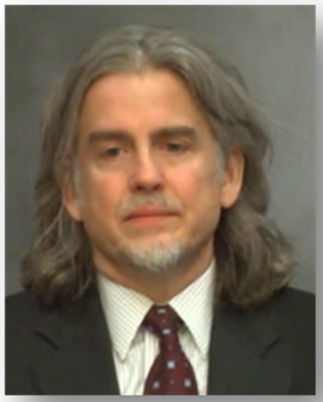
PO's Response

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

PO's Response at 43

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

> 301. 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

EX1079 (Quackenbush D. Ct Report) ¶ 301

IPR2023-0876 Decision: Patent Owner Disavowed "Entire" Tagged Polynucleotide Construction

Final Written Decision

court proceedings." Pet. Reply 3–4 (citing Ex. 1058[5]). In its Sur-Reply and at the hearing, Patent Owner explicitly disavowed any construction that would require sequencing tagged polynucleotides in their entirety. *See* PO Sur-Reply 8–9 (Patent Owner stating that its prior arguments are "[f]ar from construing the claims to require sequencing the ***entirety*** of the tagged polynucleotides." (brackets and internal quotation marks omitted)); Tr. 50:1–4 (Counsel for Patent Owner: "With respect to the scope of the claims and sequencing -- the sequencing limitation, we are not asking for construction that the claims require sequencing the entire polynucleotide. We aren't construing the claims to require that the entire polynucleotide is sequenced.").

Linnarsson's Sequencing Disclosure Is Robust

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-0876 Decision: Linnarsson's Disclosure Of Sequencing Is "Robust"

Final Written Decision

> Petitioner never argued that the "sequencing" limitation requires sequencing tagged polynucleotides in their entirety. Nor did Petitioner assert that Linnarsson sequences tagged and unfragmented cDNA molecules in their entirety. In any event, the evidence cited by Petitioner, *in its Petition*, that Linnarsson teaches "sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences," as recited in claim 1, is robust. Pet. 57 (citing Ex. 1003, 4:8–13, 19:28–32, 21:13–25). We are persuaded that Linnarsson teaches this limitation.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 30

Linnarsson: Teaches "Shotgun Sequencing" And Reassembly

The cDNA library can be sequenced by any suitable screening method. In particular, the cDNA library can be sequenced using a high-throughout screening method, such as Applied Biosystems' SOLiD sequencing technology, or Illumina's Genome Analyzer. In one aspect of the invention, the cDNA library can be shotgun sequenced. The number of reads can be at least 10,000, at least 1 million, at least 10 million, at least 100 million, or at least 1000 million. In another aspect, the number of reads can be from 10,000 to 100,000, or alternatively from 100,000 to 1 million, or alternatively from 1 million to 10 million, or alternatively from 10 million to 100 million, or alternatively from 100 million to 1000 million. A "read" is a length of continuous nucleic acid sequence obtained by a sequencing reaction.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 19)

EX1003 (WO2010/117620) at 22:5-13

Linnarsson: Teaches "Shotgun Sequencing" And Reassembly

"Shotgun sequencing" refers to a method used to sequence very large amount of DNA (such as the entire genome). In this method, the DNA to be sequenced is first shredded into smaller fragments which can be sequenced individually. The sequences of these fragments are then reassembled into their original order based on their overlapping sequences, thus yielding a complete sequence. "Shredding" of the DNA can be done using a number of difference techniques including restriction enzyme digestion or mechanical shearing. Overlapping sequences are typically aligned by a computer suitably programmed. Methods and programs for shotgun sequencing a cDNA library are well know in the art.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 19)

EX1003 (WO2010/117620) at 22:14-21

Dr. Cooper: Further Explains "Shotgun Sequencing"



Gregory Cooper
Parse's Expert

100. A POSA would understand that although these are short read platforms wherein the sample preparation would involve fragmenting the tagged polynucleotides prior to sequencing,[4] the full complement of fragments originating from the original tagged polynucleotides may nonetheless be subjected to sequencing (although this is not necessarily required in Linnarsson either). As Linnarsson explains, the workflow for sequencing these fragments of DNA may first involve amplification to obtain sufficient material for sequencing, and the sequencing process may then yield millions upon millions of sequence reads from the fragments of amplified DNA that are input to the sequencing process. *See* EX1003 at 21:13-25; 22:5-13; EX1002 ¶ 186.

EX1070 (Cooper Decl.) ¶ 100

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 19)

Dr. Cooper: Further Explains "Shotgun Sequencing"



Gregory Cooper
Parse's Expert

101. POSAs were well-aware at the time that algorithmic methods could then be used to reassemble the millions of DNA sequence reads into longer stretches of sequence information corresponding to the entire original tagged DNA fragments. Linnarsson, in fact, mentions precisely this, describing the method of "shotgun sequencing," and explaining that "the DNA to be sequenced is first shredded into smaller fragments which can be sequenced individually. The sequences of these fragments are then reassembled into their original order based on their overlapping sequences, thus yielding a complete sequence." EX1003 at 22:15-18; *see also* 22:19-21 ("Overlapping sequences are typically aligned by a computer suitably programmed. Methods and programs for shotgun sequencing a cDNA library are well know in the art.")

EX1070 (Cooper Decl.) ¶ 101

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 19)

Dr. Cooper: Further Explains "Shotgun Sequencing"



Gregory Cooper
Parse's Expert

102. This, in fact, was a typical workflow that was used long before the '013 patent, as reflected in the Shendure article that I cited in my original declaration. EX1046. As Shendure explains, the next generation sequencing platforms that were available prior to the filing of the '013 patent accomplished library preparation by "random fragmentation." *See* EX1046.002. The sequence read data from the individual fragments are then assembled into longer sequences using an assembly algorithm. As Shendure explains, "[s]everal assembly tools have recently been adapted or independently developed for generating assemblies from short, unpaired sequencing reads." EX1046.008; *see also id.* at Table 3 (listing several assembly tools for short-read sequencing).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 19)

EX1070 (Cooper Decl.) ¶ 102

PO's Position: Sequencing Was "Known And Conventional"

10x's Brief From Becton-Dickinson Case

> Claim 1 of the 808 and 502 patents additionally claim "sequencing" steps. The Fodor patents similarly admit that sequencing was known and conventional. 358 patent at 2:31-34 ("Tagging approaches have also been used in combination with next-generation sequencing methods."); 2:45-47 ("many analytical methods have been developed to measure the relative abundance of different molecules through sampling (e.g., microarrays and sequencing)"); 20:31-33 ("Microarray and sequencing technologies are commonly used to obtain relative abundance of multiple targets in a sample."); 13:1-5 (use of Digital PCR to quantify sequencing libraries).

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

EX1016 (BD v. 10X MTD) at 20

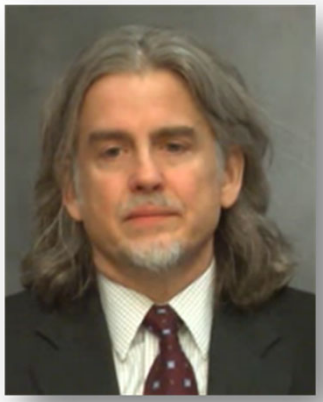
’197 Patent: Roche 454 Provided Read Length Of 400 Nucleotides

region is too long to sequence in a single reaction. For example, sequencing a polynucleotide region that is 2 kilobases or more in length using Roche 454 (Branford, Conn.) technology, in which the length of a single sequencing run is about 400 bases. In this scenario, we can design a set of

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’013 Reply to POR at 15 n.6)

EX1001 (‘013 Patent) at 17:4-15

Dr. Quackenbush: 300 Nucleotide Read Lengths Widely Available In 2009



John Quackenbush
10X's Expert

Dr. Quackenbush's District Court Report

97. After the tagged polynucleotides are amplified, they are sequenced. The details of sequencing technology are beyond the scope of this report, but the process is now more or less routine and widely available. As discussed above, sequencers, however, remain limited in the length of the individual polynucleotides that can be sequenced in one "run." The most widely used sequencing instruments today (and in 2009) are generally limited to around 300 nucleotides from one end of a polynucleotide template.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 15 n.6)

EX1079 (Quackenbush D. Ct Report) ¶ 97

Topics For Argument

Ground 1

- Ligation would have been obvious
- Linnarsson teaches sequencing the tagged polynucleotides
- A POSA would have been motivated to combine Linnarsson with McCloskey

Ground 2: Tag ratios and numerosity

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

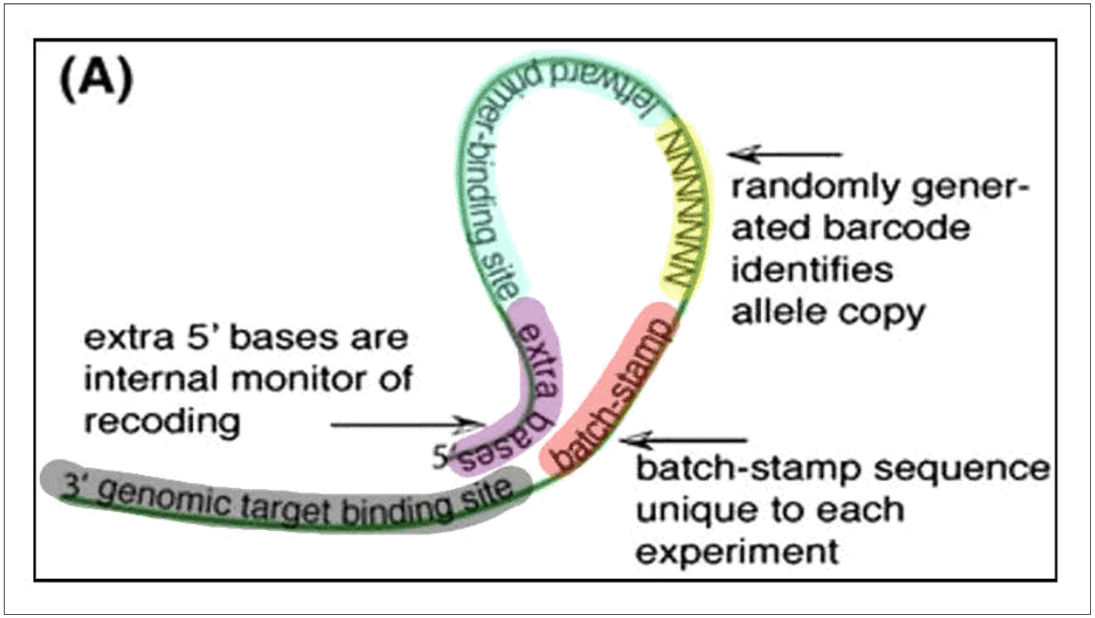
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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
('013 Petition at 21)

McCloskey: Teaches Dual Tagging



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 23)

EX1004 (McCloskey et al.) at Fig. 1A

IPR2023-0876 Decision: McCloskey Teaches MID With Two Tag Sequences

Final Written Decision

to McCloskey. Pet. 50. Petitioner persuasively argues that McCloskey teaches a MID with two tag sequences. *See* Pet. 51 ("As shown [in Ex. 1004, Fig. 1A], McCloskey's encoding oligonucleotide comprises two tag sequences: (1) a 'batch-stamp' sequence . . . to identify the experimental batch or genomic source (e.g., a single cell) and (2) a 'barcode' . . . to distinguish polynucleotide sequences "arising from different cell or allele copies."). As noted by Petitioner, in McCloskey, "the batch-stamp, unique to each experiment, specifies the DNA source such as the patient or sample identification, and the date of reaction" and "the random barcode distinguishes among sequences arising from different cell or allele copies." Pet. 51 (quoting Ex. 1004, 2).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 25-26

IPR2023-0876 Decision: McCloskey Teaches Single Cell Analysis

Final Written Decision

First, Patent Owner's factual premise regarding McCloskey is incorrect. Nothing in McCloskey precludes a "sample" from being a single cell. In fact, as Petitioner notes in its Reply, McCloskey teaches that its methods can be used for "single cell" analyses. Pet. Reply 9–10; Ex. 1004, 7 ("We recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs for forensic, clinical, single cell, and ancient DNA analyses.").

Second, and more importantly, Petitioner does not rely on McCloskey for teaching a cell-specific tag. Petitioner cites Linnarsson for that feature, and Linnarsson does teach it. Pet. 47–49; *see, e.g.*, Ex. 1003, Fig. 3 (labeling "Cell-tag"), 19:9–10 ("the tag can be used to identify which single cell from each cDNA sample originated").

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-0876 Decision: Avoid Amplification Bias Would Have Motivated Modification

Final Written Decision

> In sum, we find Petitioner's rationale that a skilled artisan would have made the proposed combination to solve the problem of amplification bias persuasive.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 40

IPR2023-0876 Decision: Modification Was Obvious Design Choice

Final Written Decision

Here, Petitioner argues that "using a MID comprising a second tag to distinguish sample polynucleotides derived from the same single cell [in Linnarsson] would have been an obvious design choice" in view of McCloskey's teaching and the fact that both references relate to tagging and amplifying polynucleotides for genetic analysis. Pet. 52 (citing Ex. 1002 ¶¶187, 192). Indeed, Linnarsson teaches the use of an encoding oligonucleotide with one tag sequence for correlating tagged polynucleotides according to one feature (cell origin), and McCloskey teaches the use of an encoding oligonucleotide with two tag sequences for correlating tagged polynucleotides according to two features (sample origin and polynucleotide). Ex. 1003, 4; Ex. 1004, 2.

Patent Owner does not show that the proposed modification would have been beyond the level of skill in the art. Nor does Patent Owner show that the modification would have resulted in anything beyond what would have been predicted based on these prior art teachings. In fact, the Patent Owner Response does not even address Petitioner's design choice rationale. PO Resp. 33–40.

We find Petitioner's unrebutted rationale of obvious design choice persuasive.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 34

Avoiding Amplification Bias Would Have Motivated Linnarsson/McCloskey Combination

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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
('013 Petition at 25)

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
('013 Petition at 25)

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
('013 Petition at 26)

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



Gregory Cooper
Parse's Expert

171. Second, a POSA would have been motivated to combine Linnarsson's method of tagging polynucleotides with McCloskey's encoding oligonucleotide comprising two tag sequences because McCloskey teaches a solution to a well-known 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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 36)

EX1002 (Cooper Decl.) ¶ 171

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



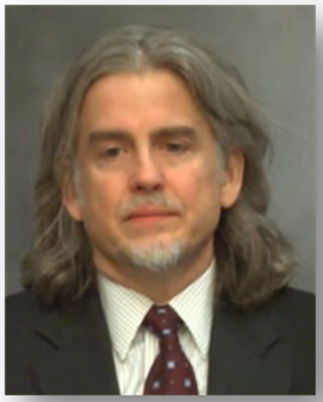
Gregory Cooper
Parse's Expert

174. 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.

EX1002 (Cooper Decl.) ¶ 174

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 37)

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 173:22-174:6

Linnarsson and McCloskey Are Compatible

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, as it is in Linnarsson, the biotin 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, ¶63. Thus, Petitioner's tag 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. EX2013, ¶63. Petitioner's CDS theory fails.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 5, 8)

PO's Response at 30-31

Parse 135

IPR2023-0876 Decision: POSA Would Know To Use Biotin In Non-Interfering Way

Final Written Decision

> Further, we are persuaded by Petitioner's argument that a person of ordinary skill in the art would have known how to use biotin in a manner that did not interfere with the proposed modification. Pet Reply 24 (citing Ex. 1059 ¶¶109–112); *see also KSR*, 550 U.S. at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."); Ex. 1057, 175:2–6 (Dr. Quackenbush: "So if there's already a biotin attached, you wouldn't be able to create that bond, hence, ligation wouldn't occur. And a person in 2009 would have understood this.").

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 54

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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



Gregory Cooper
Parse's Expert

82. 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 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
('013 Reply to POR at 12, 13)

EX1070 (Cooper Decl. ISO Petitioner's Reply) ¶ 82

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



Gregory Cooper
Parse's Expert

83. 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. I explain this during my deposition. *See* EX2020 at 15:20-16:5 ("Q. How is cleanup performed using STRT without biotin? A. Well, I think that presupposed that you have to do a cleanup, and I think there are embodiments where you wouldn't and/or you would – you know, these are things that are standard molecular biology techniques that would be within the scope of a person of skill in the art."); *id.* at 19:19-21:13 ("If you have a set of primers that are very specific and amplify very cleanly, there might be little to no benefit to doing the biotin … It's certainly one could imagine doing [solid sequencing without cleanup], and certainly texts say that cleanup could be done without biotin streptavidin conjugation."). Dr. Quackenbush's assertions to the contrary require that POSAs lack even basic skill in the art.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 12, 13)

EX1070 (Cooper Decl.) ¶ 83

McCloskey Has Enough Barcodes

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Position: McCloskey Does Not Have Enough Barcodes

PO's Response

[26] In Petitions on patents related to '013, Petitioner stated that McCloskey's 7-nucleotide barcode was to be combined with Linnarsson. EX2021, ¶¶39-43 (citing EX2022, ¶168); Pet.39-43 (citing EX2022, ¶168). Petitioner has not made that same argument here, and it is too late for Petitioner to do so now. But, even if Petitioner's 7-nucleotide barcode theory were applied here, Petitioner's Ground 1 also fails because a barcode of that length would not provide enough unique tags to satisfy Petitioner's argued-for motivation. EX2013, ¶¶87-94. And Petitioner has entirely failed to address this issue in its Ground 1 arguments despite recognizing it as an issue in Ground 2.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Response at 49 n.26

IPR2023-0876 Decision: POSA Would Know To Use Biotin In Non-Interfering Way

Final Written Decision

iii. McCloskey is not Limited to 16,384 Unique Barcodes

Petitioner argues that McCloskey's disclosure is not limited to 16,384 barcodes. Pet. Reply 13. Petitioner is correct, as McCloskey states the following:

> *Barcode*
>
> 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.

Ex. 1004, 4. Not only is McCloskey not limited to 16,384 possible barcodes, it teaches precisely how to manipulate that number as needed. *Id.* In fact, McCloskey's authors/researchers stress that using seven nucleotides is what they "currently use." *Id.*

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-00876 Final Written Decision at 39

’013 Patent, Claim 1: Requires Tagging Sample Polynucleotides

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

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

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

otides;

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

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

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

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
(’013 Petition at 8)

EX1001 (’013 Patent) at Claim 1

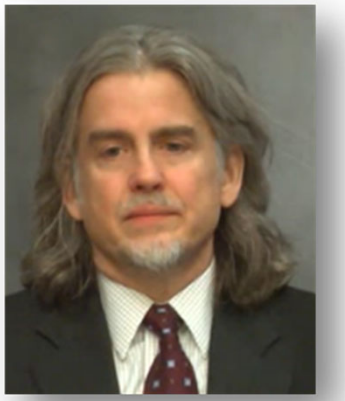
PO's District Court Position: Not All Molecules In A Cell Must Be Tagged

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
('013 Reply to POR at 24)

PO's Argument: Based On Mammalian Cells



John Quackenbush
10X's Expert

91. In contrast to McCloskey's analysis of alleles, Linnarsson is focused on analyzing gene expression by measuring and identifying the mRNA present in a cell. EX1004, Abstract. Persons of skill would expect anywhere from 50,000 – 300,000 mRNA molecules to be present in the typical mammalian cell addressed by Dr. Cooper. EX1054, Abstract; EX1002, ¶257. McCloskey's barcodes, which are intended to distinguish between a small set of *alleles* (one to two per cell), would be insufficient to distinguish among each of the vast number of *mRNA* molecules present in such a mammalian (or other eukaryotic) cell. EX1054, Abstract; EX1002, ¶256. If Dr. Cooper's assertion that 100 unique tags would be needed for every

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

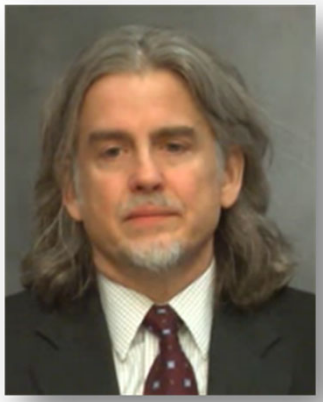
EX. 2013 ¶ 91

IPR2023-0876 Decision: Linnarsson Is Not Limited To Mammalian Cells

Final Written Decision

> Linnarsson is not limited to mammalian cells. Nor is the Petition's reliance on Linnarsson limited to mammalian cells.

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 130:7-13

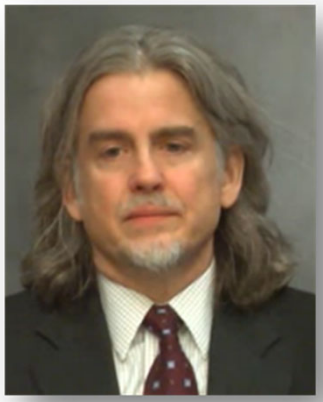
Linnarsson: Not Limited Mammalian Cells

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
('013 Petition at 22)

EX1003 (WO2010/117620) at 13:14-16

Dr. Quackenbush: Linnarsson Could Be Applied To Yeast Cells



John Quackenbush
10X's Expert

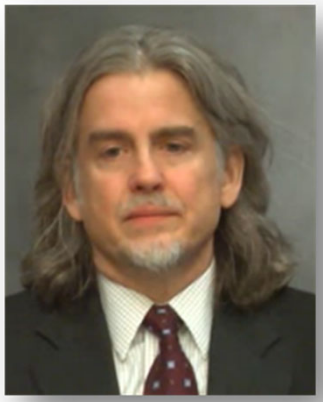
Q. In terms of Linnarsson, is it your understanding that Linnarsson can only be used with mammalian sources?

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 130:14-131:7

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 131:8-21

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



Gregory Cooper
Parse's Expert

134. Just like Linnarsson, the '013 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 14:24-30; *see also id.* at 15:3-5 ("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. EX1074.001. Furthermore, there are even simpler bacteria such as *Carsonella ruddii* that have only 182 genes and will thus have even fewer mRNA molecules. *See* EX1075.001. The total number of

EX1070 (Cooper Decl. ISO Petitioner's Reply) at ¶ 134

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 23)

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
('013 Reply to POR at 23)

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

EX1081 (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

EX1081 (Cooper Depo) at 65:8-14, 69:21-70:2

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
('013 Petition at 49)

Dr. Cooper: McCloskey's Disclosure Is General



Gregory Cooper
Parse's Expert

131. 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
('013 Reply to POR at 25)

EX1070 (Cooper Decl. ISO Petitioner's Reply) ¶ 131

Dr. Cooper: Using More Nucleotides Would Have Been Obvious



Gregory Cooper
Parse's Expert

132. In fact, the McCloskey patent application US200700264[5] (McCloskey II), 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.

EX1055 ¶ 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 my original declaration. *See* EX1002 ¶¶ 256-57.

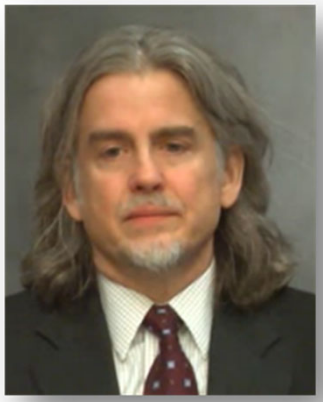
EX1070 (Cooper Decl. ISO Petitioner's Reply) ¶ 132

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 25)

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

McCloskey, Petitioner's Ground 1 secondary reference (EX1004), is a less detailed version of "US20070020640" to McCloskey *et al.* ("McCloskey II") (EX1055), Petitioner's other secondary reference. ***McCloskey II was also asserted by the Office, substantively considered, and then overcome*** in the applications leading to '013. *See, e.g.*, EX2002, 335-336, 372-373. Petitioner either

Dr. Quackenbush: No Idea How Long Labels Were In 2009



John Quackenbush

10X's Expert

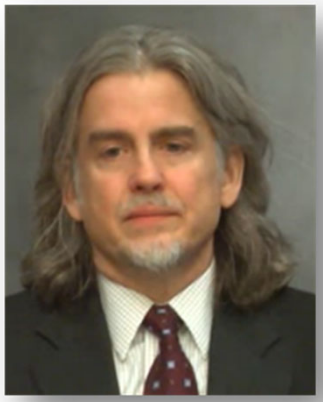
Q. No. My question to you was just a historical fact. In the 2009 time period, what were the range of lengths of labels that were commonly used by persons of ordinary skill in the art? If you know.

A. It would depend on the context. And it's not a number that I researched, because Dr. Cooper doesn't present arguments about a range of labels.

Q. Do you know if it's more or less than 50 bases?

A. The length would depend on the context and it's not something I'm prepared to testify about today.

Dr. Quackenbush: No Understanding Of Factors That Impact Tag Length



John Quackenbush
10X's Expert

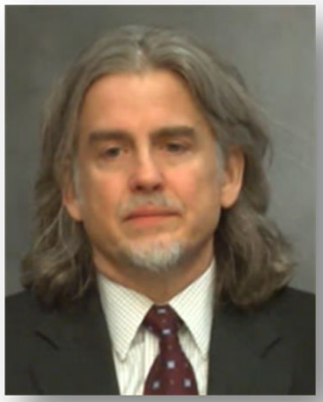
Q. What are the factors that go into the length of a label?

A. I'm not prepared to offer a fulsome testimony today because that's not something that I needed to consider in responding to Dr. Cooper's arguments.

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

EX1069 (Quackenbush Depo) at 63:21-64:1

Dr. Quackenbush: No Understanding Of Factors That Impact Tag Length



John Quackenbush
10X's Expert

Q. And just based on your knowledge as an expert in this matter, what are the different factors that a person of ordinary skill in the art would have considered in 2009 on that?

A. So sitting here this moment, I don't believe I could fully detail those.

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

EX1069 (Quackenbush Depo) at 64:12-18 (objection omitted)

Topics For Argument

Ground 1

- Ligation would have been obvious
- Linnarsson teaches sequencing the tagged polynucleotides
- A POSA would have been motivated to combine Linnarsson with McCloskey

Ground 2: Tag ratios and numerosity

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Position: Petitioner Presents Redundant Motivation

PO's Response

Petitioner's motivation to combine for Ground 1 is based on its assertion that the sample polynucleotides in Ground 1—all mRNA molecules in Linnarsson's sample—are tagged with a tag that distinguishes individual molecules in the sample (*i.e.*, each is uniquely tagged), and that this unique tagging solves the alleged amplification bias issue in Linnarsson. *See* Pet.35-36 (Linnarsson could be modified to incorporate "McCloskey's molecule tag to distinguish individual molecules within a sample because this approach addresses the amplification bias issue set forth in Linnarsson."), 45 ("As discussed above in Sections IX.A.1.d-e and g-h, the combination of Linnarsson and McCloskey discloses and renders obvious using a first tag to identify the single-cell origin of tagged polynucleotides, and using a second tag to uniquely identify each tagged polynucleotide."); EX1002, ¶¶75, 87, 173; EX2021, 44-45 ("POSA would have understood that [Linnarsson's] method was designed to be applied to substantially all mRNA molecules of a given cell"); EX2022, ¶¶91, 222. Petitioner *repeats this motivation as its motivation in Ground 2.* Pet.60 ("POSA would have been motivated to tag

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

PO's Response at 50

The Petitioner: Presented Distinct Motivation

The Petition

1. **Claim 13: The method of claim 1, wherein at least 90 percent of said plurality of tagged polynucleotides have a second tag sequence that is different from second tag sequences of the other tagged polynucleotides.**

First, a POSA would have been motivated to tag each sample polynucleotide with a unique second tag sequence. As explained above, the combination of Linnarsson and McCloskey discloses a second tag sequence used for counting and distinguishing sample polynucleotides originating from the same single-cell. *See supra* Sections IX.A.1.f, h. A POSA would have understood that increasing the number of polynucleotides tagged with a unique second tag sequence increases the accuracy of counting, and would have thus been motivated to ensure that each polynucleotides is tagged with a unique second tag sequence. EX1002 ¶ 255.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

’013 Petition at 60

Parse 164

Topics For Argument

Ground 1

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Ground 2: Tag ratios and numerosity

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-0876 Decision: McCloskey Is Prior Art

Final Written Decision

Despite the exclusion of the second Hall-Ellis declaration, there is ample evidence in the record demonstrating that McCloskey is a prior art printed publication. McCloskey itself states: "Received: 31 January 2007 / Accepted: 29 May 2007 / Published online: 23 October 2007." Ex. 1004, 1. McCloskey additionally states that it was published in a 2007 print issue of "Biochem Genet," with Petitioner adding that the full name of the journal is BIOCHEMICAL GENETICS and that McCloskey was published in a December 2007 volume of the journal. *Id.*; Pet. 29. McCloskey also includes a copyright notice by "Springer Science+Business Media, LLC" with a date of date of 2007. Ex. 1004, 1. Patent Owner argues that this is unreliable hearsay that should be excluded. PO Mot. To Exclude 4 (citing *Neste Oil Oyj v. REG Synthetic Fuels, LLC*, No. IPR2013-00578, Paper 53 at 5–7 (Mar. 12, 2015); *Standard Innovation Corp. v. Lelo, Inc.*, No. IPR2014-00148, Paper 42[3] at 13–18, 21–22 (Apr. 23, 2015)). We are not persuaded by Patent Owner's argument or its reliance on these cases. The facts before us are different.

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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PARSE EX.1004.001

Encoding PCR Products with Batch-stamps and Barcodes

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EX1004 (McCloskey et al.) at 1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 22)

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 20. The Petition, however, states that McCloskey was published online in October 2007 and is hence prior art under § 102(a) and (b). Petition at 22. Patent Owner never disputes this publication date, which appears on the face of McCloskey. EX1004.001. Nonetheless, supplied here is the non-hearsay testimony from Sylvia Hall-Ellis, further confirming McCloskey's public availability and prior art status.[4] *See* EX1085 ¶¶ 44-45, 50. As described by Dr. Hall-Ellis, the exact McCloskey article relied upon in the Petition was publicly available via multiple sources, including print and digital formats, prior to the priority date of the '013 patent. *Id.* ¶¶ 43-50. This submission is allowed on reply. *See, e.g.*, *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 15 (P.T.A.B. Dec. 20, 2019) (precedential).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petitioner's Resp to PO's Resp at 4-5

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
('013 Reply to POR at 4)

EX1085 (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).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

McCloskey: Published In 2007



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

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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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PARSE EX.1004.001

Encoding PCR Products with Batch-stamps and Barcodes

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EX1004 (McCloskey et al.) at 1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 22)

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Topics For Argument

Ground 1

- Ligation would have been obvious
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- A POSA would have been motivated to combine Linnarsson with McCloskey

Ground 2: Tag ratios and numerosity

Whether McCloskey is prior art

Whether Linnarsson and McCloskey are analogous art

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

IPR2023-0876 Decision: Linnarsson and McCloskey Are Analogous Art

Final Written Decision

We find that both references are analogous art to the '981 patent, as there is ample supporting evidence in the record, including that to which the Reply cites (citations identified in the immediately preceding paragraph). Indeed, Patent Owner does not dispute the merits of either argument. PO Sur-Reply 27–28. Rather, Patent Owner, argues that we "should not now permit Petitioner to rewrite its clearly-deficient Petition." *Id.* at 28.

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
('013 Petition at 8)

EX1001 ('013 Patent) at Abstract

Claims: Recite Using Tags For Single Cell Analysis

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

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

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

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

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

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

EX1001 ('013 Patent) at Claim 1

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 23, 27-28)

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
('013 Reply to POR at 27)

EX1003 (WO2010/117620) at Abstract

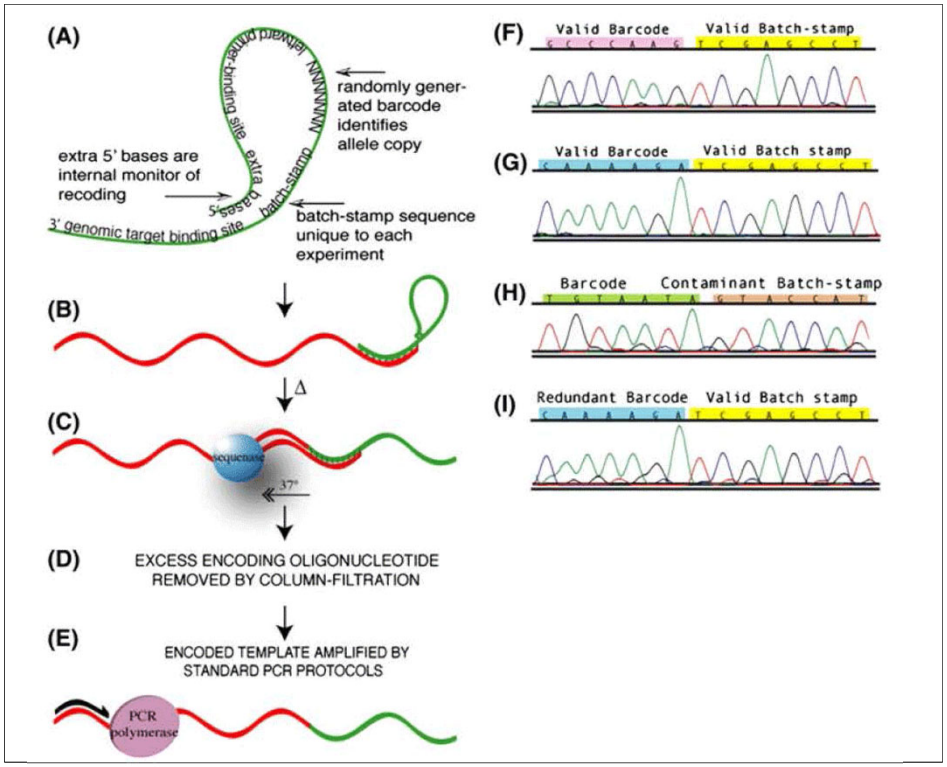
Linnarsson: Directed To Single-Cell Tagging

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 (WO2010/117620) at 10:15-30

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Reply to POR at 27)

McCloskey: Directed To Dual Tagging



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
('013 Petition at 23, 26, 35)

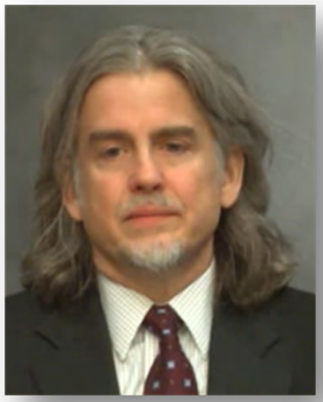
EX1004 (McCloskey et al.) at 3, Fig. 1

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
('013 Petition at 26)

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
('013 Reply to POR at 3)

EX1071 (Quackenbush Depo) at 92:6-13

Thank you.