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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

- - - - - x
PARSE BIOSCIENCES INC., : Case Nos. IPR2023-00955
Petitioner, : and IPR2023-00958
v. : U.S. Patent Nos.
10X GENOMICS, INC., : 10,240,197 and
Patent Owner. : 10,697,013
- - - - - X

Deposition of GREGORY COOPER, Ph.D.
Conducted Virtually
Tuesday, September 3, 2024
10:07 a.m. EDT

Job No.: 551594
Pages 1 - 79
Reported by: Debra A. Whitehead

1 Deposition of GREGORY COOPER, Ph.D., conducted
2 virtually.

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4
5 Pursuant to notice, before Debra Ann Whitehead,
6 E-Notary Public in and for the Commonwealth of
7 Virginia.

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1 A P P E A R A N C E S C O N T I N U E D

2 ALSO PRESENT:

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C O N T E N T S

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1 P R O C E E D I N G S

2 GREGORY COOPER, Ph.D.,

3 having been duly sworn, testified as follows:

4 EXAMINATION BY COUNSEL FOR PATENT OWNER

5 BY MS. RAYMOND:

6 Q Good morning, Dr. Cooper.

7 A Good morning.

8 Q Is it your understanding that you're here
9 to testify today about your reply declarations in
10 IPR2023-00955 regarding the '197 patent and
11 IPR2023-00958 regarding the '013 patent?

12 A Yes.

13 Q Okay. And for the record, those have
14 previously been marked as Exhibit 1070 in the
15 corresponding cases.

16 (Parse Exhibit 1070, previously marked,
17 not attached.)

18 A 1070?

19 Q 1070, yes.

20 A Oh, there it is, yeah.

21 Q And today I am going to be asking you
22 questions about both declarations. But if you

1 have a response that's specific to one or the
2 other, if you could please let me know. And if
3 I'm asking you specifically about one case or the
4 other, I'll let you know that as well.

5 Is that okay?

6 A Yes.

7 Q With respect to the two patents we're
8 talking about today, is it your understanding that
9 there is an implicit limitation that you have to
10 be able to identify the sample polynucleotide
11 sequence when you sequence it?

12 MR. WALTER: Objection. Vague.

13 A I'm not sure I understand the question.

14 Q Okay. Both patents have a sequencing
15 step. Correct?

16 A Correct.

17 Q And when you sequence, is it your
18 position that the claims have an implicit
19 limitation that you have to be able to identify
20 the sample polynucleotide sequence when you do
21 that sequencing step?

22 MR. WALTER: Same objection.

1 A So, yeah, I'm not -- I guess if you're
2 focusing on a particular claim element, I'm happy
3 to talk about that.

4 There is a sequencing step and there is
5 using a first tag and a second tag and sequencing
6 a sample sequence, but don't know -- I'm not sure
7 I follow the nature of the question, whether there
8 is an implicit requirement. It has a number of
9 explicit elements.

10 MS. RAYMOND: Okay. If we could please
11 then pull up what has now been marked as -- I'm
12 trying to get the exhibit number. Exhibit 2101.

13 (10x Genomics Exhibit 2101, previously
14 marked, not attached.)

15 Q Dr. Cooper, do you have access to that?
16 Can you find that? And maybe we can drop it in
17 the chat as well.

18 A This is a deposition transcript?

19 Q That's right. This is a deposition
20 transcript of your deposition May 2nd, 2024, in
21 IPR2023-00876.

22 A Okay. On the '981?

1 Q Correct.

2 A Yes, I see it.

3 Q Could you please turn to Page 15 of that
4 transcript.

5 A Using the page numbers at the top?

6 Q Yes. Correct.

7 A Yes. Okay.

8 Q And do you see a question there starting
9 around Line 7, "In your opinion, how much of the
10 tagged polynucleotide needs to be sequenced to
11 meet this claim limitation?"

12 A Yes, I see that.

13 Q And is that talking about the sequencing
14 claim limitation?

15 Do you agree with me on that?

16 A Yes, it looks like Claim 1g, yeah.

17 Q And then in your answer you say, So I
18 suppose there is -- or excuse me. "So I suppose
19 there's an implicit limitation there that you have
20 to be able to identify the sequence," and then you
21 go on.

22 Do you see that?

1 A Yes.

2 Q Do you agree with your testimony there?

3 A Yes. I think the context of this
4 question was whether there was some sort of
5 minimum threshold. And I don't -- I think it's
6 clear that the patent doesn't actually say what --
7 you know, the claims don't say it has to be X
8 number of bases or X percentage.

9 But you certainly have to use the sample
10 sequence, just like you use the first and second
11 tag. So yes, I would agree with that.

12 Q And I apologize, we're going to be
13 skipping around a bunch today.

14 But with respect to the Linnarsson
15 reference, you recall testifying about the
16 Linnarsson reference. Correct?

17 A Yes.

18 Q Okay. Do you agree that in Linnarsson
19 the mRNA is indiscriminately released from each
20 single cell?

21 A I don't know that that's true for all
22 possible ways that one might do it. But I think

1 there are many -- certainly part of Linnarsson has
2 disclosures where you just crack open the cell and
3 collect all the mRNA indiscriminately, yes.

4 Q Do you agree that Linnarsson's method
5 begins with releasing mRNA from each single cell
6 to provide a plurality of mRNA samples?

7 A Well, I suppose it depends on "begin."
8 But you would need to obtain a sample first. But
9 certainly extracting polynucleotides is a part of
10 at least some of the disclosures of Linnarsson.

11 Q Do you agree that a POSA would understand
12 that because the mRNA is indiscriminately released
13 from each single cell and because Linnarsson does
14 not describe any additional elimination or
15 filtration, the released mRNA sample comprises
16 substantially all mRNA molecules of said cell?

17 A I think that is certainly true about some
18 disclosures. But I think we've gone over this
19 before, about Linnarsson does talk about other
20 techniques to target; for example, designing the
21 RNA complementary sequence to be specific to one
22 or more sample mRNAs.

1 And I also don't think there's
2 necessarily a requirement that one has to do it
3 indiscriminately. If there were some other method
4 for extracting polynucleotides, I think you could
5 make that work with the Linnarsson disclosure.

6 But certainly some of the disclosure in
7 Linnarsson encompasses cracking open the cell and
8 indiscriminately collecting, you know, the RNA
9 that comes out.

10 Q And you recall in your -- in performing
11 your analysis regarding Linnarsson, you relied on
12 both Figures 2 and Figures 11.

13 Do you recall that?

14 A I believe so. Among other figures, yes.

15 Q Okay. And in both Figures 2 and Figure
16 11 you relied on the poly-A tail functionality as
17 part of generating the tag cDNA. Correct?

18 A I wouldn't say I relied only on the
19 poly-A tail. That is, you know, Linnarsson
20 describes the poly-A tail and the oligo(dT) primer
21 as an exemplary RNA complementary sequence. It's
22 not the only one, but it is certainly one of the

1 examples that Linnarsson articulates and defines
2 in their figures.

3 Q And it's an example you relied on.

4 Correct?

5 A Correct. Among other portions of text
6 and figures, yes.

7 Q And with respect to the reverse
8 transcription in Linnarsson, do you agree that the
9 CDS is an important part of that process?

10 MR. WALTER: Objection. Vague.

11 A So the CDS has -- Linnarsson describes
12 the CDS as at least one mechanism to apply tags to
13 the RNAs. It's not the only way. It talks about
14 tags on the TSO as well. So it -- you know,
15 Linnarsson has a process that includes a CDS and a
16 TSO that are both part of reverse transcription
17 and can be used in different ways, depending on
18 the experimental design.

19 Q Does Linnarsson describe any way of
20 initiating the reverse transcription process other
21 than using a CDS?

22 A I don't believe so. I think this is the

1 primary mechanism, that CDS includes an RNA
2 complementary sequence which is used to prime the
3 initial reverse transcription.

4 Q And does Linnarsson describe any way of
5 continuing the reverse transcription process,
6 other than using a TSO?

7 A I don't believe so, no; but I could be
8 wrong. But I think that's correct.

9 Q And you agree that for a -- bacteria are
10 prokaryotic. Correct?

11 A I'm sorry. Can you say that again?

12 Q You agree that bacteria are prokaryotic.
13 Correct?

14 A Yes.

15 Q And do you agree that to the extent
16 prokaryotic organisms have a poly-A tail, it's
17 used in a different way or has different
18 functionality than a poly-A tail in eukaryotic
19 organisms?

20 A So I think there are examples of poly-A
21 tails being added in prokaryotes. And I'm
22 guessing, like all other biological questions, the

1 answer to that is complicated. They're probably
2 used in a variety of ways.

3 Certainly at a high level poly-A tail
4 usage is different in bacteria or prokaryotes than
5 compared to eukaryotic cells. But they could
6 serve similar functions in some organisms and some
7 contexts.

8 And so I'm not sure about the full scope
9 of the mechanisms that poly-A tails contribute to,
10 but there are certainly differences between
11 bacteria and eukaryotes, yes.

12 Q Could we please turn to Page 64 of
13 Exhibit 2101. This is your May deposition.

14 MR. WALTER: I'm sorry. Where is that in
15 the -- is that in the files that were provided?

16 MS. RAYMOND: I believe so.

17 THE WITNESS: It's in the 955 bucket, the
18 link that I downloaded.

19 MR. WALTER: Hold on one moment.

20 MS. RAYMOND: Sure.

21 (A discussion was held off the record.)

22 BY MS. RAYMOND:

1 Q Dr. Cooper, if you could please turn to
2 Page 64. That's the page at the top of this
3 exhibit that we're looking at, your May 2024
4 transcript.

5 A Yes.

6 Q And at the bottom you were asked a
7 question, "Do you agree that only eukaryotic
8 organisms ordinarily have mRNA with a poly-A
9 tail?"

10 Do you see that?

11 A Yes.

12 Q And you answered, "I don't think that's
13 true. I think there are evidence of
14 polyadenylation in some prokaryotic organisms. I
15 don't think it's used in quite the same way or has
16 the same -- same mess -- same functionality," and
17 then you go on.

18 Do you see that?

19 A Yes.

20 Q Do you still agree with that statement?

21 A Yes.

22 Q Okay. Dr. Cooper and Counsel as well,

1 are you able to find Exhibit 2103 in the folder
2 link that was sent to you? It has not yet been
3 used in this case.

4 (10x Genomics Exhibit 2103, previously
5 marked, not attached.)

6 MR. WALTER: Yes, I have it.

7 A Yes.

8 Q Dr. Cooper, do you see that this is an
9 article from the journal Cell?

10 A Yes, I see that.

11 Q And you were asked about this at your May
12 2024 deposition.

13 Do you recall that?

14 A Not specifically, but it's certainly
15 possible.

16 Q Is Cell a reputable journal?

17 A Yes.

18 Q And if you could go to the page in this
19 article with the number in the lower left corner
20 2728, and it's Table 1 in the article.

21 Do you see that?

22 A I do.

1 Q And the fifth row down on the left it
2 says, "Lack of polyadenylated mRNA."

3 Do you see that?

4 A I do see that.

5 Q And in the text on the middle of that
6 row, the first sentence is, "Many
7 eukaryotic-focusing scRNA-seq approaches rely on
8 poly(T) primers to capture polyadenylated mRNAs.
9 However, mRNA polyadenylation is absent in
10 prokaryotic mRNAs except in transcripts bound for
11 degradation."

12 Do you see that?

13 A I do see that.

14 Q And do you agree that mRNA
15 polyadenylation is absent in prokaryotic mRNAs
16 except in transcripts bound for degradation?

17 A No. I'd have to do more work on that. I
18 don't -- I think that's a fairly strong statement.
19 And so it's -- it's sort of not clear to me that
20 that is a hard-and-fast rule and that there aren't
21 other uses of poly-A tails in prokaryotes.

22 So that seems like an aggressive

1 statement to me that I would have to do more work
2 on.

3 Q Do you have any reason to doubt whether
4 the statement in the article in Cell is true?

5 A I mean, generally absolutist kind of
6 statements in biology are things that I shy away
7 from. If you are making a hard-and-fast assertion
8 that something can't be true or is exclusive or,
9 you know, only, I think that's often a statement
10 that can be difficult to back up. Biology is full
11 of exceptions.

12 So, you know, so yeah, I think that is
13 probably more aggressive than would be my
14 understanding.

15 Q And could you see if you can find Exhibit
16 2102 in the folder.

17 (10X Genomics Exhibit 2102, previously
18 marked, not attached.)

19 A Yes, I have it.

20 Q And that's a publication of BMC Genomics.
21 Do you agree?

22 A Yes.

1 Q Have you seen this exhibit before?

2 A I don't know. It's possible.

3 Q Is it familiar from your last deposition,
4 the May -- excuse me, the May 2024 deposition in
5 the other IPR?

6 A It may be.

7 Q In your experience is BMC Genomics a
8 reputable publication?

9 A Yes.

10 Q I am going to call your attention to a
11 sequence -- or a sentence in the abstract on the
12 first page. There's a heading that says,
13 Background.

14 A I see that.

15 Q And then there's a second sentence that
16 says, "However, unlike eukaryotic cells, mRNA
17 sequencing of bacterial samples is more
18 challenging due to the absence of a poly-A tail,
19 but typically enables efficient capturing and
20 enrichment of mRNA from the abundant rRNA
21 molecules in a cell."

22 Do you see that?

1 A I do see that.

2 Q And then calling your attention to the
3 last paragraph on the same first page. The second
4 sentence says, "First, unlike in eukaryotes,
5 bacterial mRNA does not contain a poly-A tail at
6 the 3 prime end that can be used to easily enrich
7 for those molecules during reverse transcription."

8 Do you see that?

9 A I see that.

10 Q Okay. Were you -- do you agree with
11 these statements?

12 A No. Again, I think these are overly
13 assertive on what bacteria do or do not do. And,
14 I mean, we -- we know just from the previous
15 citation that you showed there are poly-A tails on
16 some bacterial RNAs, in that author's opinion
17 that's ones bound for degradation. So we know
18 that statement isn't true. There are, in fact,
19 examples of polyadenylated RNAs in bacteria.

20 So, no. It's -- again, this is one of
21 those statements that asserts a degree of evidence
22 and proof that really isn't there. And it

1 certainly is true the bacteria used poly-A
2 differently, but it's not fair to say that
3 there's -- for example, they're saying there is no
4 poly-A tail in bacteria. That's not true.

5 Q Do you agree that in bacteria there's
6 typically not a large percentage of mRNA that's
7 polyadenylated?

8 A I would say that in many studied bacteria
9 the fraction of polyadenylated RNAs is smaller in
10 bacteria than in eukaryotic cells. I don't know
11 that that's necessarily true for every species of
12 bacteria or every environmental context.

13 But yes, on average I would say the
14 literature suggests that it is lower abundance in
15 bacteria. But again, certainly not absent.

16 Q Could you please turn to Page 74 of your
17 May 2024 transcript.

18 Are you there?

19 A Yes.

20 Q Okay. And around page -- around
21 column -- try this again.

22 Around Line 4 you say, "But it is true to

1 say that it is fundamentally different that --
2 whereas, in eukaryotes a large percentage of mRNAs
3 are polyadenylated. In bacteria that's not true,
4 it's typically there -- a large percentage are not
5 polyadenylated."

6 Do you see that?

7 A Yes. And it goes on to talk about how I
8 don't agree with extreme statements that it
9 doesn't exist at all. And that's basically what I
10 just said a few minutes ago.

11 Q Okay. So you agree with the statement
12 still --

13 A Yes.

14 Q -- on Page 74?

15 A Yes.

16 Q And you agree that there's a qualitative
17 difference in the nature of polyadenylation
18 between prokaryotes and eukaryotes. Right?

19 A Yes, again from the -- from the
20 literature that exists on looking at RNAs and
21 prokaryotes and eukaryotes, yes.

22 Q And then could you turn to Page 75 of

1 that transcript.

2 A Okay.

3 Q Starting on Line 5. "Do you agree that
4 in general the rule for eukaryotes is that
5 transcripts are polyadenylated. In general, the
6 rule for bacteria is that they're not?"

7 A Right. And then I go on to say there is
8 variability, that there are counter-examples and
9 there are RNAs in eukaryotes that are not
10 poly-A-tailed and there are RNAs in bacteria that
11 are poly-A-tailed, so yes.

12 Q Then turning to Linnarsson. And that's
13 Exhibit 1003, Dr. Cooper, just in case you want to
14 pull it up and refer to it.

15 (Parse Exhibit 1003, previously marked,
16 not attached.)

17 A Okay, I have it.

18 Q And, actually, if we could turn to Page
19 24. It says 1003.024 at the bottom.

20 A Okay, I'm there.

21 Q Okay. And you see the heading Example 1?

22 A I do.

1 Q Okay. Do you recall how many examples
2 there are in Linnarsson?

3 A I believe there are at least two. I
4 can't remember, but two is my recollection at the
5 moment.

6 Q And the second example you're thinking
7 of, is that the one that's -- that starts at Page
8 1003.032?

9 A Yes, that looks right.

10 Q Okay. And at the moment you're not
11 thinking of any other examples disclosed in
12 Linnarsson. Correct?

13 A That's correct.

14 Q And would you agree that the mention of
15 Figure 3 and Figure 4 is inside Example 1 in
16 Linnarsson?

17 A Would I agree that they are mentioned in
18 Example 1?

19 Q Correct. As a matter of organization of
20 Linnarsson, would you agree that Figures 3 and
21 Figures 4 are disclosed inside Example 1 in
22 Linnarsson?

1 A So they are certainly referenced in that,
2 in Example 1, yes.

3 Q Do you know if they are referenced in
4 connection with any -- with any other portion of
5 Linnarsson?

6 A I don't know one way or another.

7 Q Okay.

8 A They're called out also in the top in the
9 brief description of the drawings.

10 Q And in your opinion, are Figures 3 and 4
11 consistent with Example 1 of Linnarsson?

12 A I think that Figures 3 and 4 are intended
13 to be examples, and they are certainly -- they are
14 helpful to a skilled artisan to understand how to
15 implement a method. I don't think there's an
16 exclusivity. I think the information they're
17 providing in Figure 3 is more general than just
18 what's performed in Example 1.

19 Q In your opinion, is Figure 3 consistent
20 with Example 1 of Linnarsson?

21 A I guess I'm more comfortable saying it's
22 not inconsistent with Example 1.

1 Q In your opinion, is Figure 4 consistent
2 with Example 1 of Linnarsson?

3 A Just like for Figure 3, I think it's --
4 there it is general information that is not
5 inconsistent with the example, but it's not
6 exclusive to that example either.

7 Q And in your opinion, is Figure 2
8 consistent with Example 1 of Linnarsson?

9 A Sorry, I'm just trying to pull up Figure
10 2.

11 Again, so like Figures 3 and 4, Figure 2
12 is a very broad general overview that certainly
13 helps a skilled artisan understand the work flow
14 of Example 1. But again, Figure 2 is more general
15 than that. So again it's the same answer, that it
16 is not inconsistent with that example.

17 Q And you'd agree that Figures 3 and 4 are
18 helpful in understanding the work flow of Example
19 1?

20 A Correct. Among other things, yes.

21 Q And you would agree that both Example 1
22 of Linnarsson and Example 2 of Linnarsson disclose

1 fragmentation and capture. Correct?

2 A I'd have to refresh my memory on that on
3 exactly what all is in the scope of those
4 examples.

5 I'm not sure I'm seeing a fragmentation
6 step in Example 2. But again, it's been a minute
7 since I read through that in detail.

8 Oh, there it is. Yes. So yes, they
9 reference cutting.

10 Q So do you agree that both Examples 1 and
11 2 of Linnarsson disclose fragmentation and
12 capture?

13 A Yes, they are part of the experimental
14 steps inside those examples. Yes.

15 Q And Examples 1 and 2 also both use
16 biotin.

17 Correct?

18 A I'm not seeing biotin listed under
19 Example 1, but maybe I just can't see that. Yeah,
20 it looks like biotin is only mentioned under the
21 text for Example 2.

22 Q Okay. So could you please turn to Page

1 96 of your May 2024 declaration.

2 A Which exhibit number is that?

3 Q That is exhibit, I think it was Exhibit
4 2101.

5 A Oh, deposition you mean?

6 Q Yes. Sorry.

7 A Sorry, I thought you meant -- gotcha.
8 I'm there.

9 Q And Page 96, Line 12.

10 A Okay.

11 Q You were asked, "And you'd agree that
12 Example 1 of Linnarsson discloses what you called
13 fragmentation and capture. Right?"

14 A Yes, I see that.

15 Q And you answered, "Yes, it looks like
16 biotin is at least one component of the process,
17 so that would imply that they're doing a
18 solid-phase capture. Yes."

19 A Yes.

20 Q Do you agree with that testimony?

21 A Yes. I didn't see it at the first glance
22 here, but yes, I'm guessing that's true.

1 Q And you see in Linnarsson itself, if you
2 go to 1003.024.

3 A Oh, there, I see it now. Yes.

4 Q You see a bio around Line 13, a CDS of a
5 bio?

6 A Yes, I was looking for biotin rather than
7 bio, so ...

8 Q Bio and biotin are the same. Correct?

9 A I believe in this text it is, yes.

10 Q You agree that Linnarsson discloses the
11 creation of a cDNA library. Correct?

12 A Yes. Yes, generation of collection of
13 cDNAs are part of Linnarsson, yes.

14 Q And there may be fragmentation involved
15 in creating that cDNA library.

16 You agree with that?

17 A Yes. In some work flows, yes, you may
18 use fragmentation, yes.

19 Q And if the cDNA library sequences are too
20 long for further sequencing, you might need to do
21 further fragmentation. Correct?

22 A That would depend on the sequencing

1 technology you're using and the sample
2 preparation. But yes, certainly in some
3 circumstances you -- that fragmentation may be
4 required to -- depending on your inputs and the
5 sequencer and that sort of thing, yes, that can
6 certainly be true.

7 Q And would you agree that Linnarsson
8 discloses further fragmentation of the cDNA
9 library, at least as an option?

10 A Yes, I think there is a dependent claim
11 that specifically claims that, so yes.

12 Q Okay. Could you please turn to
13 Linnarsson 1003.013.

14 A Okay.

15 Q And if we could go to Lines 4 through 8.

16 A I see that.

17 Q And you see it refers to, The term "cDNA
18 library" refers to a collection of cloned
19 complementary DNA, parenthesis, DNA fragments,
20 which together constitute some portion of the
21 transcriptome of a single cell or a plurality of
22 single cells.

1 Do you see that?

2 A Yeah. And it goes on as well. Yes.

3 Q What does the word "fragments" in Line 5
4 add, if anything, to the word "cDNA" or "DNA"?

5 A So I think it helps to read that, the
6 sentence that immediately follows, which is that
7 it says that cDNA is produced from fully
8 transcribed mRNA found in a cell. And so I think
9 what it's referring to is that the RNA, the
10 expressed RNAs in the cell are fragments of RNA,
11 and the cDNA fragments are the complementary DNA
12 copies that are produced from those RNA fragments.
13 So I think it's using that in a manner that says
14 that, as opposed to say a whole chromosome or
15 another large molecule that gene expression units
16 are more fragment size, I think is the reason
17 they're using that term there.

18 Q Would this statement mean anything
19 different to you -- and "this statement" being the
20 one about the cDNA labor that we're looking at.

21 A Yes.

22 Q Would it mean anything different to you

1 if the word "fragments" was deleted and just said
2 cDNA library refers to a collection of cloned
3 complementary DNA, paren cDNA, which together
4 constitutes some portion of the transcriptome?

5 A Well, it wouldn't read quite the same
6 way, it would read a little funny. You would have
7 to put something in its place. But you could
8 imagine, for example, complementary cDNA molecules
9 would be another thing they could use there. But
10 it -- it would appear kind of unusual if they
11 didn't have something in there to talk about,
12 we're talking about discrete individual molecular
13 units.

14 Q So in your view fragments here only means
15 discrete individual molecular units?

16 A I wouldn't say only, but that would be my
17 reading of it, yes. That's sort of my
18 understanding that's why they're putting that word
19 there, to help clarify they're not talking about
20 cDNA as a hypothetical or something, we're talking
21 about cloned molecules. Or not cloned. We're
22 talking about generated molecules that are part of

1 this process.

2 Q Do you recall in Linnarsson the
3 disclosure of a BtsC1 cut site?

4 A I do.

5 Q Okay. And is it your position that a
6 POSA reading Linnarsson would understand
7 Linnarsson's method to use BtsC1 and only BtsC1 as
8 a restriction enzyme cut site?

9 A So again, I think Linnarsson has a fairly
10 broad disclosure. And the specific example they
11 use is BtsC1.

12 So I think to the extent that they're
13 looking at the specific examples and matching up
14 the enzyme with the sequence that's inside the
15 exemplary oligos that they're using, that that
16 work flow is BtsC1.

17 But it is certainly possible one could
18 imagine using a different enzyme, depending on the
19 experimental context. But the only one called out
20 by Linnarsson is BtsC1.

21 Q But a POSITA wouldn't understand
22 Linnarsson to be limited to using BtsC1 as the

1 restriction enzyme cut site for the performance
2 method?

3 A I think a POSA could reasonably alter the
4 design of their oligos to use a different enzyme,
5 yes.

6 Q And it's your position that a POSITA
7 would have to actually alter Linnarsson to use
8 something other than BtsC1, as opposed to a POSITA
9 understanding Linnarsson to broadly describe the
10 use of a restriction enzyme cut site?

11 A Sorry, that was a lot to -- I guess my
12 understanding would be that if a skilled artisan
13 were building their own protocol, if they wanted
14 to use a different enzyme because for whatever
15 preference they would have to alter the sequence
16 because different restriction enzymes target
17 different cut sites. So one modification that
18 they would need to make is to alter -- at the
19 position of the cut site they'd have to alter that
20 sequence in their oligo design. That is certainly
21 within the competencies of a skilled artisan.

22 Q Your opinion is that Linnarsson is read

1 broadly, is a broad disclosure? Correct?

2 A So I think Linnarsson -- so, for example,
3 if you look at Figure 1, it provides a very
4 general overview of a process.

5 And so Linnarsson certainly encompasses a
6 range of protocols, some of which wouldn't use
7 restriction enzymes at all, for example. But
8 certainly changing a restriction enzyme is -- you
9 know, maybe an analogy would be that they talk
10 about Illumina or SOLiD sequencing. Right?

11 There are different kinds of molecular
12 biology techniques that are within the scope of --
13 or within the competencies of a skilled artisan.
14 And so yes, I think it is a fairly broad
15 disclosure.

16 Q Does Linnarsson encompass the use of a
17 restriction enzyme cut site other than BtsC1?

18 A Yes, I think that would be -- using
19 different enzymes would be within scope of what
20 Linnarsson discloses, yes. And as well as would
21 be not using any restriction enzyme.

22 Q Okay. Before, with respect to

1 Linnarsson, we were talking about Figures 3 and 4
2 and how they are relevant to Example 1.

3 Do you recall that?

4 A I do.

5 Q Okay. Could you tell me what aspects of
6 Figure 3 are relevant to Example 1?

7 A Sorry. Give me a moment to pull up
8 Figure 3.

9 So one aspect is obviously the template
10 switching portion of the molecule, that is a part
11 of however transcription is carried out. And to
12 the extent that the examples involve reverse
13 transcription, that is a key component of the
14 molecule.

15 Another example is the -- what they refer
16 to as the APS, the amplification primer I believe
17 that's called. And so PCR is employed as part of
18 the example. And so that sequence portion would
19 be necessary for -- for priming that amplification
20 step.

21 Q Anything else?

22 A So it's also disclosing a cell tag.

1 Which obviously Linnarsson has a process whereby
2 you can use a tag to track the cell of origin for
3 a given polynucleotide. And so that is where
4 it's -- an example of where they would embed the
5 cell tag inside that oligo.

6 Q Anything else?

7 A That's all that emerges right this
8 second.

9 Q And is there within Linnarsson a full
10 description of its method using Figure 3, other
11 than Example 1?

12 MR. WALTER: Objection. Vague.

13 A So I think that, you know, a skilled
14 artisan again would read Linnarsson as a broad
15 disclosure. So we can go back to Figures 1 and 2,
16 for example, that describe high-level overviews of
17 the process. And then if you look at Claim
18 language, you would read, an artisan would read
19 the claims and get the sort of step-by-step
20 process of what's required for different versions
21 of the protocol.

22 And I think Figures 3 and 4 are exemplary

1 molecules, certainly not the only molecules that
2 one might use as part of that. But, you know, I
3 think, again, Linnarsson is fairly -- fairly
4 general, fairly encompasses a wide range of
5 protocols that would involve tracking
6 polynucleotides to single cells.

7 Q Okay. That's a little bit different than
8 what I was asking, which is whether Linnarsson
9 includes a full description of using its method
10 with Figure 3, other than what's described in
11 Example 1.

12 A So I think if you look at Claim 1, for
13 example, that is an example of a start-to-finish
14 process that a POSA would read Figure 3 and
15 understand as part of how to achieve Claim 1.

16 Q Anything else?

17 A There -- again, I -- connecting to Figure
18 1, because Figure 1 talks about, if I recall --
19 let me pull up Figure 1.

20 Yeah. So Figure 1, for example, provides
21 a cartoon of the overview of the process. And to
22 the extent, for example, it talks about tagging,

1 it talks about reverse transcription, so it's
2 outlining a high-level view of a protocol that a
3 skilled artisan would read Figures 3 and 4 as
4 contributing to in the context of Figure 1 because
5 those are exemplary molecules for doing the
6 tagging and the amplification and the reverse
7 transcription that is described in Figure 1.

8 Q If I ask you the same question about
9 Figure 3, would your answer be the same; that is,
10 whether Linnarsson includes a full description of
11 using its method with Figure 4, other than what's
12 described in Example 1?

13 A Yes, my answer would be similar, that
14 it's referring to things that are claimed in Claim
15 1, it is referring to Figure 1. And again, there
16 are other places like Figure 2 is again showing
17 components of the process. So I think a skilled
18 artisan would use those figures in the context of
19 the broad disclosure of Linnarsson.

20 Q And what aspects of Figure 4 are relevant
21 to Example 1?

22 A So the -- certainly the, similar to

1 Figure 3, there's the priming site, the APS
2 portion of the molecule that's required for
3 amplification priming.

4 And there's also the RCS portion of the
5 molecule, the RNA complementary sequence, which
6 is -- we talked about earlier is a region of the
7 primer that initiates the reverse transcription.
8 And that is also how you target your sample
9 polynucleotides, depending on what your experiment
10 is.

11 So this example it's an oligo(dT), so
12 it's a series of thiamine residues. But it
13 describes the RCS as being flexible and general,
14 and you can use a range of different sequences
15 depending on which sample mRNAs you would like to
16 address.

17 So yeah, it has multiple portions.

18 Q We talked a little bit earlier about the
19 biotin and I think the use of beads. Would you
20 agree with me that if there is no biotin, you
21 can't use the beads described in Examples 1 or 2?

22 A So I believe Examples 1 and 2 use

1 streptavidin-coated beads, and biotin is the
2 binding partner for that. But there are other
3 solid substrates that one can use to purify
4 polynucleotide mixtures.

5 So I'm not saying that's the only way one
6 could do it, but streptavidin beads and biotin go
7 hand in hand within a lot of protocols.

8 Q And you agree that Example 1 of
9 Linnarsson used biotin and cut sites. Right?

10 A I believe that's true. I can go to
11 Example 1 text. Oh, it was Page 30 -- 24.

12 Q Were you able to look at Example 1?

13 A Sorry, I'm looking right now, yep.

14 Q Sure.

15 A Yes, it is within Example 1. There is a
16 BtsC1 digestion step.

17 Q And so you agree that Example 1 uses both
18 biotin and a BtsC1 cut site. Right?

19 A Yes.

20 Q Could you pull up Exhibit 2015, please.

21 (10x Genomics Exhibit 2015, previously
22 marked, not attached.)

1 A This is G-U-A-N?

2 Q Correct.

3 A I see that.

4 Q Do you recognize this article?

5 A I believe so, yes.

6 Q And the authors here are from New England
7 Biolabs.

8 Do you agree with that?

9 A Yes.

10 Q And New England Biolabs is well-known for
11 selling restriction enzymes. Correct?

12 A That's right.

13 MS. RAYMOND: Why don't we take a short
14 break, ten minutes, before we get into the next
15 piece of this.

16 THE WITNESS: Okay.

17 (A recess was taken.)

18 BY MS. RAYMOND:

19 Q Could you, Dr. Cooper, please turn to
20 Exhibit 1070. I'll be asking you about Exhibit
21 1070 in both proceedings, but perhaps we can focus
22 on the '197 paragraph numbers.

1 A '197, is that 955 or 958?

2 Q That is 955, yes.

3 A So this is patent owner's response?

4 Q What I'm looking for, what I'm going to
5 ask you about, is Exhibit 1070, which is your
6 reply declaration.

7 A Oh, gotcha, yes. I'm there.

8 Q Could you please turn to Paragraph 12.

9 A I see.

10 Q And you say, "Nowhere does the '197
11 patent disclose the simultaneous use of two tags,
12 wherein a first tag is used to encode the cellular
13 origin of a polynucleotide and the second tag
14 distinguishes among polynucleotides in a cell."

15 Do you see that?

16 A Yes, I do.

17 Q And you recall saying the same thing
18 about the '013 patent?

19 A Yeah, I'm sure I did. Yes.

20 Q Okay.

21 MS. RAYMOND: Could we pull up the '197
22 patent that is Exhibit 1001.

1 (Parse Exhibit 1001, previously marked,
2 not attached.)

3 MS. RAYMOND: And if we could go to
4 Column 6, please.

5 A So this is 1001?

6 Q This is exhibit -- sorry, Exhibit 1001.

7 A Gotcha. Okay.

8 Q And I'm looking at the '197 patent. So
9 this is in the 955 matter.

10 A Gotcha. Yeah, I'm there.

11 Q Okay. And I'm looking at the MID
12 definition here.

13 Do you see that? Starting around Line
14 33?

15 A I see that.

16 Q And do you see the reference to a tag or
17 combination of tags?

18 A I do.

19 Q And then the patent offers two types of
20 tags, a source tag and UMI.

21 Do you see that?

22 A I don't see UMI in here.

1 Q Sorry about that. I'm sorry, the words
2 "UMI" are not present. But it says, "In certain
3 embodiments, MIDS are employed to uniquely tag
4 each individual polynucleotide in a sample"?

5 A I see that.

6 Q Do you see that?

7 And do you see the reference to a source
8 tag?

9 A Well, the previous sentence talks about
10 from a pool of polynucleotides derived from
11 different sources, yes.

12 Q So do you agree with me that the '197
13 describes both a source tag and the tagging of a
14 MID with a -- that provides a correlation between
15 a polynucleotide and its source?

16 A Certainly this paragraph is talking about
17 prior art uses of tags, which individually include
18 tracking a source or using as a unique
19 polynucleotide identifier. Yes, this is an
20 overview of what's in the prior art.

21 Q And do you agree that it describes using
22 a tag or a combination of tags such that it would

1 be understood to refer to a combination of the two
2 types of tags you just described?

3 A No, I don't think that's necessarily how
4 one would read that. It talks about how a single
5 MID can be composed of a combination of tags,
6 which I think the simplest explanation of that
7 would be, you know, much in the way that
8 Linnarsson talks about using the TSO and the CDS
9 tags to identify the source. So it's talking
10 about sort of -- it doesn't necessarily imply dual
11 functionality of tags. It just says that each
12 function can be achieved with one or more
13 polynucleotide tags.

14 Q But you agree that it describes using
15 tags for multiple functions. Correct?

16 A Again, it describes prior art uses of
17 tags that have been used in different individual
18 ways. It certainly doesn't lay out an inventive
19 combination here. It doesn't specifically say use
20 this one and that one and combine them in this
21 way, this is how you do that. It's -- again, this
22 is a description of the universe of ways that

1 people have used tags in the prior art up until
2 this patent was published.

3 Q But you agree that it describes using
4 tags for different functions. Correct?

5 A It describes different functions that
6 have been used in the prior art in individual
7 ways, yes.

8 Q And you agree that it says the MID uses a
9 tag or combination of tags. Right?

10 A That is in the opening sentence of the
11 paragraph, yes. That an individual MID can be
12 comprised of a single or multiple tags, yes.

13 Q But it's your position that that -- that
14 this wouldn't be read to -- wouldn't be read to
15 describe using a combination of tags with
16 different functions?

17 A It's not -- certainly that doesn't make
18 that point clearly or explicitly. Again, this is
19 just -- I think a skilled artisan would read this
20 as a generic overview of what's in the prior art
21 regarding use of tags.

22 Q Could you return to Paragraph 35 of your

1 report.

2 A So we're back to Exhibit 1070.

3 Is that right?

4 Q Correct. And this is also Paragraph 33
5 in your '013 report.

6 A This is back to Linnarsson?

7 Q We're looking at your -- sorry, your
8 declaration, Exhibit 1070. And yes, we're talking
9 about Linnarsson.

10 A Yes. Okay.

11 Q And you say -- sorry. You say, "Thus
12 Figure 11 is only one out of numerous figures and
13 representative examples of Linnarsson's
14 invention."

15 Do you see that?

16 A Yes.

17 Q How many Linnarsson figures do you rely
18 on?

19 A I don't know the exact number, but
20 certainly Figures 1, 2, 3, 4, 11, and perhaps
21 others. I don't recall the entire -- they're all
22 called out in the document, but I don't remember

1 the full scope of all of them.

2 Q And then earlier we agreed that there are
3 two examples in Linnarsson that you could recall.

4 Is that correct?

5 A So, well, yeah. The two examples that
6 provide a protocol, sort of, and an example of a
7 working protocol from start to finish, yes. I
8 think in the more general use of examples, it
9 talks about an example -- an exemplary CDS, an
10 exemplary TSO. So it uses examples of individual
11 components. There's a lot of other examples in
12 there, where "example" is a more general term
13 about describing individual components.

14 Q Okay. So when you say "representative
15 examples" in Paragraph 35, what do you mean?

16 A Again, much in the same way that we just
17 talked about, an exemplary TSO, an exemplary CDS,
18 et cetera. So it's examples of -- of how one
19 defines or builds or constructs parts of the
20 protocol or parts of the work flow.

21 Q And with respect to Figure 11 in
22 Linnarsson, you see there's a Step A? Is it fair

1 for me to call it a step?

2 A You're talking about specifically of
3 Figure 11?

4 Q Figure 11, yes. Figure 11 you see the A?

5 A Yes. Yes.

6 Q Is it fair for me to call that a step of
7 Linnarsson?

8 A I think it is a step of Figure 11.

9 Q Okay. Sorry. And is it your position
10 that Step A shown in Figure 11 is an optional step
11 with respect to the Linnarsson method more
12 generally?

13 A I think that there are certainly
14 components here that are very optional. You know,
15 at least the two examples would be the design of
16 the RCS here, the RNA complementary sequence is
17 oligo(dt), and we know that that's only one
18 example of a sequence. The use of biotin here is
19 also not required.

20 So again, I think the -- this is helping
21 to understand the work flow a little bit better
22 from that Example 1, that capital E Example 1.

1 But certainly components of this are not required
2 for Linnarsson's process more generally.

3 Q Beyond the design of the RCS and the use
4 of biotin, in your opinion are there other
5 elements shown in Figure 11 that are optional with
6 respect to Linnarsson's method more generally?

7 A So the -- there's no cell tag on -- in
8 the CDS that's highlighted here. And certainly
9 Linnarsson makes clear that the CDS can include a
10 cell tag. Doesn't have to. It talks about CDS
11 and/or TSO. So that's another optional component
12 of what's in Figure 11.

13 The primer -- the PR region, so it talks
14 about the optionality of how you design the
15 amplification sequences. And, you know, you might
16 choose one set of primers for, you know, if you
17 were eventually going to do Illumina versus SOLiD
18 versus something else. So there are other aspects
19 here that are also optional.

20 And I guess more generally too it's also
21 the -- the input is described as generic, but we
22 know that the nucleotides coming themselves can be

1 samples of whatever you're interested in studying.
2 So it might be human cells, it might be a mouse
3 cell, it might be immune cells, it might be brain
4 cells, it might be all kinds of things. Right?
5 So that's -- it's intended to be -- that that,
6 again, is another aspect that's modular and
7 generic about this particular figure.

8 Q Okay. If you go to what's marked in
9 Linnarsson as 1003.006, there is a description of
10 Figure 11.

11 A Okay.

12 Q And you see it says Panel A shows a
13 reverse transcription step?

14 A Yes.

15 Q Do you agree with me that some sort of
16 reverse transcription step is required to perform
17 Linnarsson's method?

18 A Generally speaking, yes, it is -- it is a
19 method for doing gene expression, which often
20 involves a reverse transcription step.

21 Q And would you agree with me that -- you
22 see Panel B it says, Panel B shows a template

1 switching step?

2 Do you see that?

3 A I see that.

4 Q And do you agree with me that some sort
5 of template switching step is required to perform
6 Linnarsson's method?

7 A Yes, as to the extent that that's part of
8 how you build a cDNA, yes.

9 Q And that's part of how you build a cDNA
10 library in Linnarsson. Correct?

11 A It is.

12 Q And do you see on the next page
13 Linnarsson says, Panel C shows a single primer PCR
14 step?

15 A I see that.

16 Q Do you agree with me that some sort of
17 single primer PCR step is used to perform
18 Linnarsson's method?

19 A So I think -- I don't necessarily think
20 you always would necessarily amplify. But
21 certainly amplification is part of many work
22 flows. That would be. And I think for example in

1 Claim 1 it does include an amplification step.
2 But it wouldn't have to be a single primer, for
3 example. It's just a primer to do some round of
4 amplification.

5 Q Do you agree with me that a single primer
6 PCR step is used in Linnarsson's method?

7 A I would say it's used in -- in Figure 11,
8 but not necessarily all embodiments of Linnarsson.

9 Q Can you point me to an embodiment of
10 Linnarsson where a single primer PCR step is not
11 used?

12 A So I again would -- like we talked
13 earlier about Figures 1 and 2 and Claim 1 being
14 written to be broader than that. They -- you
15 know, Claim 1, for example, encompasses
16 amplification. So you would have to perform
17 amplification. But you might choose to use
18 different primers. You know, you can -- you can
19 design PCR in lots of different ways.

20 Q And Panel D, Linnarsson goes on and says
21 Panel D shows a fragmentation step?

22 A Yes.

1 Q And do you agree that some sort of
2 fragmentation step is used to perform Linnarsson's
3 method?

4 A Only within Figure 11. There's -- you
5 don't have to perform fragmentation in general.

6 Q Okay. And can you point me to a complete
7 description of Linnarsson's method that doesn't
8 use fragmentation?

9 A I would go back to my previous answer
10 about Figure 1 providing an overview. Figure 2
11 talking about portions of it. Claim 1, for
12 example, doesn't mention fragmentation, et cetera.

13 Q And I assume your answer would be the
14 same with respect to Panel E showing an
15 immobilization and end repair step?

16 A Correct. That's just one option for
17 purifying a cDNA library. It's not necessary.

18 Q If you could turn to Paragraph 45 of your
19 '197 declaration. Which is Paragraph 43 in your
20 '013, in the '013 case.

21 A "The key point is," is that the
22 paragraph?

1 Q That's the paragraph. And if you could
2 go towards the bottom of that paragraph you say,
3 "While that may be true of Figure 11, it is not
4 true of the embodiments based on Figure 4."

5 Do you see that?

6 A Yes.

7 Q What are "the embodiments based on Figure
8 4"?

9 A Well, any embodiment that doesn't use
10 biotin, that actually puts a tag inside the CDS,
11 for example. Because Figure 11 doesn't lend
12 itself to sequencing the tag in CDS. So in work
13 flows where you want to sequence -- you wouldn't
14 put a cell tag in there if you didn't want to
15 sequence it. So work flows that included the cell
16 tag on the CDS, that would be different than what
17 is carried out in Figure 11.

18 Q Where does Linnarsson describe work flows
19 that include at the cell tag on the CDS?

20 A So Figure 1 is another example, you know,
21 provides an overview of it. Claim 1 allows you to
22 put -- and, in fact, I think there are dependent

1 claims that specifically say put a tag on the TSO,
2 put a tag on the CDS, et cetera.

3 Q Anywhere else in Linnarsson?

4 A I guess I'm not understanding the
5 question.

6 Q I was asking you does -- where does
7 Linnarsson describe work flows that include the
8 cell tag on the CDS? And you pointed me to Figure
9 1 and the claims. And I was just wondering if
10 there was anywhere else, in your view, that
11 Linnarsson describes that?

12 A So I think basically all that -- you
13 know, I would read it sort of the opposite. That
14 the work -- it specifically talks about Figure 11
15 having optional steps. So by default I would say
16 that would not be included. And that in general
17 you would -- you know, Figure 4 would be an
18 example of a CDS that can be used in a whole range
19 of work flows. So it's giving you options at each
20 step, or options at various steps, including the
21 design of the CDS and the TSO.

22 Q Can you please turn to Paragraph 104 of

1 your '197 report.

2 A Yeah, I see it.

3 Q Okay. And this goes back to our
4 discussion about the cDNA library definition in
5 Linnarsson. And you see here again that that
6 description of the cDNA library is repeated.

7 Do you see that in Paragraph 104?

8 A Yes.

9 Q And in your opinion, is the only cDNA
10 that is not a fragment an entire chromosome?

11 A No. The -- so the -- again, I think in
12 this case the fragment is by definition it's
13 connecting to -- you're converting fully
14 transcribed mRNA into what is calling cDNA
15 fragments. So they are providing the terms of
16 that definition here, saying that the fragments of
17 cDNA that come out are complementary DNA fragments
18 driven by the fully transcribed mRNA. And so
19 they're using that term there in that way. And
20 that's -- they're giving that definition.

21 So I think the key point is that it
22 doesn't imply or explicitly say fragmentation of

1 some artificial sort. It's saying that the
2 process of generating cDNA yields cDNA fragments.

3 Q And the cDNA fragment may be an entire
4 reverse transcribed chromosome, in your opinion?

5 A No. Because there's no -- at least to my
6 knowledge, there's no example of a gene that is
7 expressed that would occupy the full length of the
8 chromosome. So it's -- again, it's just a
9 reflection of RNA in, cDNA out. The cDNA
10 represents the RNA that was put in.

11 Q So in your opinion, a cDNA fragment may
12 be an entire reverse transcribed gene?

13 A Well, an entire reversed transcribed
14 mRNA.

15 Q Okay. Could you please turn to Paragraph
16 147 of your '197 report.

17 A Okay.

18 Q And you disagree with Dr. Quackenbush
19 that ligation, as you proposed it, would add an
20 additional step to Linnarsson's method?

21 A Yeah, that his language about adding an
22 additional ligation step would increase complexity

1 in the context of his argument, yes. I don't
2 think that is a problem.

3 Q You don't think that's a problem. But is
4 it -- is it your opinion that ligating would add a
5 step to Linnarsson's disclosed process?

6 A Well, so ligating a -- well, the full
7 context is important here. It's viewing
8 Linnarsson in combination with McCloskey, where
9 McCloskey is defining the nature of the unique
10 molecular identifier tag. And how a skilled
11 artisan would be motivated to do that because of
12 the benefits of the unique molecule tag.

13 And that in that context a ligation step
14 is -- you know, is a very routine, conventional,
15 well-known step for adding tags to -- to cDNA
16 molecules.

17 So in that context I don't think it's
18 overburdensome or complicated. It's a very
19 routine thing to do.

20 Q Can you turn to Paragraph 156 of your
21 report, please.

22 A Okay.

1 Q Actually, back to -- back to what we were
2 previously talking about?

3 You do agree that ligating would add a
4 step to Linnarsson. You say it's not
5 overcomplicated, but you would agree it does add a
6 step?

7 A I would say to the extent that you are
8 adding this second functional tag. Again,
9 Linnarsson discloses two tags, right, one on the
10 CDS and one on the TSO, as an option.

11 But to the extent you're adding a tag
12 that acts as a unique molecular identifier in the
13 addition to the CDS and/or TSO, then, yes, it is
14 an additional step to -- again to incorporate the
15 benefit of McCloskey into the work flow of
16 Linnarsson.

17 Q So if you're adding ligation to
18 Linnarsson, that would add a step?

19 A Correct. To reap the benefit of the
20 redundant molecule tracking, yes.

21 Q Got it. Okay. Sorry. Back to Paragraph
22 156. And you say "Linnarsson itself even

1 discloses the process of ligating sequencing
2 adapters to the cDNA molecules following both
3 extension steps."

4 Right?

5 A Correct.

6 Q And that ligation occurs after
7 amplification and after fragmentation?

8 Is that correct?

9 A No. It would be after you make that
10 initial complementary DNA fragment but before
11 amplification or any downstream processing.

12 Q And in Linnarsson, it's your view that
13 that -- my question is about what Linnarsson
14 discloses. And do you agree that Linnarsson
15 discloses a process of ligating sequencing
16 adapters to the cDNA molecules following both
17 extension steps?

18 A Well, I think Linnarsson -- so Linnarsson
19 certainly discloses that you have flexibility
20 about the ends of the cDNA molecules in terms of
21 the design and structure. And in other parts of
22 the Linnarsson disclosure it talks about adding

1 adapters for putting onto a sequencer, for
2 example.

3 And so I think the point here again in
4 the context of a skilled artisan being motivated
5 to use the McCloskey unique molecular tag, you
6 could easily add it after the second extension
7 step that is written to Linnarsson, via ligation.

8 Q And with respect to Linnarsson's method,
9 is it your opinion that all steps in Linnarsson
10 require PCR of some type?

11 A All -- no, there are lots of steps that
12 are not PCR.

13 Q Sorry. Is it your opinion that
14 Linnarsson's method, or methods depending on your
15 view, all require PCR of some type?

16 A I guess I've not done that analysis. I
17 know, I believe amplification of some flavor is
18 baked into Claim 1. So certainly to the extent
19 that that's, you know, the main independent claim,
20 I don't know if I'm comfortable saying that all
21 conceivable embodiments would necessarily rely on
22 amplification. There could be some. But

1 certainly things that are called out by Claim 1
2 obviously need amplification. So, yeah, I guess
3 I'm not -- I don't have a good answer for that
4 question.

5 Q Okay. And if you could turn to Paragraph
6 159 of your '197 report.

7 A Okay.

8 Q Same bit as in your '013 report. But
9 does the '197 patent disclose using Hug's method
10 of ligation to add a sequence to the biotinylated
11 end of a nucleic acid?

12 A I'm sorry. Which? Can you repeat that?

13 Q Does the '197 patent disclose using Hug's
14 method of ligation to add a sequence to the
15 biotinylated end of a nucleic acid?

16 A So I'm not sure that the '197 discloses
17 use of biotin, for starters. And generally
18 speaking, you don't ligate onto a biotinylated
19 end. You know, a skilled artisan would understand
20 that that's not something one would do.

21 I believe the '197 does refer to Hug, if
22 I'm not mistaken. So I think it's cited in the

1 '197 patent, but I could be wrong about that. But
2 so I guess I'm not quite following the question
3 because it's -- you wouldn't ligate to a
4 biotinylated end.

5 Q And would your answer be the same if I
6 asked you about the '013 patent disclosing using
7 Hug's method of ligation to add a sequence to the
8 biotinylated end of a nucleic acid?

9 A They share the same specification, so
10 yes.

11 Q And in your -- in your report have you
12 suggested using a restriction enzyme to create a
13 sequence that permits the linker in Hug to --
14 well, let me ask it this way: Hug's method uses a
15 restriction enzyme in order to -- to cut the
16 polynucleotide to which the linker is attached.

17 Correct?

18 A I believe that is certainly one of the
19 steps used in at least some of the portions of --
20 some of the methods in Hug, yes.

21 Q Okay. And in your report, either in this
22 reply report or in your opening report -- and we

1 can pull that up if necessary -- do you describe
2 using a restriction enzyme to create that end that
3 permits attachment of Hug's linker?

4 A I'm not sure if I specifically called out
5 Hug's use of a restriction enzyme or not. The
6 more general point was that Hug is just one
7 example of how a skilled artisan might use
8 ligation to add the McCloskey second tag. I'm not
9 sure that I focused on whether -- whether or not
10 and which enzyme one would use or not use from
11 Hug.

12 MS. RAYMOND: If we could take a
13 ten-minute break.

14 MR. WALTER: Great.

15 (A recess was taken.)

16 MS. RAYMOND: I have no further
17 questions.

18 MR. WALTER: All right.

19 EXAMINATION BY COUNSEL FOR PETITIONER

20 BY MR. WALTER:

21 Q Professor Cooper, I have a few followup
22 questions for you. Are you ready?

1 A Yes.

2 Q All right. Do you recall on
3 cross-examination you were asked some questions
4 about Figures 3 and 4?

5 A Yes.

6 Q What is your understanding of whether
7 Figures 3 and 4 in Linnarsson are depicting the
8 type of TSO and CDS you could use with the
9 approaches in Linnarsson where you used biotin and
10 restriction enzyme to do fragmentation and
11 capture?

12 A So Figures 3 and 4 don't include biotin.
13 So the only aspects that would carry forward would
14 be, for example, the use of an amplification
15 primer site, et cetera. So again, they're part of
16 the broader disclosure, but not tied to the
17 digestion steps.

18 Q What's your understanding of whether
19 Figures 3 and 4 include a restriction enzyme cut
20 site for use with the fragmentation and capture
21 approaches that are disclosed in Linnarsson?

22 A I don't believe they include that,

1 because the portions of the molecule that are
2 depicted in Figures 3 and 4 are all demarcated
3 with whether it's part of the priming site, part
4 of the cell tag, et cetera. So there's not an
5 allocation to a cut site.

6 Q Now, you were shown an article, the Guan
7 article, pertaining to restriction enzyme cut
8 sites.

9 Do you recall that?

10 A I do.

11 Q And that was I believe an article that
12 pertains to the Bts-1 restriction enzyme cut site?

13 A Yeah, that's in the title. Yes.

14 Q Let me just make sure that I've got the
15 right article here.

16 What is your understanding of whether
17 Linnarsson is contemplating use the Bts-1
18 restriction enzyme with any of its approaches?

19 MS. RAYMOND: Objection. Scope.

20 A It is -- Bts-1 isn't mentioned. That's a
21 different enzyme than the one that is part of the
22 example in Linnarsson.

1 Q Now, you're aware there has been some
2 suggestion in this case that some of the sequences
3 that are disclosed in Linnarsson include the
4 nucleotides that happen to correspond to Bts-1
5 restriction enzyme cut site.

6 Do you recall that?

7 A I do.

8 MS. RAYMOND: Objection. Form. Scope.

9 A I do recall.

10 Q Okay. What's your understanding of
11 whether Linnarsson ever refers to those sequences
12 of nucleotides that happen to correspond to the
13 Bts-1 restriction enzyme cut site as a -- as a cut
14 site for use with any of the approaches that are
15 disclosed therein?

16 MS. RAYMOND: Objection. Form. Scope.

17 A Again, it doesn't refer to that enzyme.
18 So any -- any use of it would be totally
19 happenstance or coincidental that that sequence
20 happened to appear in the examples of Figures 3
21 and 4.

22 Q Now, you were asked a lot of questions

1 about Figures 3 and 4 appearing as part of
2 Examples 1 and 2.

3 Do you recall that line of questioning?

4 A Yes.

5 Q What is your understanding as to whether
6 the appearance of Figures 3 and 4 in the text
7 related to Examples 1 and 2 means that Figures 3
8 and 4 must be used in an approach that uses every
9 step that's disclosed in Figures 1 and 2,
10 including fragmentation and capture?

11 MS. RAYMOND: Objection. Form. Scope.

12 A So I don't think Figure 1, for example,
13 talks about fragmentation at all. Figure 1 is the
14 broader --

15 Q I'm sorry, I meant -- sorry, let me ask
16 the question again. I wasn't precise. Let me go
17 again.

18 With regard to Figure 3 and 4, what is
19 your understanding of the fact that Figures 3 and
20 4 discuss in connection with Examples 1 and 2 as
21 to whether that means that Figures 3 and 4 must be
22 used in an approach that uses every step in

1 Examples 1 and 2, including fragmentation and
2 capture?

3 MS. RAYMOND: Objection. Format. Scope.

4 A So I think it's clear that it's not
5 really possible that they're intended to be
6 understood that way.

7 For example, to the extent that the
8 capital E Examples in Linnarsson talk about only
9 sequencing one end of the molecule, that wouldn't
10 make any sense to include a cell tag in the end of
11 the molecule that you're not going to sequence.

12 So I think a skilled artisan would read
13 that, and it would be very clear that Figures 3
14 and 4 are representative examples of things that
15 are more -- more general than what is specifically
16 outlined in the -- in, quote, the Example 1.

17 And I'd say that's also in keeping with
18 the way it describes other portions about how the
19 examples are not meant to be limiting, they
20 include optional things, et cetera.

21 So I think it's not reasonable to expect
22 a skilled artisan to look at Figures 3 and 4 and

1 say they're only compatible with the work flow in
2 Example 1.

3 MR. WALTER: No further questions from
4 me.

5 MS. RAYMOND: Can we take a five-minute
6 break.

7 (A recess was taken.)

8 EXAMINATION BY COUNSEL FOR PATENT OWNER

9 BY MS. RAYMOND:

10 Q Dr. Cooper, at the end of your counsel's
11 questioning you said, "I think it's not reasonable
12 to expect a skilled artisan to look at Figures 3
13 and 4 and say they are only compatible with the
14 work flow in Example 1."

15 Do you remember that?

16 A Yes.

17 Q You would agree that it would be
18 reasonable that a skilled artisan would look at
19 Figures 3 and 4 and say they are compatible with
20 the work flow in Example 1. Correct?

21 A Certainly some aspects are, absolutely.

22 Q So you think some aspects of Figures 3

1 and 4 are not compatible with the work flow in
2 Example 1?

3 A Well, the one example of -- maybe
4 "compatibility" isn't the best word, but it's --
5 for example, where you put the cell tag, if you
6 were never going to sequence that portion of the
7 molecule, it wouldn't make sense to include that
8 cell tag.

9 That said, I don't know that including
10 the cell tag would necessarily break it; it just
11 is not -- it wouldn't make sense to do that.

12 And, you know, another modification that
13 you'd have to make is there's no biotin listed on
14 Figures 3 and 4. So an artisan would have to
15 understand that you would have to biotinylate to
16 use, et cetera. So I think there are differences.

17 But it could be -- it's helpful to for a
18 skilled artisan, but it's not an exclusive or
19 one-to-one match.

20 MS. RAYMOND: Thank you. I have no more
21 questions.

22 MR. WALTER: Okay. I have nothing else

1 either, so I think we're done.

2 (Off the record at 12:08 p.m. EDT.)

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ACKNOWLEDGMENT OF DEPONENT

I, GREGORY COOPER, Ph.D., do hereby
acknowledge that I have read and examined the
foregoing testimony, and the same is a true,
correct and complete transcription of the
testimony given by me, and any corrections appear
on the attached Errata sheet signed by me.

(DATE)

(SIGNATURE)

C E R T I F I C A T E

I, Debra Ann Whitehead, E-Notary Public in and for
the Commonwealth of Virginia, do hereby certify:

That GREGORY COOPER, Ph.D., the witness
whose deposition is hereinbefore set forth, was duly
sworn by me before the commencement of such
deposition and that such deposition was taken
virtually and is a true record of the testimony
given by such witness.

I further certify that the adverse party,
PARSE BIOSCIENCES INC., was represented by counsel
at the deposition.

I further certify that the deposition of
GREGORY COOPER, Ph.D., occurred virtually, on
Tuesday, September 3rd, 2024, from 10:07 a.m. to
12:08 p.m. EDT.

1 I further certify that I am not related to
2 any of the parties to this action by blood or
3 marriage, I am not employed by or an attorney to any
4 of the parties to this action, and that I am in no
5 way interested, financially or otherwise, in the
6 outcome of this matter.

7

8 IN WITNESS WHEREOF, I have hereunto set my
9 hand this 4th day of September, 2024.

10

11 My commission expires:

12 October 31, 2027

13

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Conducted on September 3, 2024

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