

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

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BRUKER SPATIAL BIOLOGY, INC.,

Petitioner,

v.

Case No. IPR2024-00526

PRESIDENT AND FELLOWS OF

US Patent #11,542,554

HARVARD COLLEGE and 10X

GENOMICS,

Patent Owner.

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Deposition of

DR. KIRK CZYMMEK

April 17, 2025

9:00 a.m.

Taken at:

Crown Plaza St. Louis

11228 Lone Eagle Drive

Bridgeton, MO 63044

Eileen J. Bell, CCR #833

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1 KIRK CZYMMEK, of lawful age, called for
2 examination, as provided by the Missouri
3 Rules of Civil Procedure, being by me
4 first duly sworn, as hereinafter
5 certified, deposed and said as follows:

6 EXAMINATION OF KIRK CZEYMMEK
7 BY MR. HOLMAN:

8 Q. Good morning, Dr. Czymmek.

9 A. Good morning.

10 Q. Could you please state your full
11 name and place of residence for the
12 record?

13 A. My name is Kirk James Czymmek, and
14 I reside at 603 Martin Pointe Court,
15 Pointe with an "e", Wildwood Missouri,
16 63011.

17 Q. And do you recall previously being
18 deposed in this IPR proceeding?

19 A. I do.

20 Q. And that was back in November 2024;
21 correct?

22 A. Correct.

23 Q. Has your employment status changed
24 since your last deposition, Dr. Czymmek?

25 A. It has not.

1 Q. So you're still at the Donald
2 Davenport Science Center; correct?

3 A. Yes. That is correct.

4 Q. Have you been deposed since your
5 previous deposition in this IPR?

6 A. No.

7 Q. Have you testified in any
8 litigation matters since your previous
9 deposition in this IPR?

10 A. No.

11 Q. And aside from your reply
12 declaration, which you submitted in this
13 IPR, have you submitted any written expert
14 reports or declarations in other matters
15 since your deposition in this IPR?

16 A. Again, I have my declaration and my
17 reply declaration. I have not submitted
18 any others for this case or any other
19 case.

20 Q. All right. Dr. Czymmek, you
21 understand you're testifying under oath
22 today?

23 A. Yes, I do.

24 Q. You understand you're not permitted
25 to speak with anyone about the substance

1 of your testimony today, including during
2 breaks.

3 A. Yes, I understand.

4 Q. And you understand that if you need
5 clarification for a question, you must ask
6 me for that clarification and not your
7 counsel.

8 A. Understood.

9 Q. If you need a break today, just ask
10 for one. As long as there is not a
11 pending question we can take a break; is
12 that fair?

13 A. Sure.

14 Q. And you understand that if your
15 counsel objects to a question you must
16 still answer the question unless
17 specifically instructed not to answer.

18 A. Yes, I do.

19 Q. All right. We have a court
20 reporter with us today who's transcribing
21 our conversation. So it's important that
22 you wait for me to finish my question
23 before you begin your answer. Do you
24 understand that?

25 A. Understood.

1 Q. And, likewise, I will do my best to
2 wait for you to answer before I begin my
3 next question. And, as we discussed
4 before going on the record, we do not have
5 a real time transcript in this deposition
6 today. So from time to time we may ask
7 the court reporter to read back questions
8 or answers for clarification; okay?

9 A. Understood.

10 Q. Dr. Czymmek, do you have any
11 documents with you today?

12 A. I do. I have three documents.
13 Both of my declarations, Exhibit 1002 and
14 Exhibit 1086. And I have the Chen science
15 article that was spatially resolved highly
16 multiplexed ornate profiling in single
17 cells.

18 Q. Okay. Anything else besides
19 Exhibit 1002, Exhibit 1086 and Exhibit
20 1003?

21 A. No, nothing else.

22 Q. And do those documents have any
23 markings on them?

24 A. They do not.

25 Q. Any notes in there?

1 A. No.

2 Q. Any highlighting?

3 A. No.

4 Q. Did you prepare for today's
5 deposition?

6 A. Yes, I did.

7 Q. What did you do to prepare for
8 today's deposition?

9 A. Last week I had a one hour Zoom
10 call with Derek Walter. And over the
11 weekend I spent about 16 hours reviewing
12 all of the exhibits and documents that I
13 felt were relevant.

14 And then I spent a few hours Monday
15 and Tuesday, and Wednesday, which was
16 yesterday. And I spent the day with Derek
17 preparing for today.

18 Q. In preparing for today's deposition
19 did you meet with anyone other than Derek?

20 A. I did not.

21 Q. You mentioned you reviewed some
22 documents. What documents did you review?

23 A. My 1002 document, my 1086 document.
24 Any of the exhibits for the 1086
25 declaration. And the Shroff response, and

1 the Shroff deposition. Those are the
2 things that I primarily recall.

3 Q. When you say Shroff response,
4 you're referring to the Shroff
5 declaration?

6 A. Yes.

7 Q. And when you say Shroff deposition
8 you're referring to the Shroff deposition
9 transcript?

10 A. Exactly.

11 Q. Anything else you reviewed in
12 preparing for today's deposition?

13 A. Not to my recollection.

14 Q. In preparing for the deposition
15 today did you review any documents not
16 cited in your reply declaration?

17 A. No.

18 Q. Okay. You have a copy of your
19 first and second declaration.

20 A. That's correct.

21 Q. Okay. I have copies, too, if you
22 could look at your first declaration
23 Exhibit 1002. And just turn to the last
24 page, actually, it's on the back there,
25 Page 172. I know you confirmed this last

1 time, but could you confirm that that is
2 your signature?

3 A. It is my signature.

4 Q. And you signed this first
5 declaration on January 24th, 2024; is that
6 correct?

7 A. That is correct.

8 Q. Okay. All right. Now, if you can
9 look at your second declaration, Exhibit
10 1086, if you could turn to the last page
11 of this declaration, Page 49. And can you
12 confirm that that is your signature on
13 Page 49?

14 A. Yes, it is.

15 Q. You signed this declaration on
16 March 17th, 2025; is that correct?

17 A. That is correct.

18 Q. And did you review your declaration
19 before you signed you it?

20 A. Yes, I did.

21 Q. You reviewed the entire document
22 before you signed it?

23 A. Absolutely.

24 Q. Cover to cover?

25 A. That's correct.

1 Q. How do you spell your last name?

2 A. C, as in Charles; Z as zebra; Y;
3 two Ms as in Mary; E, echo, K as in kite.

4 Q. On the cover of your declaration
5 how do you spell your last name?

6 A. Yeah. There is a typo in my last
7 name, just like the inter partes review
8 board also did, as well. This is a script
9 error.

10 Q. And if you look on the cover of
11 your first declaration, how do you spell
12 your last name?

13 A. Again, C-z-y-m-m-e-k.

14 Q. And is that how it's spelled on the
15 cover of Exhibit 1002?

16 A. Yes, it is.

17 Q. Exhibit 1002 on the front page I'm
18 looking at it appears to be C-y-z-m-m-e-k.

19 A. Oh, I'm sorry. When I said that
20 I'm saying my correct spelling, but I do
21 see that it is spelled, the alternate,
22 which to be clear is something that I'm
23 used to my entire life being mispronounced
24 and misspelled. And it's pretty easy for
25 me to even interpret my own name when I

1 see it that way, so just to be clear.

2 Q. Were you aware when you signed your
3 own declaration that your name was
4 misspelled on the cover?

5 A. If I noticed it I would have
6 requested it to be altered.

7 Q. Are you aware of any other errors
8 in your reply declaration?

9 A. No. Not that I can think of at
10 this time.

11 Q. Do you have anything in this reply
12 declaration that you would like to
13 correct?

14 A. Not that I can think of, no.

15 Q. Did you meet with anyone in
16 preparing your reply declaration?

17 A. If you're talking about this one
18 here, the reply declaration, only Derek
19 Walter.

20 Q. Yes. I'm referring to Exhibit
21 1086.

22 A. Yes. The answer is the same.

23 Q. All right. Did you meet with
24 anyone, other than Derek Walter in
25 preparing your reply declaration?

1 A. I did not.

2 Q. How many times did you meet with
3 Derek Walter while preparing your reply
4 declaration?

5 A. By Zoom, I don't know. Maybe a
6 half a dozen times. I just don't recall
7 exactly.

8 Q. So including meetings and drafting
9 time, what is the total amount of time you
10 think you spent preparing your reply
11 declaration?

12 A. About 20 to 30 hours.

13 Q. Did you review any documents in
14 preparing your reply declaration?

15 A. Every exhibit that is part of the
16 reply declaration.

17 Q. When you say every exhibit is part
18 of the replay declaration, do you mean
19 every exhibit that's cited in the reply
20 declaration?

21 A. Correct.

22 Q. Did you review any documents not
23 cited in your reply declaration, in
24 preparing your reply declaration?

25 A. I would expect, although I don't

1 recall in the 1002 I might have looked at
2 some of those, as well to see if it made
3 sense to include them. There may have
4 been some from that group as well.

5 Q. What documents did you review in
6 that group that are not cited in your
7 reply?

8 A. I couldn't recall that. They were
9 existing exhibits so I considered them
10 fair game, just whether they would tie
11 into the reply declaration.

12 Q. Okay. In preparing your reply
13 declaration did you review any documents
14 not cited in either your first
15 declaration, 1002; or your second reply
16 declaration, Exhibit 1086?

17 A. Not that I can recall. Let me just
18 make one comment. Since I was replying to
19 I believe Dr. Shroff, I would have also
20 probably reviewed documents that he had
21 included and whether they were
22 incorporated in here. Just thinking now
23 as I'm looking back about it.

24 Q. All right. So in preparing your
25 reply declaration did you review any

1 documents not cited in either the Shroff
2 declaration, your first declaration, 1002,
3 or your reply declaration on Exhibit 1086?

4 A. I believe that's everything. I
5 can't recall anything else that would have
6 made any sense to review.

7 Q. All right. In your -- if you could
8 turn to your first declaration, Page 15,
9 do you have a copy of the claim language
10 of Claim 36?

11 A. Uh-huh.

12 Q. Do you see that?

13 A. I do.

14 Q. Do you recall putting that claim
15 language there in your first declaration?

16 A. Yes, I do.

17 Q. Okay. And on the top of Page 16
18 there is a claim element. It's 36-A
19 Remanent 2. It refers to a temperature
20 control apparatus. Do you recall that
21 claim element on 36?

22 A. I do.

23 Q. And in your reply declaration,
24 Paragraph 18, you state: Starting with
25 the claim language in my opinion there is

1 nothing in the term temperature control
2 that would require both active heating and
3 active cooling. Do you see that statement
4 there?

5 A. Which page was my statement on? I
6 want to look at the context around it.

7 Q. This is in Exhibit 1086, Page 13,
8 Paragraph 8.

9 A. Okay. I do.

10 Q. Is it your opinion that nothing in
11 the term temperature control requires both
12 active heating and active cooling?

13 A. Absolutely. That is correct.

14 Q. Do you have an understanding of the
15 term active cooling?

16 A. Active cooling means that there is
17 a device that is providing some ability to
18 cool to or -- yeah, to cool the object.

19 Q. What does it mean to actively cool
20 something?

21 A. It means that the device is
22 probably sensing a temperature and making
23 a change to the device to match the
24 temperature that it has been set to.

25 Q. Is active cooling different from

1 passive cooling?

2 A. Well, in the context of the claim a
3 temperature control apparatus doesn't
4 specify active or passive, but if they
5 both achieve the same set point, then they
6 would be equivalent in performance, as
7 well as temperature?

8 Q. What's the difference between
9 active cooling and passive cooling?

10 A. Well, passive cooling is like my
11 heater in this room. I set a temperature
12 at 37 or celsius, sorry, I'll make it 70
13 degrees. If I decide to lower the
14 temperature to 68, it does not turn down
15 the heat. And the temperature in the room
16 lowers to 68. So it's passive based on
17 the ambient environment returning it to a
18 new set point.

19 Q. How does that square with active
20 cooling?

21 A. Active cooling would be that, I
22 guess, like my air conditioner, I can set
23 it to 65 degrees. And the house is 70
24 degrees. And the system will turn on a
25 cooling mechanism to bring it down to that

1 temperature.

2 Q. Do you have an understanding of the
3 term active heating as you used it in your
4 declaration?

5 A. Well, the biopics system is an
6 active heating device, and biopics
7 objective heater is an active heating
8 device; but, as I explained, as the set
9 point in the temperature in the general
10 concept you give it a set point, and then
11 there is energy applied to get it to the
12 temperature in an active way.

13 Q. What does it mean to actively heat
14 something?

15 A. I think I just described that, but
16 I'll try to repeat it again. Usually it's
17 applying a voltage or some other mechanism
18 to heat an object to get it to a set point
19 of temperature. It doesn't have to be.
20 You can heat to infinity; but if I turn on
21 my stove in my kitchen and turn the heat
22 to high, it's actively heating, putting a
23 current through the elements.

24 Again, I'm going to emphasize,
25 there is nothing in either the claim or

1 the specification that narrows it down so
2 much that there is both active heating and
3 active cooling. It just means a
4 temperature control apparatus. And
5 everything I've described to you are
6 temperature control apparatus or
7 mechanisms.

8 Q. In Paragraph 30 of your reply
9 declaration, Exhibit 1086, if you turn to
10 that paragraph for me, please.

11 A. Uh-huh.

12 MR. WALTER: Do you have a copy of
13 it so I can follow along?

14 MR. HOLMAN: Sure, Derek.

15 MR. WALTER: Thank you.

16 Q. (By Mr. Holman) All right.
17 Paragraph 30 of your reply declaration.
18 Are you there, Dr. Czymmek?

19 A. I am, yeah.

20 Q. The last sentence there you state:
21 I agree that the FCS2 instruction document
22 teaches a system capable of maintaining
23 the temperature. And as such it is my
24 opinion that it teaches temperature
25 control. Do you see that statement?

1 A. Yes, I do.

2 Q. And when you're referring to the
3 FCS2 instruction document, you're
4 referring to the biopics FCS2 close cell,
5 that's disclosed in the Chen reference?

6 A. It is disclosed in the Chen
7 reference, but I think the document itself
8 is included as part of the exhibits from
9 1002, if I recall.

10 Q. Is it your opinion that the
11 biopics FCS2 disclosed in Chen satisfies
12 the temperature control apparatus element
13 in claim 36 because Chen's FCS2 flow cell
14 maintains the temperature of the flow
15 chamber?

16 A. Well, let me give you a little bit
17 of guidance here. And I would like you to
18 go to Page 75 of Exhibit 1002.

19 Q. Okay. Page 75.

20 A. Okay. So my point here is the
21 exact reason people purchase the biopics
22 is because of its fluidics, and its
23 extensive temperature control, including
24 in combination with the objective heater.
25 So when I look at the Chen manuscript when

1 she describes the use of bioptics FCS2 and
2 objective heater a POSA, particularly when
3 it's set to 37 degrees a POSA would
4 understand that these are serving as
5 temperature control.

6 Q. Is it your opinion that the
7 bioptics FCS2 flow cell in Chen satisfies
8 temperature control apparatus because the
9 FCS2 maintains the temperature of the flow
10 cell?

11 A. It is my opinion that Chen
12 expressly discloses the use of the
13 bioptics system, which includes the
14 objective heater and the flow cell. And
15 this a POSA would understand either
16 independently or together can be used for
17 temperature control.

18 Q. Okay. Putting aside the objective
19 heater. We'll talk about that in a
20 minute. I just want to talk about the
21 FCS2 flow cell. Is it is your opinion
22 that that apparatus, the FCS2 flow cell,
23 meets the temperature control apparatus
24 element of claim 36?

25 A. This devices does exactly that. It

1 is understood by a POSA that this device
2 would be understood by anybody using this
3 in the community that it has the
4 temperature capabilities of the system.

5 Q. Is that in your opinion because it
6 has the capability of maintaining the
7 temperature?

8 A. It can go to whatever temperature
9 that you decide to set it to, but it's a
10 temperature control device. As there are
11 temperature sensors, there is a
12 temperature control unit. I owned one of
13 these. I purchased it. This is why it
14 was used in the community because its
15 precise temperature control.

16 Q. Is Chen's FCS2 flow cell maintained
17 the temperature of the flow cell?

18 A. In combination with the objective
19 and the flow cell, this is what a POSA
20 would understand that these are used in
21 concert for.

22 Q. Does Chen's FCS2, by itself,
23 maintain the temperature of the flow cell;
24 or does it require the objective heater?

25 A. No. It can do either by itself

1 objective heater is typically used in
2 combination for a number of reasons, but
3 because the objective heater also serves
4 as a heat sync, the objective serves as a
5 heat sync and so the objective also serves
6 along with it.

7 Q. But in Chen's disclosures does chen
8 disclose using the FCS2 flow cell to
9 maintain the temperature of the flow cell?

10 A. Again, I will repeat, she discloses
11 the uses of this specific flow cell in
12 here, which has temperature control that a
13 POSA would understand could be used for
14 temperature control.

15 She also discloses the use of the
16 bioptics objective heater. As you look at
17 this figure 74.4, you can see that they
18 are used in combination and that's how a
19 POSA would have understood them being
20 used.

21 Q. Is it your opinion that every FCS2
22 flow cell comes with a heating mechanism?

23 A. I don't think people would spend
24 the extra thousands of dollars. Without
25 it they would have the versions that were

1 not used by the lab that would be simpler
2 in device; but in the end this is how
3 they're used. There were things that were
4 way cheaper that you wouldn't have all of
5 this extra stuff. That is why it's
6 bought. That is what was understood in
7 the art at the time.

8 Q. Are there FCS2 flow cells that come
9 without the heating mechanism?

10 A. The FCS2 system is understood in
11 the art by a POSA to be used for heating.
12 It's cell culture work in general, but it
13 could be, it doesn't have to be live. It
14 can be fixed material.

15 Q. Are you aware of whether bioptics
16 offered an FCS2 flow cell that does not
17 come with a heating mechanism?

18 A. Well, I think you or your expert
19 made a claim for one that's a non-heating
20 version, but what's not the one that she
21 specified in the later documents used in
22 her laboratory. And I see no evidence
23 that that was available at the time. I
24 don't recall it.

25 Q. When you say she, did you mean

1 Chen?

2 A. I mean sue, okay, I want to be
3 careful. Zhuang is the PI in the
4 laboratory, so I may -- the Zhuang lab is
5 not a she. Thank you for clarifying.
6 When I say she it's because of the Zhuang
7 lab. Z-h-u-a-n-g, but it may have an "H"
8 in there.

9 MR. WALTER: Z-h-u-a-n-g.

10 Q. (By Mr. Holman) Is it your opinion
11 that the bioptics FCS2 that comes with the
12 heating mechanism is cheaper than the FCS2
13 that comes with a non-heating mechanism?

14 A. No. I never stated that. Can you
15 repeat the question because I'm confused
16 that you made that statement. So you're
17 saying with extra features and peripherals
18 it would be cheaper; or did I
19 misunderstand you?

20 Q. Well, to be clear on the record, I
21 didn't make a statement. I'm asking you a
22 question about your opinion.

23 A. Okay. You didn't ask me if I had
24 my opinion, but go ahead and repeat your
25 question again now.

1 Q. I'm asking you now if you have an
2 opinion. Is it your opinion that the
3 heated FCS2 flow cell is cheaper than a
4 non-heated FCS2 flow cell?

5 A. I don't know what the cost of the
6 two systems, but I would assume that if it
7 doesn't have heating elements, that there
8 is a reduced cost. But it's a specific
9 part number and it may actually be
10 physically different because there is no
11 requirement to heat or maintain
12 temperature or to be able to record it, so
13 it would be much cheaper I would expect,
14 but I have zero information on the cost,
15 so I couldn't give you an opinion on the
16 cost difference. Making a speculation
17 based on there is reduced hardware,
18 controllers. You don't need controllers
19 for temperature, so just as I think here
20 now, that's what my first guess would be.

21 Q. You have a copy of the Chen
22 reference, Exhibit 1003?

23 A. I have the printed paper. It does
24 not have the exhibit number stamped, so if
25 this is not eligible, then I would be

1 happy to look at your version. If you
2 accept it you can look at my. I just
3 printed it off.

4 Q. I'll just give you mine. This is
5 the actual exhibit.

6 A. Okay.

7 Q. From the proceeding. I'll hand you
8 a copy of the Exhibit 1003, which is the
9 Chen paper we've been discussing. Do you
10 recognize this paper?

11 A. I do.

12 Q. And if you could turn to Page on
13 the NanoString Page No. 011, the bottom
14 right.

15 A. Uh-huh.

16 Q. In the middle column there at the
17 bottom there is a header that says MERFISH
18 imaging. Do you see that?

19 A. Yes, I do.

20 Q. And then the first sentence there
21 refers to the biooptics FCS2 flow chamber.
22 Do you see that?

23 A. I do.

24 Q. Okay. And this is the disclosure
25 in Chen that you relied on for the, when

1 you discussed the FCS2 flow chamber this
2 is the disclosure that you're relying on;
3 correct?

4 A. In addition to the sue reference
5 that I think one of your expert witnesses
6 brought in, which also has the explicit
7 part number of the FCS2, which has
8 heating.

9 Q. Is it your opinion, Dr. Czymmek,
10 that Chen discloses using the bioptics
11 FCS2 flow chamber to maintain a certain
12 temperature of the flow cell?

13 A. Again, it is my opinion that the
14 Chen prepare expressly describes
15 temperature control of the specimen to 37
16 degrees, which includes the bioptics FCS2
17 and/or 37, or the objective heater.
18 Please remember that the objective heater
19 is operatively coupled to the specimen
20 chamber with oil, so they're essentially
21 being temperature controlled. And in this
22 case active temperature control.

23 Q. So are you saying that the active
24 temperature control in Chen's set up comes
25 from the objective heater not from the

1 FCS2 chamber?

2 A. What I have stated to you is that a
3 POSA uses the biooptics FCS2 that's
4 explicitly used here to control
5 temperature as well. Whether she included
6 that in her methods, it's just understood
7 by a POSA in the field, but for sure I
8 would use the 37 in the sample and in 37.

9 This is what a POSA would
10 understand it to be. Nevertheless, she
11 used temperature control and disclosed
12 that in her filing in this paper. She did
13 not leave these samples in Avit
14 temperature.

15 She controlled the temperature.
16 The room will not get to 37 degrees, which
17 means the chemistry and/or the drifting,
18 or whatever she was trying to control, had
19 temperature control, which meets the claim
20 36-1A or whatever it was that we were
21 looking at, a mechanism for temperature
22 control.

23 Q. And is that because in your opinion
24 this set up maintains the temperature at
25 37 degrees celsius?

1 A. At least at some point she has it
2 at 37 degrees, correct. And maintains it.
3 I mean, this is what these devices do.
4 They're very precise control of the
5 temperature.

6 Q. And is that temperature maintained
7 through active heating?

8 A. According to the literature, yes.
9 They're applying the current. They have
10 temperature sensors both on the objective
11 collar and on the FCS2 device to be able
12 to read out what the actual temperature
13 is. And they would apply the current as
14 needed in order to maintain the
15 temperature at the set point.

16 Q. What literature are you referring
17 to when you say according to the
18 literature?

19 A. Well, I mean, you can look at the
20 exhibit here on 75. Let's go back to Page
21 75 of Exhibit 1002. Temperature sensors,
22 heater contacts, perfusion connect, the
23 connections. Okay. And the objective
24 heater. So it's stating in here that it
25 has temperature sensors and heater

1 contacts. I believe we also in my
2 document, I could go a little further. We
3 show a temperature controller where you
4 can set that.

5 You can change that temperature.
6 37 is just a number she used for
7 hybridization, which would be obvious to a
8 POSA, something you might want to do to
9 improve specificity or reduce background
10 in affixed materials.

11 Q. What happens in this system, in
12 Chen's system if the temperature goes
13 above the set point of 37 degrees celsius?

14 A. Repeat that again.

15 Q. Let me rephrase the question. How
16 does Chen's system maintain a temperature
17 of 37 degrees celsius?

18 A. It will have a sensor that is
19 reading the current temperature. And if,
20 you know, it's not going to get hotter if
21 the room is not hotter. So it may turn
22 down the current or turn off the current
23 to stay within the window of the
24 controlled temperature device and the set
25 point that they maintained.

1 Q. And what happens if the temperature
2 goes above the set point? What does the
3 system do?

4 A. Again, I said it would turn off or
5 reduce the current. You know, it's
6 measuring these things. And it has a fast
7 readout for it.

8 Q. Is that considered passive cooling
9 by turning it of?

10 A. It's temperature controlled, so
11 whether you're passive cooling or
12 whatever, it's still temperature
13 controlled.

14 Q. Is that passive cooling by turning
15 it off, bringing the temperature back
16 down, is that passive cooling?

17 A. It's temperature controlled, so it
18 doesn't matter whether it's passive or
19 active. It's temperature controlled.

20 Q. But is it passive cooling? You're
21 not answering my question.

22 A. Just like in your, in this room in
23 here, it's passive cooling, but, as I said
24 for claim 36, it doesn't specify.

25 Q. If I have a cup of hot coffee and I

1 leave it sitting out and it cools down, is
2 that passive cooling?

3 A. I guess you could use that analogy
4 of passive cooling where there is, I mean,
5 nobody is applying a temperature. I
6 suppose if you turn the temperature down
7 in the room it will cool to that
8 temperature at some point, the set point.

9 Q. So in Chen's system when you said
10 it turns off or reduces the current, is
11 that a mechanism of passive cooling to
12 bring the temperature down?

13 A. Again, it's temperature control as
14 per the claim 36. So passive cooling
15 simply turning it off, I suppose, but it's
16 still temperature control. My house when
17 I sat in this room, again when I set this
18 temperature I'm controlling the
19 temperature.

20 So whether it's passive or not,
21 turning it off means it's not actively
22 cooling it, correct, but it's still
23 temperature control. A POSA would
24 understand this that you're controlling
25 the temperature. And there are many ways

1 to go about controlling the temperature.

2 Q. And that control in this system, in
3 Chen's disclosed system, when you referred
4 to turning off or reducing the current,
5 that comes through the objective heater
6 control; is that right?

7 A. Well, it can be either.

8 Q. What does Chen disclose using?

9 A. Chen discloses using a temperature
10 controlled bioptics system called the
11 FCS2. And she specifies the objective
12 heater bioptics as well. Just because she
13 didn't say it doesn't mean, it would be
14 obvious to a POSA that that could be used
15 the same exact way. She also uses an
16 objective heater, irrespective operatively
17 coupled to the sample and its temperature
18 control.

19 It's temperature control. Not
20 ambient temperature in the room. She
21 moved it to a set point to the chemistry
22 she needed.

23 Q. In your opinion it's temperature
24 controlled because it's maintaining that
25 temperature for Chen's case, 37 degrees

1 celsius.

2 A. I believe your Shroff witness said
3 that setting to a set point is temperature
4 control. Whether you want to get into
5 semantics whether it's active or passive,
6 we can do that, but it's temperature
7 control.

8 Q. Well, I asked you about whether
9 it's passive cooling. And I think you
10 agreed that it is passive cooling. You
11 also have an opinion that it doesn't
12 matter whether it's active or passive.

13 A. That's true, yes.

14 Q. But for the record, you do agree
15 that that's passive cooling when it turns
16 off the current?

17 A. Yeah. If it's not pulling away the
18 heat in an active way using an electronic
19 mechanism, it would be passive, but it's
20 still temperature control.

21 Q. Earlier I believe you mentioned a
22 sue reference.

23 A. Uh-huh.

24 Q. Do you recall reviewing a reference
25 first author sue?

1 A. I do. It's been a bit, but I do
2 recall that.

3 Q. And, actually, in your reply
4 declaration, Exhibit 1086, turn to
5 Paragraph 28, please.

6 A. All right. Let me read it for a
7 moment. Okay.

8 Q. Third sentence there on Paragraph
9 28. You refer to the 2020 publication by
10 Sue. And you state that it was published
11 by the same group, published Chen, in
12 wherein they provide additional
13 information regarding the MERFISH system.
14 Do you see that statement there?

15 A. Yes, I do.

16 Q. And is it your opinion that Sue
17 provided additional information regarding
18 Chen's MERFISH system?

19 A. It provided in the context of this
20 particular frame, it provided the part
21 number that explicitly shows the
22 temperature control features that your
23 expert witness said did not have
24 temperature control. And I showed the
25 part number that it was not the

1 non-temperature control version of the
2 FCS2.

3 Q. Is it your opinion that Sue
4 discloses using the FCS2 flow cell to
5 maintain the temperature of the flow cell?

6 A. As I stated previously, she states
7 this particular flow cell that has
8 temperature control and the bioptics, as
9 shown on Figure 75, that's the typical
10 assembly that a POSA would understand
11 would enable temperature control.

12 So temperature control was
13 disclosed using a bioptics temperature
14 control micro fluidic system with the
15 objective. So a POSA would understand
16 that it was being used that way.

17 Q. But do you know if Sue discloses
18 using the FCS2 flow cell to maintain the
19 temperature flow cell.

20 A. Again, the point of Sue was to show
21 that she was using the temperature control
22 bioptics system, which means a POSA would
23 understand it's temperature control. As
24 soon as I hear that someone is using that
25 system, I'm thinking they're using it for

1 temperature control. She explicitly
2 states 37, as a POSA would understand
3 they're using those together.

4 Q. All right. I'm going to hand you a
5 document that's been marked Exhibit 2009.
6 Do you recognize this document, Dr.
7 Czymmek?

8 A. Yes, I do.

9 Q. And is this the sue reference we
10 were just discussing?

11 A. I believe so. I can go to the
12 materials and methods, and see if they
13 match up; but if it's the exhibit that's
14 part of our -- 2009, then yes, it is.

15 Q. And you reviewed Exhibit 2009 in
16 preparing the opinions in your reply
17 declaration.

18 A. Yes, I did.

19 Q. Did you review Exhibit 2009 in its
20 entirety in preparing your opinions in the
21 reply declaration?

22 A. I did at the time I had to make any
23 opinions on it.

24 Q. All right. If you could turn to
25 Page E7 in Sue.

1 A. Okay.

2 Q. And are you there on that page?

3 A. I am.

4 Q. And in the middle, well, I guess
5 more toward the top of the page, there is
6 a header that says: Sequential
7 hybridization of readout probes for
8 sequential or commentarial FISH imaging.
9 Do you see that header there?

10 A. Yes.

11 Q. Okay. And is this the section that
12 you refer to in your declaration, your
13 reply declaration that discusses the FCS2
14 flow chamber?

15 A. Yes. That's the one where they
16 describe the flow chamber.

17 Q. Is it your opinion that this
18 section in Sue discloses the bioptics FCS2
19 flow chamber that was used in the Chen
20 paper?

21 A. It is my opinion that this was the
22 same one that was used in the other paper
23 because I, you know, they basically, the
24 system that is described in detail in the
25 float existing configuration section. So

1 if you don't mind, I would like to read
2 ahead to that. I'm just trying to find it
3 so I have all the context.

4 Is that -- I'm trying to find the
5 fluidic system configuration. Is that
6 actually included in this document; or is
7 that supplemental, because it looks like
8 it might be supplemental. Oh, here it is.
9 I found it. On Page E5, sorry. I'm just
10 looking at all the context on here that
11 you're referring to.

12 Okay. They also show, they also
13 had it to the same chamber. Okay. All
14 right. So continue.

15 Q. Going back to Page E7 that section
16 we were looking at, sequential
17 hybridization of readout probe. Is it
18 your opinion that this section that
19 discloses the FCS2 flow chamber -- strike
20 that.

21 Is it your opinion that this is the
22 section of Sue that discloses the biopics
23 FCS2 flow chamber that was used in the
24 Chen paper?

25 A. Yes, it is.

1 Q. Is it your opinion that the MERFISH
2 methods disclosed in Sue were also used in
3 Chen?

4 A. Well, they have been modified and
5 changed for a different application and
6 specimen; so, as I stand here before you,
7 there is lot of differences between the
8 paper, but they use the similar workflow.
9 It's not identical, or it wouldn't be a
10 new paper, I guess, in the publication.

11 Q. All right. If you could turn to,
12 turn back one page to E6 in Sue.

13 A. Uh-huh.

14 Q. There is a header that says cell
15 culture preparation primary/encoding
16 hybridization. Do you see that?

17 A. I do, yeah.

18 Q. Okay. And is it your understanding
19 that this header depicts a section
20 describing the methods of primary/encoding
21 probe hybridization?

22 A. Well, I'm looking at it. That's
23 what the title states, so I'm assuming
24 without reading every single word and
25 ingredient that was done, this is the

1 encoding probe section. And so these are
2 done as steps that are separate from, my
3 recollection is from the actual automated
4 steps.

5 Q. Okay. And so for the encoding
6 probe hybridization, it's your
7 understanding this takes place outside of
8 the FCS2 flow chamber.

9 A. Well, in this particular they're
10 using those cover slips I'm reading here
11 now. Let me just make sure that I have my
12 record accurately. A lot of the steps are
13 showing how they're growing the cells on
14 the biooptics cover slips that are used in
15 the heating FCS2.

16 How they permeabilize it, and they
17 are doing basically the initial
18 hybridization of the coding probe, except
19 for they're doing DNA hybridization rather
20 than RNA, it seems to me, because they're
21 working with chromosomes.

22 Again, a lot of these steps are
23 done pre-readout. That's how I understand
24 it. It could take me about ten minutes to
25 walk through the whole thing, if you want

1 me to go in. It depends on how much
2 detail you would like me to go get to.

3 Q. About midway down, the paragraph
4 that begins to prepare for whole
5 chromosome imaging. Do you see that?

6 A. Uh-huh.

7 Q. About midway down that paragraph
8 there is a sentence that says, it begins
9 with, next, the cell cover slip was
10 inverted. Do you see that sentence?

11 A. Okay. What's the first word on the
12 left column in the sentence, binding? Or
13 I'm trying to read that.

14 Q. Next.

15 A. Okay. All right. Understood.

16 Q. Okay. And so this sentence reads:
17 Next the cell cover slip was inverted and
18 placed on a drop of 50 microliters of
19 hybridization buffer.

20 A. Uh-huh.

21 Q. And there is a parenthetical of
22 buffer. And it goes on to say:
23 Containing a mixture of primary/encoding
24 probes at 20 micro or more total
25 concentration with or without 10

1 micrograms human COT-1 DNA.

2 A. Correct.

3 Q. And there is a part number in there
4 that says 60 NA 60 millimeter pi tree
5 dish. Okay. Do you see that sentence?

6 A. Uh-huh, I do.

7 Q. I think you may have mentioned this
8 earlier, a 60 millimeter pi tree dish,
9 this is different from the bioptics FCS2
10 flow cell; is that correct?

11 A. Sure. This is the encoding probe
12 step, which is always done outside of the
13 system that she uses for imaging.

14 Q. Okay. And then Sue goes on to say
15 that this dish is partially, I'm just
16 reading from the next sentence: The dish
17 was partially submerged in a water bath at
18 90 degrees celsius for 3 minutes. And
19 incubated at 47 degrees celsius in a
20 humidified chamber for 16 to 36 hours. Do
21 you see that sentence there?

22 A. Yes, I do.

23 Q. And, again, this is the encoding
24 hybridization, which takes place outside
25 of the FCS2 flow chamber; is that correct?

1 A. In the same page as the Chen paper.

2 Q. Okay. So is it your understanding
3 that the Chen paper does a similar process
4 of encoding probe hybridization outside of
5 the FCS2 flow chamber?

6 A. The encoding probe stuff is done
7 outside. And they're all done at once, in
8 one step. It's one of the nice elements
9 of the protocol.

10 Q. Okay. And then on the next page,
11 on E-7, when we get to the section that
12 refers to the FCS2 flow chamber, that
13 section is titled sequential hybridization
14 of readout probes for sequential or
15 commentarial FISH imaging. Do you see
16 that title?

17 A. Uh-huh.

18 Q. So is it your understanding that
19 that section is discussing the secondary
20 readout probes, the sequential
21 hybridization of the readout probes; is
22 that right?

23 A. It is, yes.

24 Q. And is it your understanding that
25 the Chen, the Chen paper follows a similar

1 sequential hybridization process?

2 A. I can't state that without -- I
3 mean, there it one thing that I would have
4 to tell you is this way they structured
5 this description is disconnected. And so
6 it doesn't necessarily have to be true.

7 The point of this article is to
8 show that they had the heating version.
9 Now, whether they used it in this or not,
10 her original paper taught temperature
11 control.

12 Even if this doesn't, it's showing
13 that they have the temperature control
14 system. She recycled it from the other
15 version. I thought this one also had the
16 objective heater in it, but without me
17 having a search function in here of she
18 placed it in this document, I don't
19 recall.

20 Q. In this section, the second, the
21 beginning of the second paragraph, it
22 begins, it says: Each round of
23 hybridization consisted of the following
24 general steps. Do you see that sentence?

25 A. Uh-huh.

1 Q. Is it your understanding that this
2 is referring to the steps of the
3 sequential readout probe hybridization
4 that is taking place in the FCS2 flow
5 cell?

6 A. Let me read it for a few minutes.
7 Yeah. So she flowed the hybridization
8 with the allogeneically type probes for
9 each round. She watched, then she imaged.
10 Okay. Continue.

11 Q. Is it your understanding that this
12 workflow depicted is referring to the
13 rounds of sequential hybridization of the
14 readout probes that takes place in the
15 FCS2 flow cell?

16 A. For DNA molecules in this
17 particular section that it's specifying
18 for the DNA molecules.

19 Q. In step one here refers to flow of
20 the hybridization buffer with the set of
21 allogeneically type probes specific to each
22 round; is that right?

23 A. Uh-huh.

24 Q. And in step two cites incubating
25 for ten minutes at room temperature; is

1 that correct?

2 A. Yes. I see in this particular
3 instance, they did not apply temperature
4 control.

5 Q. All right. You can put that aside
6 for now.

7 (Thereupon, a short recess in the proceedings was
8 had.)

9 Q. (By Mr. Holman) All right. Dr.
10 Czymmek, you have Chen reference Exhibit
11 1003?

12 A. Yeah. If you don't mind, I would
13 like to make one statement about the Sue
14 reference. The point of that reference
15 was to show that that particular model
16 that she didn't disclose in the Chen paper
17 was exactly the heating model.

18 To be clear, the Sue content is DNA
19 MERFISH. And depending on probe design or
20 whatever, she may not have used it in that
21 particular case, but that's not the same
22 as saying that Chen didn't teach
23 temperature control in hers. I just want
24 to make that clear for the record.

25 Q. So is your understanding that the

1 methods, the workflow, as far as
2 hybridization methods in Sue are different
3 from those that were used in Chen?

4 A. She is looking at DNA MERFISH,
5 which may have different requirements for
6 hybridization and background that would
7 require temperature or not; so she
8 specifies in one section that she was at
9 room temperature at that point, which just
10 means that she didn't require it for DNA
11 MERFISH because DNA hybridizes at a
12 stronger affinity. It may be the
13 background is less of an issue. It is
14 Jung lab. I don't know if Sue is a male
15 or female. My comment, this is just to
16 show that it's here. Whether she used it
17 for DNA MERFISH. It can be different than
18 RNA MERFISH as far as probe design the
19 requirement for temperature. Chen's paper
20 discloses temperature control. Sue shows
21 that the particular FCS system, which is
22 being questioned by your team was actually
23 the temperature control version.

24 Q. And I think you said that you're
25 relying on Sue for its disclosure of the

1 FCS2 flow cell.

2 A. That it's being the temperature
3 control version because your expert or
4 whatever it was that said that there is a
5 non-flow cell for non-temperature control
6 version. And this is to show that that
7 was not the case. It was not about me
8 using that protocol in prior art. It was
9 simply to show that connection that it
10 was, indeed, the heat version.

11 Q. And it's your opinion that Sue's
12 reference to the FCS2 flow cell
13 specifically discloses that that very FCS2
14 flow cell is the same one used in Chen.

15 A. It has the part number that is
16 assigned the same one. And if you look at
17 her thing, she references a fluid exchange
18 in this part of the protocol which she's
19 using the custom built fluidic system.

20 And then she references her Chen
21 paper in the same paragraph. So, yes, I
22 would say she recycled it. She didn't go
23 out and buy a new one. In this particular
24 case whether she required temperature
25 control is irrelevant, the Chen paper did,

1 and was specified.

2 Q. Okay. Let's take a look at the
3 Chen reference, Exhibit 1003. Do you
4 still have that handy?

5 A. Yes, I do.

6 Q. If you could please turn to Page 12
7 NanoString Page No. 12 of the document.
8 And the middle column of Page 12, the
9 first full paragraph. At the very end of
10 that paragraph Chen refers to tiling
11 images. Do you see that sentence there?

12 A. I do, yeah.

13 Q. Chen states: Tiling images of
14 adjacent areas and adjacent focal planes
15 could be used to improve the accounting
16 accuracy. Did I read that correctly?

17 A. Yes, you did.

18 Q. Do you have an understanding of
19 this tiling process that's referred to
20 here in Chen?

21 A. I understand what tiling images is
22 and I understand what adjacent focal
23 points is.

24 Q. And when Chen refers to tiling
25 images, so Chen refers to tiling images in

1 adjacent areas and adjacent focal planes.

2 A. Uh-huh.

3 Q. So when Chen refers to tiling
4 images, we'll take these one at a time.

5 When Chen refers to tiling images in
6 adjacent areas, what is Chen referring to
7 there?

8 A. Well, you have to, this is a little
9 bit more context. The previous sentence
10 says: This number accounts for the
11 majority, but not RNA or molecules within
12 a cell because a fraction of a cell could
13 be outside the imaging area for focal
14 depth.

15 So when she's doing this she is
16 tiling to multiple locations. Okay? And
17 what she's saying is that you can also
18 look at adjacent focal planes, suggesting
19 3D so you don't miss anything because most
20 cells are flat and a POSA would have been
21 motivated to do this in 3D and had a good
22 chance of success because she states:
23 Tiling of images of adjacent areas and
24 adjacent focal areas could be used to
25 improve the counting accuracy.

1 Q. For so adjacent areas, is that
2 referring to adjacent fields of view?

3 A. Yes. I would call it that.

4 Q. And is that adjacent area, adjacent
5 fields of view, that's in the XY lateral
6 plane?

7 A. Tiling of adjacent areas would be
8 lateral plane, exactly in, my view.

9 Q. Okay. And then for tiling of
10 adjacent focal planes.

11 A. No. That's not what it says.

12 Q. I'm asking you a question. For
13 tiling of adjacent focal planes, that's
14 referring to adjacent planes on Z-access;
15 is that right?

16 A. So the way she's wording the tiling
17 of images of adjacent areas and adjacent
18 focal planes means that you can tile to
19 another location, and also look in the
20 Z-access in adjacent focal planes.

21 This is how you would get counting
22 accuracy. It wouldn't make any sense to
23 just tile to another location. And if
24 you're restricting your volume, this is
25 all in the context of cells have

1 three-dimensional space. This is why I'm
2 going to the sentence previous, but you
3 don't get it all if you look at a thin
4 slice. And a POSA would have been
5 motivated to do statistically more cells,
6 but also to get account accuracy by
7 looking at adjacent planes because you're
8 missing information if you just do one
9 plane in most cases.

10 Q. Sir, so you're saying that tiling
11 of adjacent areas and adjacent focal
12 planes means you're looking at adjacent
13 fields of view and up and down Z-access
14 adjacent focal planes.

15 A. She's saying tiling images of
16 adjacent areas, which means another batch
17 of cells; and adjacent focal planes is
18 possible, correct.

19 Q. Okay. Is tiling the same as Z
20 scanning?

21 A. So some people might refer to that.
22 In general the understanding is tiling
23 would be a patch, a next adjacent patch,
24 and a patch in a tile, like montage way.
25 The way she framed this, some people may

1 also interpret tiling to be, when you say
2 adjacent focal planes, it could mean that
3 you're combining tiling with adjacent
4 Z-stacks.

5 Okay. So it could be used
6 together, which is how she kind of framed
7 this. If you want to increase counting
8 accuracy because you're missing
9 information, you look at your adjacent
10 focal planes, which is Z-stacking.
11 Adjacent focal planes is Z-stacking.

12 Again, you have to look at the
13 contents. If you're missing some of them
14 because your one plane doesn't have it.
15 And you don't want to miss them if you
16 want higher accuracy.

17 This is exactly what people would
18 want to do in spatial elements, is to not
19 take one thin sliver of a cell and use
20 that for your interpretation because
21 they're three-dimensional.

22 Q. And in your previous answer I think
23 you mentioned Z stacking. Is Z scanning
24 the same as Z stacking?

25 A. I would say there is a couple ways

1 that people, they call them optical
2 sections and things like this. So Z
3 stacking and Z scanning -- well, Z
4 scanning and optical sectioning oftentimes
5 are used interchangeably. Adjacent focal
6 planes is in my view synonymous.

7 Q. Okay. So tiling adjacent focal
8 planes, Z-stacking, Z-scanning optical
9 sectioning are all --

10 A. There may be others, it's just
11 depending on, you know, who taught you or
12 which paper you read and what you are
13 referring to.

14 Q. But it's your opinion those are
15 considered synonymous.

16 A. In general off the top of my head
17 there is always context that might change
18 that, but in what I understand when people
19 are saying adjacent focal planes they're
20 talking about capturing a volume,
21 Spatially distinct Z positions in a
22 certain location.

23 Q. Okay. And when Chen refers to
24 improving the counting accuracy --

25 A. Uh-huh.

1 Q. What is Chen counting there for
2 accuracy?

3 A. She's talking about the spots. The
4 number of counts, this number of counts.
5 So she's talking about the copy of numbers
6 of RNA species per cell. So if you want
7 to copy the number of RNA species in a
8 cell, and you only have part of the cell,
9 if you want to improve accuracy, you would
10 capture the volume of it by using adjacent
11 Z-planes and adjacent areas. If you want
12 to also include statistics of more cells.

13 Q. So counting the spots is, the spots
14 are RNA species. Is that what you said?

15 A. Yes.

16 Q. Okay.

17 A. That's one intent of spatial
18 elements is to know how many messages per
19 cell, yeah.

20 Q. And so when Chen is referring to
21 improving the counting accuracy, is it
22 fair to say that Chen is referring to
23 counting the RNA molecules?

24 A. This number accounts for the
25 majority, but not all RNA molecules. So

1 I'm going to make that linkage, yes.

2 Again, to be clear, she is explicit
3 because a fraction of the cell could be
4 outside the imaging area or focal depth.
5 Both of those areas is where the tiling
6 comes in. Focal depth is where adjacent
7 focal planes come in.

8 Q. And when, in this tiling of
9 adjacent focal planes is Chen, is this
10 process referring to looking at different
11 RNA molecules from the primary focal
12 plane; or is it the same RNA molecules,
13 just one plane below or a plane above?

14 A. Okay. Every cell is different.
15 And if you're thinking of a tissue, I
16 can't say, for example, that they're going
17 to be identical because that's the whole
18 point of, you know, the cell variation and
19 the messenger RNA is produced, even within
20 the cell type it could be the same. What
21 my understanding here is that she has one
22 slurry, one probing cluster. Maybe it's
23 100 probes. It's going to be the same
24 probe she's hybridizing. Whether that
25 given cell expresses how many, would

1 depend on the cell and its location and
2 it's relationship and the condition it's
3 grown under.

4 So it would be the same 100 she's
5 probing for. Whether it has it or not is
6 going to depend on the plane you're in and
7 the cell type. And, you know, the cell
8 experience that would trigger its
9 expression of that molecule. Is that
10 clear enough?

11 Q. I think so.

12 A. She has a fix kit. I didn't mean
13 to interrupt. She has a fixed number.
14 She's probing for all of them. If they're
15 there or not, it's really dependent on
16 whether the cell expressed it.

17 Q. In counting RNAs in different
18 planes, adjacent focal planes or adjacent
19 areas together, does that result in
20 duplicative counts of the same RNA
21 molecule?

22 A. It depends on how they set up the
23 scanning conditions. So, theoretically,
24 there is one true focal plane where a
25 molecule will have the most intense

1 signal, but these are thresholding
2 conditions or spot holding conditions
3 where you could determine that. So, you
4 know, if they have the condition set right
5 on their analysis, the answer could be no.
6 If they do very small stepping you will
7 see overlap. This is understood on how it
8 works by a POSA.

9 If they make bigger steps, then the
10 answer could be no, depending on which
11 type of technology they're using. Some
12 are better than others of making sure
13 there is no duplicative information from
14 the spot.

15 Regardless, having the
16 three-dimensional information and the spot
17 more intense in an adjacent plane, you can
18 do fits to know there is one of them. And
19 so there are mechanisms to deal with that.

20 Q. When you say do fits, what do you
21 mean by do fits?

22 A. Well, you have to identify a spot.
23 So, you know, Gaussian fit -- 3D fit or
24 whatever approach is used to identify that
25 spot and assign its, you know, it's

1 encoded message what it is.

2 Q. Uh-huh. All right. In Chen if you
3 could turn back one page, Page 11.
4 Right-hand column at the top, about six or
5 seven lines down, there is a sentence that
6 begins: Constant focus was maintained.
7 Do you see that?

8 A. Uh-huh.

9 Q. Do you see that sentence there?

10 A. Okay. Maintained. Yes. Constant
11 focus was maintained throughout the
12 imaging process with a home built auto
13 focusing system. Got it.

14 Q. Yes. That's the sentence. Now, is
15 it your opinion that Chen's auto focusing
16 system includes a Z access motion control
17 system?

18 A. Well, in order for you to make
19 corrections in auto focus they would have
20 to have the Z position element.

21 Q. Is that a yes?

22 A. That's a yes.

23 Q. Is it also your opinion that the Z
24 access motion control system -- strike
25 that. Do you still have your first

1 declaration Exhibit 1002?

2 A. Uh-huh.

3 Q. If you could turn to Paragraph 183
4 there. It's on Page 91.

5 A. Yes. I'm reading through the
6 paragraph. Okay. Go ahead.

7 Q. And the first sentence there you
8 state that to the extent patent owner
9 contends that the claim for prior
10 motorized automation of the Z access
11 motion controlled system. And this Jung
12 which we're calling Chen now does not
13 expressly teach this. Automation by
14 motorization would have been obvious in
15 view of Jung/Chen. Do you see that
16 sentence there?

17 A. Uh-huh.

18 Q. So is it your opinion that the Z
19 access motion control system of claim 36
20 would have been obvious in view of Chen
21 alone?

22 A. So I'm looking at the claim.

23 Q. Uh-huh. Okay.

24 A. So two things, number one is the
25 claim specifies a Z access motion control

1 system configured for Z motion of an
2 objective focal plane through set volume;
3 okay?

4 Q. Uh-huh.

5 A. So the focus control that she had
6 on here implies that she has Z access
7 control because how else can she position
8 it? Also the same exact system was used
9 to take the Z stacks.

10 Now, whether she used a different Z
11 motor on a different part of the system or
12 a piezo Z stage, nevertheless, she is able
13 to have Z access control on her system.

14 So I guess that's what I'm trying
15 to say here. How would you like me to go
16 further on that?

17 Q. Well, I just want to make sure I
18 understand the statement correct. In your
19 previous declaration testimony, is it your
20 opinion that the Z access motion control
21 aspect of claim 36 would have been obvious
22 based on Chen's disclosure alone?

23 A. Okay. Two things. She has Z
24 access control as specified in the patent
25 because it allows the objective to be

1 positioned in a very specific plane. So,
2 period, that's the reality. The reason
3 why we also included Chen and Cai, C-a-i.
4 I don't know if that was in this one, was
5 to remove any doubt that these systems are
6 configured. They come equipped. If you
7 also look at the Olympus manual, these are
8 equipped. It's just understood by a POSA
9 that you have Z control on your
10 microscope. Otherwise, you can't focus
11 your sample. Okay? So the answer is it's
12 there, a POSA would have understood. It
13 would have been obvious. So by her using
14 an Olympus it's fine. We have additional
15 supporting documents in the Olympus
16 manual. And in Chen and in Cai access
17 control is obvious.

18 Q. Does Chen allow render Z access
19 motion control obvious?

20 A. In my view, yes.

21 Q. Going back to your reply
22 declaration, Paragraph 38. Are you there?

23 A. Yeah. I'm just reading through.

24 Okay.

25 Q. All right. In the first sentence

1 of Paragraph 38 you state that Dr.
2 Shroff's own discussion of optical
3 sectioning in Paragraph 36 of his
4 declaration describes this as a method for
5 generating 3D data.

6 A. Okay.

7 Q. Do you see that? Did I read that
8 correctly?

9 A. Yes.

10 Q. All right. I'm going to hand you a
11 copy of Exhibit 2024, the Shroff
12 declaration. Do you recognize Exhibit
13 2024 as the Shroff declaration?

14 A. Yes, I do.

15 Q. Okay. All right. If you could
16 please turn to Paragraph 36.

17 A. Uh-huh.

18 Q. It's on Page 32.

19 A. Uh-huh.

20 Q. All right. The first sentence in
21 Paragraph 36 of Dr. Shroff's declaration
22 states: The optical sectioning is one
23 technique for improving SNR and SBR that
24 would have been understood by a POSA. Do
25 you see that sentence?

1 A. Yes. I see that sentence, yes.

2 Q. And here Dr. Shroff is discussing
3 optical sectioning to improve SNR and SBR;
4 is that correct, for that sentence?

5 A. Yes.

6 Q. Okay. The next sentence Dr. Shroff
7 says: Optical sectioning techniques
8 require images of thin slices of an
9 otherwise thick specimen while removing
10 florescent's contribution by out of focus
11 light in the imaged plane. Do you see
12 that sentence?

13 A. Uh-huh.

14 Q. All right. And the second sentence
15 discusses optical sectioning as a
16 technique for removing florescence from
17 out of focus planes; is that correct?

18 A. Uh-huh.

19 Q. Okay. All right. And then the
20 next sentence from Dr. Shroff says: This
21 basic process is depicted in the figure
22 below. And provides an image from Exhibit
23 2078. Do you see that, that sentence and
24 the figure there?

25 A. Yeah. Confirm which one was it

1 again.

2 Q. The third sentence of Paragraph 36
3 in the Shroff declaration. He states:
4 This basic process is depicted in the
5 figure below. And he provides a figure
6 from Exhibit 2078. Do you see that?

7 A. Yes, uh-huh.

8 Q. And this figure he has shown here
9 shows, depicts optical sectioning; is that
10 correct.

11 A. Yep. It shows optical sectioning
12 of a 3D object.

13 Q. And the figure legend there states
14 that contamination could be removed by
15 imaging processing -- image processing,
16 conflict imaging, or two futon excitation
17 microscopy; is that correct?

18 A. Yes, that's correct.

19 Q. Okay. And when this figure is
20 referring to contamination, is it your
21 understanding that it's referring to
22 florescence contamination from other
23 planes?

24 A. Well, to be clear, optical
25 sectioning is simply focusing the system

1 into different focal planes. So you can
2 use a confocal to clean the optical
3 section, but I would argue that even wide
4 fields have optical sectioning because
5 you're plane, moving into a physical
6 plane. Optical sectioning on certain
7 devices reject out of focus lights. Some
8 better than others.

9 Okay? Either by just imaging in
10 that plane only. Others will exclude the
11 light. Others will use mathematical
12 process to reassign that height and create
13 basically these optical sections.

14 In this particular case the reason
15 I referenced it is because he shows
16 basically the ideal of optical sectioning
17 creating a 3D object, so it would be
18 understood.

19 It also can with some technologies
20 have the benefit of reducing a background
21 or out of focus information.

22 Q. What's the contamination being
23 referred to in this figure capture for
24 your legend?

25 A. In this particular case it's

1 showing out of focus information.

2 Q. All right. Back to Shroff's
3 testimony on Paragraph 36, just under this
4 figure we were looking at, there is a
5 sentence, the next sentence in this
6 paragraph, Dr. Shroff states: As
7 illustrated above optical sectioning
8 involves focusing a microscope's objective
9 on a single plane, plane J in the figure,
10 while removing background florescence
11 sourced from other planes in a big sample.
12 For example, how to focus planes K in the
13 figure above. Do you see that sentence?

14 A. I see that sentence.

15 Q. All right. And this sentence in
16 Dr. Shroff's declaration is referring to,
17 again, removing this background
18 florescence from other planes. Is that
19 what he's discussing here?

20 A. Again, an optical section is as he
21 described. So optical sectioning is a
22 term that is used in the art by a POSA to
23 also refer to creating three-dimensional
24 volumes. And because his diagram
25 illustrates that clearly, yes. It's a

1 benefit of an optical section, but even,
2 again, focusing on different planes, they
3 call it optical sectioning because the
4 objective lens has a specific region that
5 is in focus. You can optical section
6 without a focused light. You can get
7 optical section techniques which are
8 better than others at rejecting that out
9 of focus light.

10 So to be clear, he's talking about
11 removing background florescence with
12 explicit techniques that are better than
13 others who are doing it. And he's using
14 an example of the 3D optical section,
15 which is exactly what a POSA would have
16 understood, and would have been motivated
17 to try on a cell if you wanted 3D.

18 So, yes, it reduces background to
19 improve signal to noise. Exactly what a
20 POSA would have understood to do if that
21 was a challenge. And it's just as it's
22 been referred to in the Chen paper that
23 other optical sectioning techniques can be
24 used.

25 So my point is, yes. It's there,

1 he talks about it. I'm telling you
2 optical sectioning and the way his diagram
3 is, it's showing an example of 3D. And
4 when you ask him does optical sectioning
5 create a 3D data, his answer was yes.

6 Q. I understand your opinion is that
7 optical sectioning can be used for 3D
8 imaging, but you agree that paragraph 36
9 of Dr. Shroff's declaration he talks about
10 removing background florescence.

11 A. He's talking about removing
12 background florescence illustrating an
13 example a POSA would understand is the
14 typical reason you use optical sectioning.
15 It's not to go on a giant brain tissue and
16 extract out one thin plane in itself, by
17 itself, you do get other focus
18 information, but you're using it to
19 collect volumes and to get clear. There
20 is other things it does. It gives you
21 high resolution on some of these
22 techniques, but he's showing a 3D example.
23 That's the point of my comment. It shows
24 evenly spaced a 3D object. He refers to
25 optical sectioning in some of the

1 modalities that will reduce and improve
2 background. I agree with that, but I'm
3 telling you he's using an example that
4 shows a 3D dataset which is exactly how a
5 POSA would have understood it. In fact,
6 that's probably why he did it because
7 that's how a POSA understood it.

8 Otherwise, he would show just a 2D
9 slice. And show something different. He
10 would have gotten rid of all these other
11 3D slices that make this a 3D object.

12 Q. So do you not using optical
13 sectioning to remove out of focus light
14 from a 2D image?

15 A. I just want to make sure because
16 that sounded like a double negative. Can
17 you rephrase it for me?

18 Q. Sure. Sorry that was not a clear
19 question. Can you use optical sectioning
20 to remove out of focus light in 2D
21 imaging?

22 A. An optical section on its own is
23 inherently 2D.

24 Q. Is that used to remove out of focus
25 light in 2D imaging?

1 A. An optical section?

2 Q. Yes.

3 A. Not on its own because I have a
4 broader definition of optical sectioning.
5 I think you can use a light microscope and
6 set up and take a Z stack. And it would
7 essentially be optical sectioning, but it
8 is out of focus information. It depends
9 on the technology she's using to remove
10 it. Whether it's an exitation print vocal
11 principle; or if it's a mission print
12 vocal principle, like a spinning disk or a
13 confocal would be. Optical section is
14 just where the objective plane is focused.
15 You put them together in a certain way you
16 can get a volume. Very easily. Very
17 understood. It's like that's why they
18 have these optical sectioning systems.
19 That's what their primary bread and butter
20 is.

21 MR. WALTER: I was just going to
22 say slow down a little bit.

23 THE WITNESS: I apologize.

24 A. I know quit well for sure, but I
25 just want to be clear, optical sectioning

1 is not one off, and his diagram
2 illustrates exactly a 3D object that is
3 optically sectioned.

4 Q. (By Mr. Holman) All right. I'm
5 going to hand you an exhibit marked 2078.
6 Do you recognize this document, Dr.
7 Czymmek?

8 A. Yes. It's been a bit, but I do.

9 Q. And if you turn to Page 25 of this
10 exhibit.

11 A. 25. Okay. Got it.

12 Q. Is that, does that appear to be the
13 same figure we were looking at in the
14 Shroff declaration?

15 A. Yes, it is.

16 Q. Okay. The first page of Exhibit
17 2078 at the bottom it says: Published
18 online August 14th, 2020. Do you see
19 that?

20 A. Okay. I'm looking right now. It's
21 Page 27 you said?

22 Q. No. The first page, Page 1.

23 A. Got it.

24 Q. Page 1, the bottom of the page, it
25 says published online August 14th, 2020.

1 A. I see it, yes.

2 Q. Okay. Is it your understand that
3 this paper published online August 14th,
4 2020?

5 A. I understand that according to this
6 it was published on August 14, 2020,
7 right.

8 Q. Do you understand that because it
9 was published in 2020 Exhibit 2078 is not
10 prior art to qualify for the patent?

11 A. I understand that it would not
12 considered prior art, but it was
13 introduced in the exhibits.

14 Q. All right. Let's take a look at
15 the Cia reference. Do you have a copy of
16 Cia with you?

17 A. No. I do not.

18 Q. I'll give you one. All right.
19 Here we have Exhibit 1004. Do you
20 recognize Exhibit 1004?

21 A. I do.

22 Q. And that's the Cia reference you
23 used in both of your declarations;
24 correct?

25 A. Correct.

1 Q. All right. Did you review Cia in
2 preparing your opinions in your reply
3 declaration?

4 A. I did to the extent that I cited
5 particular sectioning in it, but I
6 reviewed it completely at some point.

7 Q. If you could turn to Page 35 in the
8 NanoString page numbers, Page 35.

9 A. Okay.

10 Q. And column 11, the left-hand column
11 there, beginning Lines 17 discusses Figure
12 16. Do you see that paragraph there?

13 A. Yes, I do.

14 Q. In here Cia discloses clarity with
15 Niss1 or, sorry, do you know if it's
16 Niss1?

17 A. Yeah. It's N-i-s-s-1.

18 Q. Okay. Thank you. Cia discloses
19 clarity with Niss1, one millimeter thick
20 coronal section -- there is a
21 parenthetical there -- of a Thy-1 EYFP
22 mouse brain was cleared and stained with
23 NeuroTrace florescent Niss1 stain.

24 A. Uh-huh.

25 Q. Do you have an understanding of

1 what a Thy-1 EYFP mouse is?

2 A. Okay. I know that they use it.

3 They're using it as a marker for specific
4 neurons in a three-dimensional brain. And
5 he's using this as an example of 3D
6 optical sectioning in the light sheet that
7 would be relevant to the ability to do
8 allnuk-utilization. In this particular
9 case the Thy-1 EFP is just simply, again,
10 I want to be a little bit careful. It's
11 been a bit, but I know they use this Thy-1
12 EFP mouse all the time.

13 Q. Do you know what is -- strike that.
14 I think you said that the Thy-1 labels
15 specific neurons.

16 A. Well, that's what I believe, but
17 I'm not a neurologist. I know just know
18 that they use Thy-1 EFP mice all the time.
19 To me it's not off the top of my fingers.

20 Q. Do you know what EYFP is?

21 A. Yeah. Yellow, enhanced yellow
22 florescent protein. It's a genetically
23 encoded protein.

24 Q. So is the EYFP a protein expressed
25 in these neuron cells?

1 A. Yeah. It's some component in the
2 mouse. My assumption is a specific
3 population of neurons.

4 Q. Sorry. It's your understanding
5 that the EYFP is expressed in a certain
6 population of neurons.

7 A. I mean, again, don't hold me to it.
8 I just, that would be my guess. They're
9 working with brains on it. And they're
10 looking for some -- I'm looking at it
11 right now. So I would have to look at the
12 methods to see if the Nissl was just
13 stating things generally. If these arrows
14 are pointing -- let me look at the legends
15 for just one second. So it's 16 clear
16 because the arrows indicate aprical
17 dendrites of the para middle neurons,
18 right florescent Nissl green EYFP. So if
19 I had a color picture of this handy, I
20 could tell you which one is which. It
21 might be the green on these, but I can't
22 tell in the black and white photograph.
23 So Nissl may be, again, my recollection
24 was the background was red, but this is --
25 do you have a color version, if you want

1 me to look?

2 Q. This is version that Bruker
3 submitted in this proceeding. This is
4 what we have.

5 A. Okay.

6 Q. The same version you submitted with
7 your first declaration.

8 A. Yes. This isn't a patent.
9 Sometimes they come across that way, so --
10 I mean, we could go to the Cia's lab
11 paper, maybe they used it. I don't know.
12 All right. Either way, maybe, I believe
13 it's here. Let's just go under that
14 assumption for the moment, but I'm going
15 to say without having a color photo I
16 don't know if those arrows are pointing to
17 the EYFP version based on the figure
18 legend without the color, but this is a
19 three-dimensional image of a brain,
20 showing both the single optical slice,
21 which would give you 2D and Z position
22 information within a much larger volume
23 that they tiled into 3D stacks. Something
24 a POSA would have understood and been able
25 to do.

1 Q. So in this image on Figure 16 the
2 eYFP is expressed in some cells. That's a
3 protein that we're seeing.

4 A. Uh-huh.

5 Q. And then the other florescence is
6 coming from the Nissl stain; is that
7 correct?

8 A. Correct.

9 Q. And forgive me if you mentioned
10 this earlier, what is Nissl?

11 A. I mean, it's just some other
12 proteins. I mean, brains are very lipid
13 rich. There may be some lipids inside of
14 there that brains would have picked up and
15 used as a nice background of staining of
16 material, of everything else in your
17 target.

18 Q. So Nissl stains everything?

19 A. No. It has no specific chemistry.
20 It's binding, but it's maybe more of a
21 general set of plasmic, but since I don't
22 do brain work every day, I don't have that
23 particular dye off the top of my head, but
24 I know Nissl stains is probably just the
25 generic, you know, color stain to -- we

1 use generic stains sometimes to label
2 general cell information in addition to
3 our target.

4 Q. So does Nissl stain, does it stain
5 an entire cell?

6 A. Again, I'd have to, you know, do a
7 little bit of homework on it, but that's
8 not the point. I want to make a point
9 here that a POSA would look at, you know,
10 this Cia patent, talking about using
11 nucleic acid and coding methods with the
12 like sheet inside of brains. And then he
13 gives explicit examples, such as Page 21,
14 which is Figure 18, where he shows a 3D
15 reconstruction of beta-Actin messenger on
16 it using hybridization chain reaction. So
17 you have to look at this together that a
18 POSA would have been motivated, 3D, 3D,
19 optical slice in 2D within a whole volume.
20 Every optical slice has an X, Y and Z
21 position. First spatial information. So
22 these are things that a POSA would have
23 understood what the capability would have
24 been, and been motivated to use 3D to see
25 this type of thing.

1 Q. Is figure, the data on Figure 16
2 did you say that's images in the light
3 sheet as well?

4 A. Well, let's see if he specified
5 that. 16, clarity, Nissl. I believe it's
6 the SPIM. In that particular figure he
7 doesn't mention it. But he talks about
8 SPIM in the Actin cells on Figure 18. You
9 may have to go into the context of the
10 document of some other imaging technique,
11 but remember a POSA would have used the
12 appropriate technique depending on what
13 their application and what they needed to
14 see. So SPIM or not is providing these
15 sections that are clear and crisp that are
16 3D in representations. And in combination
17 with everything else that is disclosed in
18 here, including Figure 18, a 3D
19 reconstruction of a nucleotide, which
20 everybody would have been motivated to
21 basically seeing this data because they
22 demonstrated it. It's possible.

23 Q. Figure 16 doesn't use nucleus
24 probes; is that correct?

25 A. It doesn't, but it demonstrates

1 what a POSA would have understood. It's
2 possible to use an optical sectioning
3 technique. And this is meant as an
4 illustrated purpose for potential for
5 large brain slices; or, as I mentioned in
6 Figure 18, smaller chunks of tissue and/or
7 individual cells within those small chunks
8 of tissue.

9 Q. Yeah. Let's look at Figure 18 in
10 Cia. Do you have an understanding of
11 that, what's depicted in Figure 18?

12 A. Yeah. I'll read it. SPIM detects
13 single messenger RNAs in 100 micron
14 clarity brain slices. The slice was
15 scanned over 100 microns. The images were
16 then registered and stitched to a 3D
17 reconstruction. Diffraction limited dots
18 in the image corresponded to single actin
19 beta messenger RNA, which is detected by
20 HCR.

21 And this is the actual figure is
22 showing because it's a three-dimensional
23 volume, individual spots that can be
24 detected. It's representing 3D, which
25 would, again, motivated a POSA to use this

1 type of approach to look at thicker
2 tissues if they chose to.

3 Q. And, for the record, you were just
4 reading from Column 11 in Cia right around
5 Line 27; is that correct?

6 A. Figure 18, it looks like it would
7 be 27, yes.

8 Q. And so in Figure 18 the florescent
9 spots we're seeing are labelled actin aRNA
10 molecules; is that right?

11 A. Yeah. Single beta actin messenger
12 RNAs.

13 Q. And is that just one color of
14 florescence being omitted?

15 A. In this particular example? Yes.
16 It's one or more, single nucleic acid, so,
17 yes. It's one in this particular case.
18 One in 3D.

19 Q. Is this -- so this is a single
20 target one nucleic acid target image.

21 A. Yes. It's something a POSA would
22 have looked at and been motivated to
23 expand. It could have been more, it could
24 have been one. I can understand the
25 patent claim 36 specifies one or more. So

1 that particular claim element would meet
2 that requirement. That one, doesn't mean
3 he did everything else the same.

4 Q. Uh-huh. And to image this beta
5 actin in Figure 18 they used HCR; is that
6 right?

7 A. Yes, hybridization chain reaction,
8 correct.

9 Q. Is that a type of implication?

10 A. Yes, it is. It uses, actually, I
11 do this regularly in my laboratory. And
12 it's actually appropriate for this
13 particular tissue when you want to amplify
14 the signal far more because you basically
15 form, you have a hairpin that forms a
16 chain reaction of florescent signal.

17 By using nucleic acids to amplify.
18 And it reduces background. So, yes, I'm
19 familiar with it.

20 Q. Were these -- these were also the
21 tissue in this Figure 18, was also CLARITY
22 cleared; is that right?

23 A. That's correct, yes.

24 Q. What is the CLARITY clearing
25 process -- strike that. What is the

1 purposes of CLARITY clearing?

2 A. Okay. Clearing in general is a
3 process in which you improve the optical
4 qualities of a particular material. The
5 chemistries can vary on how you do that,
6 but you're usually denaturing or removing
7 certain elements to make it translucent or
8 transparent.

9 So that the imaging is easier. At
10 the same time it may also reduce some
11 background, but CLARITY is used in brains
12 quite frequently because it's compatible.
13 It's a technique that detects single
14 messenger RNAs.

15 You can use them together or in
16 combination. If you look at his paper, he
17 actually would use different color encoded
18 strategies to label the single messages in
19 a multiplexing way.

20 Q. Did you say, sorry, did you say
21 CLARITY is a technique?

22 A. No, HTR, I'm sorry, he used HTR as
23 one of his approaches. If I said CLARITY
24 I misspoke. If you look at the record,
25 thank you if you caught that, but that was

1 just me misspeaking. CLARITY is just used
2 for clearing brains or other types of
3 tissues. If I said anything otherwise HDR
4 is used to look at single messenger RNAs
5 because of the application. And it can be
6 colors. I do it three color in my lab. I
7 do it multiplexing, so, yep.

8 Q. You have, do you have an
9 understanding of point spread function or
10 PSF?

11 A. Yes, I do.

12 Q. Is it your opinion that a POSA
13 would not consider PSF at all when imaging
14 thin samples which still have a 3D volume?

15 A. I think I had a question like this
16 in my previous one. You know, this is
17 always a qualifier on it. A lot of POSAs
18 can go in and take a three-dimensional
19 image.

20 And when they do that they try to
21 match the optic of the media and the
22 sample qualities because they know it
23 could be impacted, but they understand the
24 point spread function can be influenced.

25 And depending on the question, you

1 know, they do their thing. Depending on
2 the optic, depending on the condition, the
3 PSF can change. It may not matter at all
4 in answering the question they need. It's
5 a consideration.

6 I don't think anybody loses sleep
7 on it overnight; but if you're trying to
8 do it, you have to know that it's there.
9 If you need more resolution you have to
10 take steps to try to improve it. And
11 those steps were known, and they existed.
12 And there is lots of ways to handle it.

13 Q. How does point spread function
14 affect imaging in thin samples which still
15 have a 3D volume?

16 A. So point spread function still
17 exists. If you're looking at single cells
18 near the coverslip, it will be near ideal.
19 If your tissue has match refractive index
20 with it, as you move further away from the
21 coverslip you get something called spirit
22 elaboration where it can get asymmetrical
23 and cause more distortions. Again, it's
24 part of the reason why people use things
25 like CLARITY or matching in other effects

1 next to the media with their sample; or
2 using an optic, using oil lenses into
3 watery samples. You wouldn't do if you're
4 going deep, but you can use an oil lens
5 with a watery sample right near the
6 coverslip because it's tolerant and it
7 doesn't have an effect that you couldn't
8 handle.

9 Q. What variables must a POSA consider
10 to account for PSF when imaging thin
11 samples would still have a 3D volume?

12 A. So, okay, state that again because
13 this can become, you know, there is lots
14 of things that can influence it.

15 Q. Sure. So you mentioned that, you
16 know, if you're imaging cells are really
17 close to the coverslip maybe PSF is less
18 of an issue, farther away it might become
19 more of something to deal with.

20 A. Uh-huh.

21 Q. So I'm asking what other, in
22 addition to the closeness to the coverslip
23 of what you're imaging, what other
24 variables a POSA would consider to account
25 for PSF?

1 A. All right. I'll name a few now.
2 Whether it's exhaustive, I'm just going
3 out of a stream of consciousness here.
4 Number one is the numerical aperture of
5 the injective lens. Okay? The higher the
6 numerical aperture and under ideal
7 conditions, the smaller the PSF would be.

8 The second thing is that I would
9 look at the refractive index of the
10 mounting media. And so the closer I have
11 that matched to the optic that I'm working
12 through, the less the light is going to
13 change as you go deeper, but, again, near
14 the coverslip it's quite tolerant.

15 The other thing that I would look
16 at is the emersion media. Okay? So you
17 don't use air emersion for a lens that's
18 designed to be used with, for a lens
19 that's been designed to be used with water
20 or oil.

21 You may have a correction collar on
22 your objective lens that you can actually
23 have motorized or not, but you can
24 actually optimize a point spread function
25 using a correction collar. You are

1 matching it with your sample.

2 You could look at the scattering
3 properties of your sample. You know, if
4 it's causing distortions and the light is
5 being distorted, that could influence
6 point spread function. Again, clearing or
7 techniques that would match that optical.
8 There is many ways, but CLARITY is one of
9 a whole list of them.

10 The other thing that you might
11 consider is the wave length you're working
12 with. So if you go down to the shorter
13 wave lengths like UV the point spread
14 function is generally better.

15 You could use deconvolution so you
16 could use a model or an imperially
17 measured on point spread function. You
18 could actually measure it to correct for
19 any distortions.

20 You could close the pinhole down.
21 If you're using the confocal or change the
22 aperture size. The smaller you make the
23 pinhole, the smaller your point spread
24 function is. You could use a structured
25 illumination or techniques that are like

1 super resolution, which help break the
2 diffraction limit. There is a whole host
3 of those; but those are techniques that
4 you could use when you're considering
5 point spread function.

6 I mean, I can keep going, I think,
7 but my comment is these are the things
8 that I would just like off the top of my
9 head be hitting through. Coverslip
10 thickness matters. Some people get very
11 precise on the coverslip.

12 Now, I mean, I list all of these
13 things because they're known to a POSA
14 and, you know, only when I have a sample
15 that I have to go to the limits do I maybe
16 care about that. But the vast majority of
17 my stuff we come in and do it routinely
18 with a given objective lens. And these
19 are things that are not unreasonable for
20 someone to be able to do. They understand
21 it. They know when to apply it when it's
22 needed.

23 Q. In that, and forgive me, we don't
24 have a real time transcript, so I think
25 you mentioned two types of media, atavtobe

1 index and immersion.

2 A. Yes. There is a mounting media.

3 What you put your sample in. Emersion

4 media is what you connect the objective

5 lens to the coverslip with. That's like

6 oil was being used by the Chen group.

7 Water dipping lenses, that's maybe buffer.

8 A lot of times if their coverslip, if

9 they're water lenses, they can also have

10 water emersion versus water dipping.

11 Water emersion just has a drop of

12 water instead of oil. And all of those --

13 and then there could be air, which is

14 nothing. Right? And people who image air

15 to air, you know, good luck with their

16 samples but sometimes you work with

17 materials and it's fine. So, okay. Maybe

18 I gave you too much information.

19 Q. And all these variables you

20 provided relate to addressing point spread

21 function; is that correct?

22 A. Well, they influence it. Depending

23 on the question, and if it matters that

24 you need to do A, B or C to optimize it

25 for your answer, there is known ways of

1 doing it. And they could be used. But
2 day-to-day, you know, people have their
3 three ways. They go in and the mount it
4 with the same coverslip. It's known, it's
5 imbedded. If I'm work with a sample
6 that's thicker I will use this lens. It's
7 very simple and straightforward to make
8 sure that you could address it to get the
9 best result. It's very understood.

10 Q. Okay. Do you have an understanding
11 of single to noise ratio, SNR?

12 A. Yes. I do understand that.

13 Q. Is it your opinion that a POSA
14 would not consider SNR at all when imaging
15 thin samples which still have a 3D volume?

16 A. So I wouldn't frame it that way. I
17 think this is another depends thing. If
18 someone comes in with a bright sample
19 that, you know, is above background or a
20 very strong signal compared to -- and I
21 consider noise, electronic noise that
22 comes from the system, noise from the
23 laser, things like this, just to be clear.
24 It's kind of like a ren noise that
25 distributed over your sample. If the

1 signal is strong they don't really have to
2 think about it, 99 percent of the time.
3 The signal is weak, then you have to look
4 at ways to address it, which could be as
5 simple as opening an aperture on a pinhole
6 to let more signal in relative to the
7 noise in the sample. You can address it
8 by amplifying your signal more. That's
9 exactly what HCR does and the Jung lab.
10 The Chen work does is they decorate it
11 with 96 probes. Okay? So that's a lot of
12 signal. That's one of the things they do.
13 And I do it in my, I have plant samples.
14 That's why I use HDR. I also can
15 suppress, again, I want to differentiate
16 noise from background. Background could
17 be from all the florescence or something
18 in the tissue that's nonspecific. But in
19 the case of noise, you know, we use
20 brighter probes for that. We use probes
21 that are less resistant to photobleaching.
22 So there is a lot of ways to address it.
23 So the answer is, yes, sometimes; but we
24 don't go to those extremes because most
25 systems are sensitive enough with high

1 efficiency detectors that 95 percent of
2 the time they're not at that limit.

3 And to be clear, when noise does
4 become a problem is when you have single
5 fluorophores. When you're trying to see
6 one fluorophores versus a single molecule
7 where you amplify it like crazy, like
8 messenger RNAs. So that's where I start
9 getting to that noise, Flora the
10 electronics. And then I care about it.
11 But day-to-day our systems are quite good.
12 People aren't just sitting there fretting
13 about this all the time.

14 But as soon as you get these
15 amplification type techniques, like Jung,
16 that's one of the things that are helpful
17 about them. It becomes less of an issue
18 for many types of cells. Not everything
19 for sure. Some are more difficult. Maybe
20 you don't have a long enough stretch in
21 messenger RNAs, so you can't get as much
22 probes on. You deal with that. You know,
23 you have to solve it. That doesn't say
24 everybody is thinking about losing sleep
25 over it. The answer is less likely so,

1 particularly with all of the
2 amplifications they're doing.

3 Q. When you said 95 percent of the
4 time you don't need to go to these
5 extremes or something along those lines.

6 A. Uh-huh.

7 Q. I apologize I don't have real time
8 to look back, but when you're talking
9 about the extreme, are you talking about
10 re-amplifying the signal? Or what did you
11 mean by the extreme?

12 A. Meaning most signals from the
13 samples are bright enough. Noise from
14 electronic and laser noise is not an
15 issue. If you're imaging, extremes are
16 like imaging super fast, like I'm doing
17 200 frames per second. You're capturing
18 signals so quickly, those are dynamic
19 events. Nothing to do with what's
20 happening in these spatial Omics type of
21 techniques because they're dead. So you
22 could sit there and integrate longer and
23 the noise can be averaged out. That's an
24 example. A single molecule, real single
25 molecule, single fluorophores where you're

1 looking at one fluorophores moving around
2 in the sample where you would run into
3 these issues or you run at high speed are
4 two examples of the 5 percent. Most
5 people come in and we're not sitting there
6 fighting that battle.

7 Q. So for dealing with SNR imaging of
8 thin samples, which still have volume,
9 some of the things a POSA might address, I
10 think you mentioned, opening the aperture
11 is one, amplifying the signal is something
12 else. Using a bright probe was another
13 one you mentioned. What other variables
14 must a POSA consider to account for SNR
15 for thin samples?

16 A. Exposing longer if the signal
17 happens to be a little bit weaker.
18 Increase your exposure time so exposure
19 becomes less. You can increase the light
20 intensity on the sample. So exposing is
21 increasing the time of data collection.
22 Light intensity is getting more photons
23 out per, you know, acidtation event. You
24 can use things like photobleaching where
25 the signal is irreversibly lost; however,

1 in those instances you can decrease laser
2 power and you also, and/or could put an
3 antifade agent in. Something that would
4 prevent photobleaching from occurring.

5 These are all understood. They're
6 all also probes that are more resistant.
7 Now, I'm getting into photobleaching, but
8 this is an instance where the signal will
9 decay over time. If you recall, though,
10 in the Chen paper, and I think even in the
11 Cia, they use photobleaching as a
12 strategic to eliminate a specific probe.
13 So they have to sit there. Sit for a bit
14 of time to get rid of it under certain
15 chemical conditions.

16 So it doesn't happen all the time.
17 Mostly it's controllable in a thin sample.
18 It's a lot easier because you're just
19 imaging distance and a couple of exposures
20 don't make a big deal. In a thicker
21 sample, then I would go to an acidtation
22 imaging strategy where you're just
23 illuminating that plane, so you're not
24 touching the other one outside, so it's a
25 multi photon and SPIM are good examples.

1 Where you could prevent photobleaching to
2 occur, which would effect potentially your
3 signal to noise.

4 Q. Do you have an understanding of
5 seeing the background ratio, SBR?

6 A. Yeah. This is now a very cell
7 specific thing. Cell type specific thing.
8 Food you gives the cells can affect it.
9 There is plenty of things that I work with
10 that don't have cell background issues.
11 For example, I work with plants. And it
12 turns out that they have chlorophyll in it
13 that autofluoresces, and they have cell
14 walls that can autofluoresce, but the part
15 I care about inside the cell doesn't
16 autofluoresce at all. And so I have no
17 problem with background. Background can
18 come oftentimes from autofluorescence or
19 nonspecific binding of a probe will give
20 me background. The probe is staying or
21 being stuck in a particular part of the
22 tissue. It's elevating stuff that aren't
23 important to me. So we have strategies to
24 reduce the nonspecific binding. We put
25 blocking things in there. That's why even

1 if you look at the hybridization mix, they
2 have to make sure they they're not hitting
3 off targets. And so they'll have blocking
4 strategies to reduce that. When it comes
5 to biology things that autofluoresce you
6 can find wave lengths that they don't
7 autofluoresce. And it's going to be
8 dependent. Some things I look at have
9 nothing, some have more. Then the next
10 strategy is can I use reagents that will
11 suppress autofluorescence; or can I use
12 wavelength that don't influence that
13 autofluorescence; or if it's not a
14 specific binding do I change my probing
15 strategy?

16 These are all things that are known
17 out there. And normally what happens is a
18 POSA will come in and use a standard
19 protocol, if it arises, then they go in
20 and say, okay, I would use A, B or C.

21 The third thing is that there is
22 reagents that you can use that will
23 suppress that and will reduce that type of
24 background, as I mentioned.

25 Q. And these potential issues of

1 autofluorescence are nonspecific probe
2 binding. Are those a factor, regardless
3 of the sample thickness, whether it's a
4 thick sample or a thin sample having a 3D
5 volume?

6 A. Autofluorescence is
7 autofluorescence if you have the tissue
8 happens whether it's thick or not. A
9 nonspecific binding, which would raise
10 background, if I want to call it that,
11 might be elevated and thicker tissues
12 because you didn't wash enough; right? So
13 if you come in and you try to treat it or
14 the probe gets stuck in there because of
15 incomplete washing.

16 Now, it turns out that I have
17 worked with a fair bit of thick tissues,
18 particularly when I'm using hybridization
19 chain reaction. It actually is designed
20 to reduce nonspecific binding to because
21 you need two probes that are end-to-end to
22 be together before the reaction can occur.

23 So one random portion of the
24 messenger will not be enough to cause a
25 chain reaction. And so therefore the

1 specificity goes up. And these probes are
2 small enough they can penetrate even
3 through plant cell walls under very easy
4 conditions.

5 So my comment is, yes, I could
6 imagine a thicker tissue you would have to
7 be careful of washing. Maybe get elevated
8 background, but there are strategies that
9 actually get past that either through
10 blocking or just longer incubation times.
11 Mostly the front end steps that you were
12 describing when they're doing the
13 hybridization. You know, again, the
14 patent doesn't explicitly say we always
15 have to go to the extremes. There is a
16 ton of stuff are non-issues with that a
17 POSA would have been motivated to do and
18 had reason for success.

19 Q. What variables must a POSA -- what
20 additional variables did a POSA consider
21 to account for SBR when imaging and
22 samples were still beyond autofluorescence
23 or nonspecific probe binding?

24 A. Those are the two primary things
25 that we're dealing with. When you're

1 talking about background; right? It's
2 either autofluorescence or nonspecific
3 probe binding. Those are the primary
4 things. Anything else that are out there
5 off the top of my head, I mean, I'm sure
6 there are others.

7 Maybe even, you mentioned it, you
8 know, I usually work like this 90 percent
9 approval; okay? I solve the 10 percent.
10 This is the number one thing that I would
11 be seeing that would get in the way.

12 So other things are probably not
13 important, but it doesn't mean they
14 couldn't be for a particular system, but
15 it doesn't mean that I missed something
16 else, but those are the primary things
17 that I see.

18 Q. When there is florescent signal
19 coming from other focal planes, is that
20 other focal planes in addition to, beyond
21 the one that you are imaging. Is that
22 considered background?

23 A. Okay. I call that signal, just to
24 be clear.

25 Q. Okay.

1 A. I'm distinguishing background from
2 being something that is not signal that's
3 your target. Now, I don't disagree that
4 that out of focus information can,
5 depending on your optical slice,
6 contribute to the sample. For example,
7 that's what his cartoon was showing that
8 you were going on. I get that point. I
9 just would call it something different.

10 That's signal, that's exactly why
11 things like decompilation are used when
12 those things happen. Is you take a stack
13 and it reassigns that out of focus, and it
14 actually uses it to your benefit to put it
15 back into the focal position.

16 So my comment is, yes, it's there.
17 You use an optical sectioning technique as
18 he's described to reduce it, but even when
19 you use optical sectioning, the right
20 object in an adjacent focal point can
21 still cast something in. I just call that
22 out of focus information.

23 And I would just differentiate
24 that. It doesn't mean either of us are
25 necessarily right or wrong on that. It's

1 just how I would characterize background
2 being from other things that's out of
3 focus information.

4 By the way, 3D is the perfect thing
5 a POSA would have been motivated to
6 address. Because no matter what you are,
7 if you're just going in 2D everywhere,
8 it's going to be there, except for maybe
9 the techniques that are just using
10 excitation not focal where you're not
11 exciting that out of focus information.
12 I'm sorry, I'll slow down a little bit.

13 I tend to talk fast, but you're
14 doing fast typing there.

15 Q. In your reply declaration Exhibit
16 1086, Paragraph 14, if you turn to that,
17 please.

18 A. Okay. All right. It's a pretty
19 long paragraph. It looks like to me maybe
20 you can start with your question and if I
21 have to go further. I see that it's
22 talking about sample thickness.

23 Q. Yes. So it's actually on Page 10
24 of your declaration.

25 A. Okay.

1 Q. Still on Paragraph 14. You have a
2 sentence there it starts with whatever
3 difficulties may have arisen. It's about
4 the middle.

5 A. Yes. I see that.

6 Q. And you refer to, you say these
7 deep tissue issues are not relevant for
8 thin or small samples, which still have 3D
9 volumes. So my question is: You refer to
10 thin or small samples. Are those
11 different or the same?

12 A. Okay. And just to, I guess maybe
13 this is a good question for distinction.
14 Small samples are like a single cell near
15 the coverslip that has a 3D volume. This
16 is things that have the coverslip. So
17 when they're doing spatial element they're
18 looking at somethings spread on a
19 coverslip that might be small. A Ye cell
20 is 5 micrograms in diameter, for example.
21 Now, the particular cell I use has a
22 little less functionality, but the vast
23 majority of the cells I work with have
24 additional dimensions. And they're
25 smaller cells, as opposed to a big bulk

1 brain, slab of a brain from a 10
2 centimeter object that was sliced out.
3 That's what I mean.

4 Q. Okay. And when we were discussing
5 PSF, SNR, SBR and different factors and
6 aspects of those, is your answer any
7 different whether we're talking about a
8 thin sample or a small sample having a 3D
9 volume?

10 A. So here's my point here. You can't
11 pick the most extreme thing and use it to
12 discourage you from moving forward when
13 there's tons of biology where those really
14 don't play a big role in a vast majority
15 of the time.

16 This is the whole thing about
17 signal density. I mean, you know, I think
18 if you look at the Chen paper they say
19 well, 10 percent of expression molecules
20 would have this problem, but there is a
21 lot that don't.

22 So my comment to you is, yes,
23 spread function is still there. Singleton
24 noise is there, but they're really trivial
25 compared to trying to go after these more

1 extreme examples, as a saying it would be
2 impossible.

3 And that's kind of how I, as an
4 expert witness, my expert opinion, as I
5 was reading the material there seemed to
6 be this thing about extremes. Taking five
7 slices. We do a lot of biology. And
8 those things really would have been in my
9 view something that would have been very
10 reasonable for a POSA to achieve, as
11 opposed to just picking the most, you
12 know, extreme example, or the ones that
13 might not work. And that's why I use his
14 own examples where he's done hybridization
15 in tissues to show, hey, if people are
16 doing FISH in it, that means they can
17 solve the ability to see single molecules.
18 And whether you're doing more or not, your
19 patent doesn't specify it. It's one or
20 more nucleic acids. So to me, you know,
21 if you have a big giant embryo, you cut a
22 slice of it and you put it down near the
23 surface. Those are all addressable. Yes,
24 the point spread function is there, but if
25 you mount it in a very simple way that's

1 known with the right reflective index your
2 point spread function is manageable.

3 Q. And so in that last example where
4 you gave where a point spread function is
5 there, that applies for a thin sample
6 where there is 3D volume, or a small
7 sample with a 3D volume; is that fair?

8 A. So the point spread functions is
9 always there when you're taking a point
10 object in an optical microscope; however,
11 my point is those don't have an extreme
12 weight. They're very addressable by a
13 POSA. And to me it's a nonissue. What my
14 framing is here, not about that it doesn't
15 exist. It certainly does exist, but it's
16 not a problem in my view because I'm doing
17 FISH, I'm doing ACR FISH all the time. I
18 don't have to sit there and stare about my
19 point spread functioning slice. I can
20 look at my spot. If I have good optical
21 qualities and I set up my experiment
22 correctly, it's there, but it's
23 manageable.

24 Q. All right. And so likewise, the
25 same question for SNR. Is it your opinion

1 that it's there for a thin sample or a
2 small sample having a 3D volume?

3 A. Again, signal to noise there is,
4 but these very, very, very strong signals
5 that are coming off in these multiple
6 fluorophores with decent cameras, it's a
7 nonissue. So, yes, it's there. I gave
8 you some examples where you're imaging --
9 if you wanted to suddenly dwell on your
10 multiplexing and spatial elements ten
11 times faster, the way you could do that is
12 you could expose shorter times in order to
13 speed it up, then those could come in, but
14 you're picking examples where most POSAs
15 would be able to really understand the
16 bread and butter things they could do
17 everyday. It wouldn't have stopped them
18 in any way. It would have been reasonable
19 to be successful rather than picking
20 examples where you had a windy probe. You
21 just fix that. So, yes, it's there. It's
22 just some of those other adorations that
23 are coming as you're going deeper are not
24 a problem in the same way they are for
25 thicker tissues is what I'm stating.

1 Q. And the same question for SBR, is
2 it your opinion that SBR is there for thin
3 or small samples which still have a 3D
4 volume?

5 A. They can be under certain
6 situations, but in many instances they're
7 not. And, again, it wouldn't change the
8 motivation for someone to do it. And it
9 would have been able to overcome in a vast
10 majority of samples. Maybe dead cells or
11 whatever, you can always find an example
12 where it would have been a problem. But
13 clearly people are doing spatial elements
14 all the time right now, including the
15 MERFISH examples; right? And it's being
16 done; right? Because they're amplifying
17 the signal. A lot of cell lines, a lot of
18 tissues. A lot of things can be done as
19 even as a state of the art stands now, and
20 back then.

21 Q. When you said just now something
22 being done all of the time right now, are
23 you referring to MERFISH being done all
24 the time right now?

25 A. No. Doing any of the hybridization

1 approaches; right? It's single molecule
2 FISH in general, which MERFISH is a
3 different form of FISH you might use. You
4 can use it with a lot of probes, you can
5 use MERFISH with a few probes. But it's
6 just FISH techniques in general. I mean,
7 clearly there are lots of examples of
8 people doing FISH. And doing FISH in 3D,
9 MERFISH would be no different, but in all
10 those cases they just can easily get
11 around it.

12 It depends on the probe. It
13 depends, there is always exceptions, but
14 it wouldn't stop someone from motivating
15 them. It's just they were doing FISH.
16 They might have, you know, long, and
17 single molecule FISH they might have gone
18 and used the more sophisticated if they
19 wanted to see more probes. It just
20 depends.

21 Q. What's the difference between
22 MERFISH and FISH?

23 A. So FISH is just florescence in
24 citron hybridization. MERFISH is, you
25 know, multiplexed error-robust FISH, which

1 means she just using an encoding scheme
2 that does correction; versus seek FISH,
3 which is more along what the Cia patent
4 does, which is using an HCR and you're
5 striping and going and so forth. So
6 they're just different versions of FISH.

7 They're taking all the nucleotides,
8 they're matching up the sequence with a
9 readout probe in some form or another.
10 That's what I'm going to call it. It's
11 some signal that we don't know. It could
12 be florescence.

13 FISH is florescent specific. There
14 is also ish, which is, you know, citrus
15 hybridization release, color metric
16 methods. So it's just a general technique
17 where you're hybridizing against a nucleic
18 acid; okay? And it's just different forms
19 of it to get the result.

20 (Thereupon, a short recess in the proceedings was
21 had.)

22 Q. (By Mr. Holman) Dr. Czymmek,
23 during the break did you talk to anybody
24 about the substance of your deposition
25 today?

1 A. I did not.

2 Q. And during the previous breaks did
3 you talk to anybody about the substance of
4 your deposition today?

5 A. I did not.

6 Q. Okay. If you could in your reply
7 declaration, please turn to Paragraph 13.
8 It begins on Page 7. Are you there?

9 A. I am, yep.

10 Q. All right. And then on Page 8 of
11 your dec, same Paragraph 13. At the top
12 of the page there you have a sentence it
13 says, it ends with, there are several
14 modalities that have substantially reduced
15 PSFs in the Z direction, including SIM, 3D
16 SIM, palm storm and iPalm. Do you see
17 that?

18 A. Uh-huh.

19 Q. All right. Do you have an
20 understanding of the macross modality
21 Ipalm?

22 A. I am familiar with it.

23 Q. What is iPalm?

24 A. I'm familiar with the technique in
25 able to getting higher resolution.

1 Interferometric, photo activation,
2 localization mucro cuspids, I guess. I'm
3 not able to get further into it than that,
4 but it's able to produce high resolution.
5 X, Y and Z images and small samples and it
6 has a geometry constraint, if my
7 recollection serves me.

8 It's a more exotic technique that
9 not many folks are using, but it exists.

10 Q. What do you mean by more exotic
11 technique?

12 A. Meaning that I don't see them
13 sending, selling them into every
14 institution and laboratory because they're
15 universally easy to work with. Like it's
16 possible if you needed that resolution
17 gain you might go that route, but it's a
18 little bit more specialized.

19 Q. Does iPalm require certain types of
20 fluorophores to move for photoswitching?

21 A. Well, if it's photoactivation,
22 localization, microscopy the answer would
23 be yes, but, again, I didn't study that.
24 That's how I would interpret the use of
25 P-A-L-M.

1 Q. When you say you didn't study that,
2 you mean you don't study iPalm?

3 A. No. I don't sit there, I haven't
4 since it's a little bit less common. I
5 don't sit there and study exactly. I just
6 know generally this approach exists. And
7 it can get smaller you can imply from the
8 name.

9 I'm aware of it. And I know it has
10 some constraints on it. It can be used if
11 you need it smaller, a palm; but, again,
12 my comment is it's just one way of getting
13 a point spread function. And if you look
14 at the picture, it's probably the most
15 extreme way, if something was needed that
16 way.

17 The patent, and Chen mentions, you
18 know, any optically sectioned technique,
19 so if you can do it, it could be one
20 option for the right experiment.

21 Q. How does photoswitching
22 fluorophores operate in iPalm?

23 A. Well, again, in palm generally
24 you're looking for a molecule to be put
25 into photoactivation localization

1 microscopy. And I'm, again, just general,
2 I often oftentimes use a high-powered
3 laser to put it in a dark state. And when
4 it comes out of the dark state you'll
5 image usually a four or five laser. It
6 depends on the molecule. And then as it's
7 coming out of that dark state, it will
8 blink. And those blinking events are used
9 to localize a single molecules. You can
10 do a Gaussian fit and get resolutions.
11 Again, in palm, you know, down to, you
12 know, a few tens of nanometers or less,
13 depending on the strategy you're using and
14 how many glitz you get and everything
15 else.

16 So they are specialized molecules
17 that are florescent proteins that blink.
18 Somewhat like storm, which uses the
19 fluorophoe that can do certain things
20 under the right chemistry or chemical
21 environment.

22 Q. Is that, when you're talking about
23 palm, is that the same for Ipalm?

24 A. Again, I'm assuming the method that
25 they're using to excite these is using a

1 similar photoactivation like strategy.
2 I'm just telling you how it works in palm.
3 Whether that extrapolates, I just didn't
4 sit there and read in full detail because
5 it's, again, a more exotic technique.
6 It's just one of many ways in which
7 someone could reduce, that a POSA would go
8 to. It's not one that I would necessarily
9 jump to. It has the easiest
10 implementation because of that more
11 extreme situation.

12 So at this point you could do it.
13 I'm not really going to get into the
14 theoretical side because I have a little
15 less direct experience because it's not
16 like a commercial tool that's sitting
17 there in every laboratory like all of
18 these other ones I have worked with.

19 Q. Do you know if iPalm uses a
20 specific optical configuration?

21 A. Again, as I stand here I told you I
22 did not spend much time looking up the
23 nuances of iPalm. I would assume it would
24 have a specific configuration. My
25 recollection is that it has some very

1 limited geometry with it. It's very small
2 and thin. That's recollection. And the
3 last time I read an iPalm paper was quite
4 some time ago. And I know Harry was an
5 inventor on that topic is my recollection.
6 But, again, if I can't use it in my lab
7 day-to-day, it's not a restriction of the
8 patent. It's just one possibility if you
9 want to reduce the point spread function
10 so we can talk about the mechanics of how
11 it's working; but I'm not really prepared
12 to give much further than this very high
13 level experience for it, which is one way.
14 Not the first thing that I would be
15 trying.

16 Q. Does iPalm use two objectives in
17 the configuration?

18 A. Again, from a interferometric thing
19 I believe that's the case, but it's been a
20 while since I've looked at this technique,
21 and I'll tell you the same thing. So the
22 answer is I believe so. That rings a
23 bell, but I'm still telling you that it's
24 just another technique that makes a small
25 point spread function. A sample can fit

1 under it. I guess that's about the
2 relevance that would go here to be a 554
3 patent.

4 Q. Do you know if Ipalm uses a
5 three-way beam splitter?

6 A. Okay. The same answer, I have no
7 idea. I have studied that. It's been a
8 long time ago since the paper came out.
9 If you send me the paper now and you want
10 to give me some time, I'll go review and
11 answer those if you need to have those
12 answers explicitly. But at this point I'm
13 not prepared. Again, it's just another
14 uncommon technique that someone might use
15 to improve a PSF, if that was their
16 desire.

17 Q. When you say a paper came out, what
18 were you referring to?

19 A. I just remember reading about Ipalm
20 and maybe the Strauss paper, I don't know.

21 Q. So you're not sure which paper
22 you're referring to?

23 A. I mean, it was referred to. I
24 think it's one of the methods in here.
25 It's referred to, my recollection it is in

1 some of the patent documents. I don't
2 have a citation name. I'm just aware of
3 the technique. I read it at some point
4 but studying the schematics is not
5 required to know the basic fundamental
6 thing as it can make a smaller PSF. And
7 it's a way to reduce that if needed.

8 I would only go and approach that
9 if I had a sample required, which would
10 be, you know, again, the patent says one
11 or more. You know, I would have to look
12 at that on here. It's identifying one or
13 more. If we go to patent 36, whatever, I
14 don't necessarily need to resolve that to
15 find my single molecule at that level.

16 So I'll continue to answer your
17 questions. I'm telling you that I just
18 don't recall much detail about the paper.
19 It's a very, very, very high level. That
20 if I needed to go to that small of a point
21 spread function, then I would care about
22 whether those geometries matter to me in
23 the configuration of the system.

24 Q. In your declaration, still on Page
25 8.

1 A. Uh-huh.

2 Q. Underneath the figure there, you
3 state, the second sentence there: To the
4 extent a POSA was concerned with PSF in
5 attempting to adapt MERFISH to 3D, he or
6 she could have simply selected a
7 macroscopy modality with a sufficient --
8 he or she could have simply selected a
9 macroscopy modality with a sufficiently
10 low PSF.

11 So is it your testimony that a POSA
12 would not have selected Ipalm because it
13 is such an exotic extreme optical
14 configuration that very few labs have?

15 A. Well, no. It depends on the
16 question. What I state here is sufficient
17 low. So, again, I use HCR with a super
18 resolution microscope. And I use it with
19 a confocal microscope. And it's
20 sufficient with the population density of
21 the molecules I'm working with to be able
22 to detect them and see them without
23 overlap. So you don't go to these other
24 levels unless you have a need to do that.
25 So, again, the patent doesn't talk

1 anything about -- 554 patent doesn't talk
2 anything about density and where that
3 would be a requirement because there is
4 tons of things that i can do without. So
5 if you look at it sufficiently low, which
6 is a lot of microscopy techniques out
7 there that are well before coming to this,
8 again, more exotic, less commonly
9 available system, so folks wouldn't go to
10 it first choice. It doesn't mean it can't
11 be used. I didn't state that. I said it
12 could be used with the right sample.

13 Q. What's the example for the right
14 sample for using iPalm?

15 A. Well, based on, again, my
16 recollection of a very thin geometry, it
17 would probably have to be a very think or
18 small cell or tissue, whatever geometry
19 that can fit in the device.

20 And where you might have certain
21 report of molecules that you want a
22 readout on that are extremely close
23 together under high density. Again,
24 that's some biology, but the vast majority
25 wouldn't necessarily require it.

1 Q. In addition to limited, did you say
2 limited sample depth or strong cell?

3 A. It's geometry. That could be any
4 dimension. I just don't recall what the
5 constraints were exactly on what cell size
6 restriction that would be. You know, was
7 it ten microns, was it five microns, I
8 just don't recall.

9 If you're matching objectives I
10 think about techniques, you know, you have
11 to have a coverslip on both sides. Again,
12 this is just me thinking off the top of my
13 head. When I hear that I would just
14 generally think without going back and
15 looking closely at the paper. So you have
16 some constraints. It would probably have
17 to be equal distance between both lenses
18 to work properly. And some symmetry to
19 it. That's just a ballpark guess.

20 Q. Are you aware of any other
21 constraints with Ipalm?

22 A. Again, since it's been quite some
23 time since I reviewed those documents in
24 detail, I can't speak to it now. And,
25 again, I still say, if you look at my

1 paragraph sufficiently means most people
2 are going to be using tools that are using
3 traditional confocal or super resolution
4 techniques. Ones that are generally more
5 available. You can use it. If it's got
6 to be small, then you have got to have
7 high enough potential density is one of
8 your reasons to be able to use it.

9 Q. So what's the difference between
10 Ipalm and palm?

11 A. Well, a palm system, which I have,
12 is just a super resolution technique where
13 you can use a high-powered laser. Certain
14 wave lengths. And you have the specific
15 photoactivatable florescent protein. And
16 you put it into the dark state. You wait
17 for it to blink. And you collect
18 thousands of images.

19 And then you try to localize the
20 center. Again, I made the comment
21 inter-for-magic palm may be what's
22 happening on the exitation side. I don't
23 recall because it's been a while. I'm
24 assuming palm is an equivalent term. It's
25 photoactivation localization microscopy.

1 I'm assuming he's using a
2 florescent protein to network. And that
3 they're also having to collect many images
4 to get the localization effect. This is
5 just an assumption. I can explain how
6 palm works, which I am much more confident
7 in.

8 Q. Does palm require certain types of
9 these photoswitchable fluorophores?

10 A. Yes, it does.

11 Q. Okay. And how do the
12 photoswitchable fluorophores operate in a
13 palm system?

14 A. Well, normally they have a
15 biologic, I just want to be clear. In
16 palm it's a genetically encoded recorder
17 versus storm, which can use a florescent
18 readout that can be attributed to nucleic
19 acids.

20 So we're talking about is a protein
21 localization technique. Just so I'm clear
22 about it. Okay? So I think we have
23 encherry will do it, photoactivated will,
24 GFP. There is a few molecules that are
25 specific.

1 And, again, just like these single
2 molecule localization techniques, you only
3 turn on a few molecules at a time. That's
4 really when you put them in a dark state.
5 And as they start coming, start blinking,
6 then you can see and identify individual
7 molecules rather than all of them being
8 turned on at the same time.

9 So all the molecules are there.
10 You just switched off most of them. And a
11 few are turned on with time. You take
12 lots of images. You do a Gaussian fit
13 from the center point. There is 3D palm.
14 So I have a 3D palm system where I can put
15 in a faceplate and get 3D positional
16 information off of the same technique of
17 this blinking events of a subpopulation of
18 the total molecules that are in a
19 particular localization.

20 And, again, they're genetically
21 encoded proteins. Storm is the equivalent
22 technique using antibodies that could be
23 used as a readout for FISH techniques.

24 Q. You mentioned Mcherry GFP as
25 examples.

1 A. You know the two that I think --
2 actually, we've used actually MEOS, it's
3 called actually, I think MEOS is a better
4 one, MEOS-3 for our work. Mcherry, if you
5 want to do multi color. So m, small m,
6 which is monomeric and then and E-O-S.

7 Q. Any others, GFP, mEOS mCherry?

8 A. PAJFP was the one. I mean, mEOS is
9 the one that I use. I'm sure there are
10 some new ones now. Those are the ones
11 that come to mind.

12 Q. And how do these turn on and off in
13 a palm system?

14 A. Generally they'll flores. Some of
15 them are for switchable, some will turn a
16 different color. Some of them will become
17 in a dark state. Some normally use a
18 high-powered UV laser.

19 Then you look at the art state.
20 And then you look at the appropriate color
21 and capture images, and the small molecule
22 is blinking. I'm going to say small
23 molecules, maybe I been should say single
24 molecules is blinking, is the right way to
25 put it.

1 Q. So with the palm these
2 fluorophores, are those, does palm use
3 nucleic acid probes?

4 A. No. It uses a genetically encoded
5 florescent protein.

6 Q. And that's marking certain cells of
7 interest?

8 A. Yeah. So you would, let's just say
9 you picked actin. You would put this
10 emeos molecule with florescent protein on
11 it when it's expressed in a living cell.
12 It will show up if you fix it. To be
13 clear, storm is the equivalent. So you
14 can do an antibody against the genetically
15 encoded protein. And once that happens
16 you can actually use, you know, certain
17 things; but it's looking at proteins
18 specifically; okay?

19 The storm is the chemical molecule
20 version, which you would apply toward
21 these other techniques.

22 Q. You said storm was chemical?

23 A. Yeah. So you could use an organic
24 dye as opposed to genetically encoded.

25 Q. I see. Okay. And that's

1 conjugated to the antibody probe? Where
2 is that?

3 A. Well, the organic dye you're
4 talking about, organic dye can be
5 confiscated to a nucleic acid in sequence
6 or it can be to an antibody, or it can
7 just be a stain that is affixing, like,
8 you know, binding just a probe that has
9 infinity in some of the molecules.

10 Now, the cell has a range of
11 things. Generally you want it to be
12 targeted. In the case of FISH then you
13 would have it attached as one of the
14 fluorophores, like Sy-5 or Sy-3 that are
15 storm compatible. And those analogues to
16 palm without the genetic encoding element.

17 Q. So nucleic acid probes are not used
18 in palm; is that right?

19 A. So you could do an experiment where
20 you're doing both. You know, a lot of
21 these, you know, in my multiplexing I look
22 at both protein and nucleic acids. So you
23 would probably want the readout to be the
24 same.

25 So you could use nucleic acid at

1 the same time. You could come in and use
2 a genetically encoded version in
3 combination with it; okay? But the, it's
4 genetically encoded unless there is some,
5 you know, indirect way to take that
6 genetically encoded signal and bind it to,
7 you know, nucleic acid. It's direct
8 readout is the localization of the
9 florescent protein, itself.

10 Q. I see. Now, how about buffers?
11 Does palm require certain buffers to be
12 used for these fluorophores?

13 A. I mean there is always conditions
14 that work better than others. I just use
15 heat buffer. Storm requires special
16 buffers because of the way you have to get
17 the molecule to blinking.

18 Palm is a little bit more forgiving
19 because you can do palm in living cells.
20 So you can. When I do fixed materials I
21 use a heat buffer. You could also put in
22 other buffers, but in the end it's
23 different.

24 In the chemical reactions of storm
25 are you have to push it in a certain

1 direction with different chemistries. I
2 don't recall those chemistries exactly
3 because I usually get them as a mix and
4 make them up, but it's been a couple years
5 since I did storm. But palm I can do in
6 live cells, which means, you know,
7 whatever environment it's in. It can be
8 in a cellular environment, so it's less
9 sensitive, which is one thing I like about
10 it.

11 Q. Does palm require specific types of
12 lasers for the photoswitchable
13 fluorophores?

14 A. Yeah. They have to match the
15 special characteristics of the sample. My
16 recollection of AMIOs is they have to hit
17 it with UV and it turns, I'm trying to
18 remember, if it goes green to red. It's a
19 photoswitchable, so it's actually
20 switching to a different color.

21 But you would need different lasers
22 lines to be able to see and detect those.

23 Q. Aside from the -- so I want to
24 compare and contrast palm and storm.

25 A. Uh-huh.

1 Q. They're both considered super
2 resolution microscopy techniques; is that
3 correct?

4 A. Yes. They're both super molecules,
5 super resolution techniques. Single
6 molecule could mean I could look at a
7 single molecule, or, I guess, you could
8 also use it as, of course, in the case of
9 FISH or MERFISH when you're decorating
10 with a lot you still would want to turn on
11 a few at a time if you're going to that
12 level, so --

13 Q. Are they interchangeable? Are palm
14 and storm interchangeable methods?

15 A. They use a similar strategy, but
16 every fluorophore will have a different
17 laser. You'll have different chemistries
18 that you'll have to use.

19 I have never thought about storm
20 buffers, what effect they would have on
21 palm because I've never done it, but it's
22 something a POSA could go look up and do,
23 if they needed to. I'm just saying that I
24 could imagine it's possible.

25 Q. The reason I ask is in your

1 declaration on Page 8 when you mention
2 palm and storm, you mention it as
3 palm/storm.

4 A. Yes.

5 Q. As opposed to palm, storm. So I'm
6 asking, are they commonly grouped
7 together?

8 A. So, yes, palm storm are generally
9 grouped together because you use the same
10 kind of process. You put them into a dark
11 state. And then you watch the blinking
12 molecules. You use the same software to
13 do that.

14 You might use different lasers with
15 different buffers to get that same effect.
16 They are very equivalent. So I can use my
17 3D super resolution system on both of
18 those molecules. In that case they're
19 very, very closely related. It's just
20 that one uses a florescent protein, the
21 other one uses organic dye.

22 And, you know, the point is a POSA
23 would have known those, you know, those
24 methods to improve PSF are out there. I
25 mean, that's the point; right? And, you

1 know, but clearly there is some
2 restrictions on which molecules you're
3 going after in the cell based language,
4 which approach it is.

5 Q. What are some examples of the
6 photoswitchable organic dyes that are used
7 in storm?

8 A. Sy-5, Sy-7, Sy-3. I use Alexa 650,
9 I think, another one. So there tend to be
10 signing dyes are very good at it. There
11 is a list of dozens. Some of them are
12 more effective than others.

13 Those are the ones that are
14 typically use. And I tend to just focus
15 on the ones that work in my hands.

16 Q. And how about probes? What kind of
17 probes are use inside storm?

18 A. Well, nucleic acids are just
19 coupled to any organic dye that is
20 compatible with; so you can use any of
21 those organic dyes. Whether they do an
22 end labeling however they bind to the
23 nucleic acid. I don't think there is any
24 restriction, as long as the chemistry
25 there is applied to the nucleic acid

1 backbone or end labeling or however they
2 decide to do it.

3 Q. So you conjugate the label of the
4 dye with the nucleic acid probe?

5 A. Exactly. So it's directly labeled.
6 So wherever that molecule is, it goes in
7 hybridizes, a readout probe wherever it
8 hybridizes, that molecule will rest.

9 Q. Does Storm require certain buffers
10 to be used it?

11 A. It does, yes.

12 Q. What type of buffers does storm
13 require?

14 A. It's related to photobleaching and
15 trying to get them into the right dark
16 state. I just don't remember. Like, I
17 want to say, I want to be careful here
18 because I just didn't study this before.
19 I usually have a cocktail that's made up
20 of it. It's a few things that are related
21 to photobleaching them into a dark state
22 because of the reox effect to get the dye
23 in a darkened state, but I just don't
24 remember them today. Glox is one of the
25 buffers we would typically use. I think,

1 if you want to we can go to the paper and
2 look at the storm number that she used in
3 one of her materials. She used some of
4 it. My comment is, it's out there. Glox
5 is one of them. I just don't remember
6 what all the agents are, what it stands
7 for.

8 Q. Are you saying the buffers are
9 related to photobleaching, is it in an
10 effort to prevent photobleaching? How is
11 it related? Where does photobleaching
12 come into play?

13 A. All right. It's been a bit. I
14 would have to study this. And the
15 mechanism. I've used it before. It's
16 been a bit. The Glox buffer is out there.
17 You're inducing it into a dark state and
18 so they become blinking. As I sit here
19 today I don't remember the chemistries.
20 It would take me a few minutes to read it.
21 And then I could explain it to you. I
22 just don't remember as of today.

23 It's known by a POSA. They could
24 go look it up very easily, make the
25 chemistry. I have done it. I just can't

1 remember what it was.

2 Q. And does Storm require certain
3 types of lasers for the photoswitchable
4 organic dyes?

5 A. Just like palm has a match,
6 typically you're using a 405 UV laser of
7 some type and then whatever laser to see
8 the blinking molecule when it come out of
9 the dark state.

10 So, you know, it would be in the
11 600s if you were trying to do Sy-5, for
12 example. Sy-3 might be in the 500 thin
13 meter range.

14 Q. Sorry, you said if it was Sy-3
15 might be in the what meter range?

16 A. 500, I don't know. I don't work
17 with Sy-3 very often because it's an old
18 generation dye. And for storm I'm
19 typically using Sy-5 and Alexa 650. They
20 are newer generation dyes. I just haven't
21 --

22 Q. So are you actively using Storm in
23 your lab?

24 A. I have, but actively five years
25 ago, four years ago, the last time I did a

1 Storm experiment, than Palm as an
2 experiment.

3 Q. Well, that's what earlier you were
4 saying, you stated you weren't really
5 familiar with buffers. That's why I
6 asked.

7 A. Yeah. Five years ago. I just
8 don't remember. I know we did it.

9 Q. That's fair. What are some
10 limitations of Storm imaging?

11 A. One of the limitations is that you
12 need special chemistry, okay, which I
13 described. The chemistry is generally
14 toxic to living cells. Again, in cell
15 chemistries. You have to collect lots of
16 images. It takes times. Thousands of
17 images. Typically if I'm doing a palm or
18 storm experiment it would be, you know,
19 10,000, but depending on the resolution
20 that I need to have. The number of
21 photons that it omits to be able to
22 determine a localization event, if you
23 don't get enough photons coming out of it
24 while it's linking, then your localization
25 precision goes down. Since you're taking

1 thousands of images, you have to do prost
2 processing to that data in order to turn
3 it back into something useful and
4 meaningful. Looking at an image with five
5 spots on it it's hard for you to tell what
6 it is until you assemble everything back
7 together. So there is a fair bit of prost
8 processing to do it. And it's using
9 usually a Gaussian fit on the center of
10 the molecules to get the extra resolution.
11 If you don't go long enough or you don't
12 get enough blinks out of it, your
13 resolution is not as good as the potential
14 of the technology.

15 Q. Is slow speed considered a
16 limitation of Storm?

17 A. Well, if you have to take thousands
18 of images technically you're requiring a
19 very high speeds, but the time it takes to
20 get your result and your answer you might
21 call that slow; as opposed to taking a
22 single frame, one and you're done. You're
23 going to have to do the processing.
24 That's the price to pay to break the
25 diffraction limit and use the approach

1 like that.

2 Q. Does Palm or Storm, do Palm or
3 Storm require two photon microscopy or
4 light sheet permeation?

5 A. They don't require it.

6 Q. Do they use it?

7 A. I don't see why they couldn't as
8 long as you can put it into a dark state.

9 Q. Your testimony is that neither Palm
10 or Storm requires two photon microscopy?

11 A. I haven't done it personally. I
12 suppose I could go in there and determine
13 that. I just haven't done it. So
14 potentially it could be. I just don't
15 know the answer to that as i stand here
16 today because I just haven't run across
17 the paper where I noticed it.

18 Q. When you say you haven't done it,
19 what haven't you done?

20 A. I haven't done Palm or Storm with
21 the two photon system. I used it with my
22 Y field super resolution system, which is
23 a different technique. That's the bread
24 and butter technique. It may or may not
25 be used in those other ones. If I was a

1 POSA I would simply go and look in the
2 literature, but that doesn't stop them
3 from using non Storm based techniques in
4 localize molecules. So you're kind of
5 using them for potentially any other
6 purpose where you didn't need to have the
7 higher PSF. But when it's needed, I would
8 have to do a little homework on that.

9 Q. All right. I'm going to hand you
10 exhibit marked as 1019. This is the
11 Fischer paper. Do you recognize this
12 document?

13 A. Yes. I recognize it.

14 Q. You refer to this document in your
15 first declaration, at least in your first
16 declaration; correct?

17 A. Yes. The point is to show that
18 there is lots of 3D options available to
19 somebody, a POSA, who would have seen
20 MERFISH or Cia, and recognize that you
21 could use other optical sections and
22 techniques.

23 Q. When we were discussing Palm and
24 Storm were your answers in the context of
25 3D Palm and 3D Storm or 2D?

1 A. I described both to you. I told
2 you can get 2D or 3D.

3 Q. Okay.

4 A. You can put a faceplate or you can
5 put an asymmetrical effect on the point
6 spread function.

7 Q. All right. So in Exhibit 1019, if
8 you could turn to Page 20, NanoString Page
9 20, Table 1, in the back of the documents.

10 A. Uh-huh.

11 Q. Do you see that table there?

12 A. I do, yes, yeah.

13 Q. Okay. And on the left side column
14 there is different modes for microscopy
15 modes.

16 A. Uh-huh.

17 Q. The second to the last one there is
18 3D Palm, 3D storm. Do you see that there?

19 A. Yes.

20 Q. And then the two columns over --
21 three columns over from there is a column
22 called limitations. Do you see that
23 there?

24 A. Uh-huh.

25 Q. And the first limitation listed for

1 3D Palm and 3D Storm imaging depth. Do
2 you see that?

3 A. Okay.

4 Q. Why is limited imaging depth a
5 limitation?

6 A. Well, again, everything is
7 relative. So I work with fungi that have
8 10 microns in diameter or plant sections
9 that are 15 microns thick. So I have a
10 big sample that I fit in under the
11 protocol. So, you know, if you go too
12 deep the ability for the laser to be able
13 to have enough power to put it into a dark
14 state or to be able to get the readout of
15 the signal without background may
16 influence it. But, again, if your working
17 on tissues, tissue sets are single cells.
18 It works perfectly fine. So limited depth
19 means, apparently, this is another extreme
20 example, maybe you wouldn't use it on
21 thicker tissues. Wherever that borderline
22 is I'm not sure. Yeah. It says 10
23 microns right here. So up to 10 microns.
24 That's a lot of biology if you section
25 bulk materials. I don't consider that

1 limiting.

2 Q. Where are you --

3 A. Practical imaging depth, microns.

4 The next column right over.

5 Q. Okay.

6 A. So that's a lot of stuff including

7 many single cells and tissue slices.

8 Q. So is it your understanding that

9 this is, this table, this disclosure is
10 limited to thicker samples of 10 microns?

11 A. Ten or eleven, yeah. Less than 10

12 microns. Again, it's a cell. That's a

13 tissue slice. So just to be clear, you

14 can take a soft embryo. It can be

15 millimeters, and you can cut it the 10

16 micron thickness. And you can use this.

17 And a POSA would have understood that.

18 Q. Back the limitations. The next one
19 was slow speed. Do you see that?

20 A. Uh-huh.

21 Q. Why is slow speed considered a

22 limitation for using Palm or Storm?

23 A. It just takes longer. It's a

24 tradeoff. So if you want the resolution

25 to get down, you know, in order of

1 magnitude better than the refraction
2 limit, you've got to take a lot of images.
3 So that takes time and processing. So I
4 don't know how long it takes me to take
5 10,000 images, but it's on the order of a
6 number of minutes as opposed to a quick
7 picture you might be able to do with a
8 spinning disconfocal, for example, which
9 is in milliseconds to seconds.

10 Q. The next one listed there is
11 reducing out of focus activation requires
12 either a TPM or light sheet elimination.
13 Why is that considered a limitation of 3D
14 Palm or Storm?

15 A. So I guess he's not aware or didn't
16 consider when he was doing this the other
17 implementations. For example, I worked at
18 Zeis. I was the head of the global
19 applications team. And we had 3D Palm.
20 And when we put a faceplate in we could
21 get one image. We could move 10 microns
22 through a cell and get 3D data at each
23 particular slice. We did not require a
24 two photon microscopy. I think that's an
25 overly general statement. It may improve

1 it for thick tissues.

2 Q. Do you recall this is a paper that
3 you selected and included in your
4 declaration?

5 A. Sure. Just is an example that
6 there is a lot of optical sectioning 3D
7 techniques that a POSA would have known
8 about.

9 Again, you apply, this is the thing
10 you have to understand, if we keep going
11 for the extreme events, there is a ton of
12 stuff that you can do with things that are
13 off the shelf, even spinning disc confocal
14 or regular confocal or a SIM microscope.

15 So a spinning disc or regular
16 confocal. You can keep going exotic if
17 you need to, but your patent keeps it so
18 that you could do these things if you
19 wanted to. But one embodiment is not
20 having to do that. The many embodiments
21 that don't have to do this. It's just
22 routine stuff.

23 Q. Where you said keep going for
24 extreme events, what are extreme events?

25 A. Again, it seems that somehow

1 because it's more difficult to use an
2 Ipalm or it takes longer to do a Storm,
3 it's possible if you need to go there, but
4 all of these techniques if you use fewer
5 probes you don't need to do a bajillion if
6 density is not an issue. You know, I
7 could keep going after the exceptions, but
8 a POSA, you know, if they had to go into
9 thick brain slices, that's why Cia used
10 the light sheet for sure; okay? And they
11 used clearing to solve that problem.
12 Localization microscopy is just another
13 way if you run into that problem.

14 But I'm doing these all the time
15 with my own samples. And, you know,
16 looking at a handful of probes, which is
17 within the claim and it's not a problem.

18 So it doesn't stop a POSA just
19 because there is some extreme conditions
20 that you want to go after.

21 Those are different challenges that
22 need to be solved. A POSA would be able
23 to think about it, and address it if it
24 applies.

25 Q. The next one listed there is

1 limited subset of dyes/PA-FPs.

2 A. Yes.

3 Q. What are PA/FPs, do you know?

4 A. Photoactivatable florescent
5 proteins.

6 Q. Okay. And so this would be the
7 dyes for Storm.

8 A. Yes.

9 Q. And the photoactivatable florescent
10 proteins for Palm.

11 A. Yes, or they could be
12 photoswitchable. He just doesn't mention
13 that. They came out after.

14 Q. And when it says limited subset,
15 why is a limited subset used as a
16 limitation for Palm?

17 A. Because they had to find out
18 molecules that would behave the way and
19 the right chemistry. And not every
20 molecule will blink under the certain
21 conditions.

22 So they had to identify what those
23 molecules were. And there is a very small
24 subset of them that can do it in a good
25 enough way; okay?

1 So you just, you know, I can give
2 you an example. I'm sorry, I'll just add
3 a teeny bit to it. If you don't use
4 photoactivation and photoswitching, if you
5 just used traditional organic dyes. Even
6 Sy-3 and Sy-5, which can blink. You can
7 use them in a non-blinking way and still
8 identify your single molecule.

9 It's only if you want to get
10 advantage of the resolution you need the
11 10X gain. And some of those molecules,
12 there is a much smaller pool that will be
13 able to have the right properties; okay?

14 Q. Uh-huh. The last one listed there
15 is mostly fixed cells. First of all, why
16 are these methods limited to mostly fixed
17 cells?

18 A. There, has been some live stuff on
19 it, but, you know, it's pretty tough to
20 drop it on to a high-powered laser onto a
21 sample. You know, part of it has to do
22 with either the photoactivation. With
23 photoactivation you have a chance. I have
24 seen some live cells work on it.

25 And then the same thing, the

1 chemistries can be toxic to them or change
2 their biology. So fixed is the lowest
3 hanging fruit to go after. You have to be
4 very careful you're not messing up your
5 biology by creating these other reagents.

6 Q. Do you have an understanding of the
7 microcolony modality SIM, S-I-M?

8 A. I do. Structured illumination
9 microscopy.

10 Q. How does structured illumination
11 microscopy work?

12 A. So in general you have an image, a
13 wide field image, for example. And if you
14 collect that image and you look at the
15 frequencies in that image, you'll get
16 frequencies that are related to
17 diffraction. The limit, meaning, when I
18 say look at the frequencies, I look at the
19 fast forward A transform.

20 In structured illumination
21 microscopy I actually put multiple
22 patterns over the image, shifted in phase
23 and directions. To the people you rotate
24 it. And then when you look at the
25 frequencies of these images you can double

1 the resolution. And depending on the
2 computational side, you're going to get up
3 to 4X improvement in resolution. Using
4 structural illumination, that's where the
5 name comes from.

6 Now, I'm saying your putting a
7 pattern. Of course, your example has a
8 frequency. This has a known frequency.
9 And you can access double, two to four
10 times better frequencies depending on your
11 algorithm.

12 I have a lattice structured
13 illumination system. And I also have one
14 that does a grid-based strategy. The nice
15 thing about SIM that I like about it is
16 that I can get under a 100 nanometer
17 resolution with the right sample setup.

18 And I can use any organic dye with
19 it. So that's one of the advantages of
20 it. It becomes more universal with probe
21 sets. You don't need to do blinking. It
22 takes a little bit longer because you have
23 to collect a few images to do the math.

24 Q. So does SIM require specific
25 optical configurations?

1 A. I mean, you need to be able to take
2 your illumination source. I use lasers on
3 mine. And be able to insert an element in
4 the device that will force it to make a
5 pattern on top of your sample, a grid of
6 some type. In my case a grid or a
7 lattice. So, yes, there would be an
8 optical configuration on the acidification
9 side.

10 Q. You mention a grid or a lattice.
11 Are there any other optical configuration
12 possibilities?

13 A. Possibly. Those are the two most
14 common ways. There is different ways, you
15 know, where people actually implement how
16 it makes the pattern on the sample, but
17 those are the two that come to mind.

18 Q. What are the known limitations of
19 structure illumination microscopy?

20 A. Well, it's 2 to 4X improvement.
21 Two is the most common, depending on the
22 older generation systems, which would be
23 actually more germane to it at the time.
24 The 4X is a more recent improvement. The
25 2X is fine.

1 You have to take multiple images.
2 So there is a little bit of a time
3 element. If your signal is strong, it's
4 still only a few seconds microscopy. You
5 can use it with 3D, so you can do any
6 optical sectioning with it readily.

7 Because of multiple exposures there
8 is a temporal cost to it. Meaning, you
9 know, if you're looking at something
10 dynamic, like in a living cell, you may
11 not go as fast as if you took one image by
12 itself.

13 Taking multiple exposures increases
14 the chance, the risk of photobleaching.
15 Photobleaching is remedied because I do
16 some all the time. I either, you know, a
17 sensitive detector.

18 Detectors are usually very, very
19 sensitive, and have a high efficiency
20 Cmos or EMCCD cameras. Those are just a
21 few things that come to mind. Other than
22 that, it's real easy to teach my folks how
23 to use it because they come in with their
24 same sample.

25 Now, I will make one other comment,

1 I generally do not use SIM for super deep
2 samples because the degradation of the
3 pattern on the sample can have an
4 influence. So generally under 20 microns
5 I can get a reliable result, which, again,
6 is a lot of biology.

7 Q. These points that you are talking
8 about for SIM does it also include 3D SIM
9 or are you just talking about --

10 A. 3D SIM is as simple as putting a Z
11 -- well, okay, 3D SIM, the other
12 approaches, by the way, I use SIM in 3D,
13 so it's different than the other 3D SIM.
14 I don't have a, the one he's calling 3D
15 SIM, but any SIM technique is 3D simply by
16 optically sectioning as Z stack might.

17 So in the traditional SIM sense, if
18 you just go plane, plane, plane, plane, do
19 the processing you have a 3D volume.

20 Q. And what's the difference between
21 that, what you just described, and 3D SIM?

22 A. I haven't spent as much time on the
23 3D SIM. I just know that it's a little
24 bit -- well, you know, he's calling 3D SIM
25 here. I want to differentiate that

1 because what he's showing here on 3D SIM
2 is showing resolution that is 2X better
3 than the diffraction limit. But that's
4 more like what he has SIM in his diagram.

5 So I'm trying to reconcile that
6 approach, to be honest with you. So he
7 has 3D-SIM, but it's not clear why or how
8 he's differentiating those.

9 And I didn't have, I don't recall
10 looking at -- okay. He has another little
11 language in here. So calls 3D SIM with an
12 asterisk. So he's got a lot of things on
13 here, so I'm looking at it. Under
14 resolution he has 100 nanometers XY,
15 250 -- so under resolution it says 100
16 nanometers XY, 250 nanometers Z, but he
17 says 100 nanometers XYZ with 3D SIM. It
18 specifically says a 4 -- it looks like a 4
19 pi configuration.

20 So that's just a different beast.
21 That's, again, a less common technique
22 that I don't know as deep about, but the
23 numbers that I would go with is what I
24 call 3D SIM.

25 But just to be clear minus optical

1 sectioning like you would use in a normal
2 florescence microscope focal where you are
3 just taking the thing and moving it a
4 certain distance in an equal way for your
5 steps.

6 Q. So when you refer to 3D SIM in your
7 declaration, are you referring to your
8 version of 3D SIM or --

9 A. I would have to look at the
10 language. I would modeled what he had
11 done with his description if I'm referring
12 to that figure. That's my recollection.

13 But, again, I mean, we can get into
14 the weeds on this, but the reality is SIM
15 is a way to get an improved resolution and
16 point spread function on the system
17 regardless of one technical implementation
18 versus another because there is lots of
19 ways to do this. The 3D SIM as he
20 describes looks like it's isotropic, but I
21 haven't had experience with that directly.
22 I just don't have a 4 ply system, which is
23 what I think he described.

24 Q. All right. I'm not trying to get
25 into the weeds. I'm trying to understand

1 your testimony. You used the word.

2 A. So let's go to, if you could direct
3 me to the paragraph I'll let you know what
4 I was thinking at that time; okay?

5 Q. Page 8, still Paragraph 13.

6 A. Okay. I'll tell you exactly. I
7 might have just referred to his diagram.
8 Okay. So if you look in here what I wrote
9 is:

10 As Dr. Shroff's figure shows while
11 the LFSM microscope, which is laser
12 scanning florescence microscope, modality
13 has a relatively extended PSF. That might
14 be light sheet florescence microscope.

15 Yes, it's light sheet. My
16 apologies, in the Z direction there are
17 several modalities that have substantially
18 reduced PSFs in the Z direction, including
19 SIM and 3D SIM. So in this case I'm
20 referring to 3D SIM as he described it on
21 here, this 4 ply version.

22 However, SIM and palm and confocal,
23 even if the word is not there, they are 3D
24 imaging tools, if that helps clarify.

25 Q. I think I understand now. So when

1 you say 3D SIM you're referring to the 3D
2 SIM that's mentioned, or described in
3 Exhibit 1019 we were just referring to.

4 A. I'm referring to his own language
5 in his diagram showing that there were
6 lots of different optical sectioning
7 modalities. The SIM and all of them will
8 be able to do 3D, which is the point of
9 this thing. So you have the higher
10 resolution you can do them all in 3D. The
11 3D SIM I'm referring to there is based on
12 Shroff's version. SIM is the one that's
13 more universally used by many
14 laboratories.

15 (Thereupon, a short recess in the proceedings was
16 had.)

17 Q. (By Mr. Holman) All right. Before
18 the break we were discussing Exhibit 1019
19 and the different modalities.

20 A. 1019 or 1086? I just want to make
21 sure.

22 Q. Well, 1086 is your declaration.

23 A. Okay. You were looking at both.
24 Okay. Understood.

25 Q. And a few times you mentioned, I

1 think you said, like his definition of 3D
2 SIM he's referring to 3D SIM in a certain
3 way, 4 or 5 configurations and things like
4 that.

5 A. Uh-huh.

6 Q. When you were saying he or him, who
7 are you referring to?

8 A. Well, I'm using Shroff based on
9 his, including in his declaration and so
10 forth. And to be clear, you know, people
11 use 3D SIM in the other alternative way.
12 It's just that this one is explicitly 3D
13 SIM. And it's just different. It's got a
14 dash in it. And it's subtle differences.
15 They're both using structural
16 illumination. I wanted to make sure that
17 we were differentiating that correctly.
18 And that's why I call it SIM, but SIM is
19 also understood to be 3D, as well. I call
20 it 3D SIM. So that's why we just need to
21 make the clarification. We're saying the
22 same thing. It's just that he puts the
23 dash. And I was trying to refer to his
24 language; okay?

25 Q. Got it. All right. So in Exhibit

1 1019, Table 1, which we were looking at on
2 Page 20. Do you still have that in front
3 of you? In the 3D SIM row on the
4 limitations column, the first limitation
5 there is slow speed. Do you see that?

6 A. Yep.

7 Q. Why slow speed considered a
8 limitation for 3D SIM?

9 A. Okay. And, by the way, I just want
10 to step back. He's calling 3D SIM without
11 a dash. Both of them collectively
12 together. And 3D SIM with a dash is the
13 alternative approach, so I just wanted to
14 make sure for the record that that's
15 clarified.

16 So it's slower speed because you
17 have to take some time to half it
18 depending on your setup. Half a dozen
19 images, sometimes you take more. So
20 you're taking multiple images at every
21 plane.

22 Again, if the signal is strong
23 you're talking about a few seconds. I can
24 take SIM stacks, full SIM stacks within a
25 few seconds. So if you have a fast camera

1 and a strong probe, it's not a limitation,
2 but it is slower because you have to take
3 multiple planes. As opposed to confocal,
4 which is point scanning or spinning disc,
5 where you actually get the whole field to
6 view at the same time, but you don't get
7 the whole resolution gain.

8 Q. And the next one is listed as
9 photodamage possible. Why is photodamage
10 a possibility considered a limitation in
11 3D SIM?

12 A. As I mentioned, since you're taking
13 multiple images, some samples,
14 fluorophores that are being sensitive, are
15 more likely to photobleach. But as I
16 mentioned, that is addressable by a number
17 of strategies that a POSA would know.

18 Q. And the next one says multiple row
19 images needed per 3D-SIM image. Why is
20 multiple row images being considered a
21 limitation for 3D-SIM?

22 A. I'm trying to look at his asterisk
23 here because his asterisk is a little bit
24 three-dimensional structure illumination
25 microscopy. So to be honest with you, I

1 still, I'm still trying to understand what
2 he's differentiating here when he's
3 calling 3D SIM versus 3D-SIM versus 3D no
4 dash SIM.

5 So if I was a reviewer I would
6 probably have a problem with making that
7 there; however, I'm going to assume
8 because SIM takes multiple images in order
9 to access the additional frequency
10 information, that you have to take
11 multiple images.

12 It's not like you have one shot and
13 you're done. And you got your high
14 resolution image. You have to take
15 multiple to a make a sequence.

16 But I'm also making a note on the
17 record that he has 3D SIM written multiple
18 different ways on the same page, which I
19 feel is a little confusing and may have
20 been an error on how they were formatting
21 it.

22 Q. Okay. You selected this paper;
23 right? This is your --

24 A. Well, yeah. But it's just an
25 example that all of these optical

1 sectioning when Chen said is for any other
2 optical sectioning. Here's all the
3 material. You know, whether there is
4 clarity, the point is that you have other
5 optical sectioning techniques. And they
6 also can effect resolution, if you need to
7 have it; okay?

8 For example, they have light sheet
9 on here. And that's just exactly what Pi
10 did. It's lower resolution, but you can
11 see single molecules with it. I just want
12 to make sure you understand they're out
13 here. They all have their own tradeoffs.
14 A POSA knows that.

15 And it's just a different way in
16 order to get the result they're looking
17 for to answer their biological question.

18 Q. All right. The next limitation
19 lists is shot noise not removed. Do have
20 an understanding of what shot noise is?

21 A. Yeah. Shot noise is usually from,
22 you know, your detectors. I am not sure
23 exactly why that would be the case. I'd
24 have to do a little bit more research on
25 the source of that particular shot noise.

1 It's electronic noise somehow in
2 the system.

3 Q. Why is shot noise not removed
4 considered a limitation for 3D SIM?

5 A. Well, it just means if your signal
6 is a little lower than it may. This is
7 where we're talking about signal to noise.
8 If you have a strong signal it wouldn't be
9 a limitation, but if you have a weak
10 signal it could be a limitation and your
11 image may not get the full benefit of the
12 processing.

13 Q. The last one listed is complex
14 optical configuration. What is the
15 complex optical configuration it's
16 referring to?

17 A. I mean, you have to insert a device
18 that will allow you to put a pattern on
19 your sample. So, I mean, it's not like a
20 Y field where you can just come in and you
21 can put an objective and you're done.

22 You're going to have to insert
23 elements in the pathway to account for
24 those. It's something that you would just
25 be able to do instantly.

1 Q. Why is it a complex optical
2 configuration considered a limitation of
3 3D SIM?

4 A. I don't know. I mean, the end in
5 practice to the enduser, it's not a big
6 deal. If you're going to make one from
7 scratch or whatever. I mean, I don't have
8 a problem with it. I've been doing it
9 with SIM for quite some time.

10 It's transparent to me, to be
11 honest with you. Behind the scenes on how
12 they implement. It may be just from a
13 design perspective, or maybe there is an
14 additional cost.

15 Q. So other than a design perspective
16 or additional cost, is there any other
17 reasons the complex optical configuration
18 would be considered a limitation for 3D
19 SIM?

20 A. I mean, if they're using this 4, 5
21 configuration it's more complex, but in
22 traditional SIM, it's transparent to use,
23 as I find it very easy to use. I went
24 through the I pieces, I focus, I mark my
25 top and my bottom and I take my stack.

1 So it's, from an enduser
2 perspective a POSA would actually use it,
3 and use a commercial system, not an issue.

4 Q. What is your understanding of 4 pi
5 configuration?

6 A. They have multiple objective lenses
7 coming in to take multiple angles of the
8 sample. I guess I'm going to be thinking
9 about this in a tomography way, where if
10 you get multiple angles you can improve
11 the resolution in all the other axis.

12 Again, these are more specialized.
13 I know of them. They were out around, I
14 think certainly before this. I just,
15 again, a POSA would be aware of them.
16 They have limited geometry as well because
17 you have, I think it's have four
18 objectives.

19 That's why I think they call it 4
20 pi, multiple objectives. You have your
21 sample that has to sit there in a very
22 precise spot. My recollection is that,
23 you know, you have to be very careful
24 about sample geometry to get that to work.

25 Q. Does I palm also use a 4 pi

1 configuration?

2 A. I thought it was only two objective
3 lenses, but as I've stated to you before,
4 I haven't studied it for quite some time.
5 I think it's just two and four, but you
6 have the 4 pi, as the name implied, four
7 to my recollection.

8 Q. All right. I'm going to hand you
9 exhibit marked 1073. This is a 237
10 patent. Do you recognize this document,
11 Dr. Czymmek?

12 A. I do, yep.

13 Q. You discussed this patent in your
14 reply declaration; correct?

15 A. I did, yes.

16 Q. And I believe you state in your
17 declaration that you reviewed this patent;
18 correct?

19 A. I did, yes. If you happen to be in
20 the section with it. Please continue.

21 Q. All right. If you could turn to
22 Page 78 of the 237 patent. The page
23 numbers are at the bottom. I'm looking at
24 Example 5 there on the right-hand side.
25 That's Column 48. Do you see that?

1 A. Uh-huh.

2 Q. And the text begins there just
3 under Example 5 it states: This example
4 illustrates the measurement of 140 genes
5 with MERFISH using a 16 bit MHD 4 code.
6 To test the feasibility of this error
7 robust multiplexed imaging approach, this
8 example uses a 140 gene measurement on
9 human fibroblast cells IMR 90 using a 16
10 bit MHD 4 code to encode 130 RNA species
11 while leaving 10 code words as missed
12 identification and controls. And it
13 refers to Figure 20. Did I read that
14 correctly?

15 A. Yes, correct.

16 Q. Okay. Now, do you still have the
17 Chen paper, Exhibit 1003 with you?

18 A. I do, yep.

19 Q. All right. And keep the 237 patent
20 handy. We're going to come back to it,
21 but in Chen, if you could turn to Page 3,
22 NanoString Page 3 of the document.

23 A. Uh-huh.

24 Q. And on the right-hand side under,
25 there is a section that begins measuring

1 140 genes with MERFISH. Do you see that?

2 A. Uh-huh.

3 Q. And in the first sentence there
4 Chen states: To test the feasibility of
5 this error robust multiples imaging
6 approach we performed a 140 gene
7 measurement on human fiberglass cells, IMR
8 90, using a 16 bit MHD 4 code to encode
9 130 RNA species while leaving 10 code
10 words as missed identification control in
11 reference to Table S1.

12 A. Uh-huh.

13 Q. Would you agree that with the
14 exception of Figure 20 in the 237 patent
15 in table S1 in Chen that this is the same,
16 referring to the same experiment, 140 gene
17 MERFISH experiment?

18 A. I would agree that Example 5 is one
19 embodiment of the technique that used that
20 number of probes.

21 Q. All right. In the 237 patent, the
22 same section we're looking at, Example 5,
23 beginning on Line 51 Column 48, the patent
24 states: The florescent spots
25 corresponding to individual RNAs were

1 clearly detected. And were then
2 efficiently extinguished via a brief
3 photobleaching step. And it refers to
4 Figure 6A. Do you see that?

5 A. Uh-huh.

6 Q. Okay. Now, let's keep your finger
7 on that page, but I would like you to turn
8 to the patent to Figure 6A, so we can look
9 at that together.

10 A. 6B, 6A, got it.

11 Q. All right. Would you agree that
12 Figure 6A in the 237 patent appears to be
13 the same as Figure 2-A in the Chen
14 reference?

15 A. Yep.

16 Q. All right. I just kind of want to
17 draw these parallels here. So in the
18 patent if you turn to the next figure, on
19 the next page, Page 6B and 6C on Page 17
20 of the patent.

21 And then in Chen would you agree
22 that Figure 6B and 6C in the patent appear
23 to be the same as figures 3B and 2C in
24 Chen?

25 A. Okay. 6B and 6C are the same as --

1 Q. 2B and 2C.

2 A. They look the same except for I do
3 not have color in this Exhibit 1073, but
4 they do look the same.

5 Q. Fair enough. And then if you turn
6 the page in the patent to the next Page 18
7 there is Figure 6D and 6E.

8 A. In the patent Page 18?

9 Q. In the patent Page 18.

10 A. The next page.

11 Q. And if you could compare Figure 6D
12 and 6E to Figure 2D and 2E in Chen, would
13 you agree that those appear to be the
14 same?

15 A. So I'm going to be honest with you,
16 they look like they're representing the
17 same data, but 6D is not the same as 2E.
18 There is a difference in how the hashing
19 in the graft was. And so I'm just making
20 that statement. The color is missing.
21 They appear to represent the same data,
22 but there seems to be some differences in
23 that actual graft besides color.

24 Q. Okay. One more in the next page in
25 the patent, Page 19, there is Figure 6F,

1 6G, and 6H. And I'd ask would you agree
2 that those appear to be the same as
3 Figures 2F, G and H in Chen?

4 A. Again, they look like they were
5 regrafted, but they appear to be
6 representing the same based data. They
7 regraft these. They're not identical, but
8 they represent the same thing.

9 Q. Okay. All right. Now, on the
10 patent we're going to go through a few
11 more of these, Page 20. So turn one more
12 page. Figure 7A, 7B. Would you agree
13 that the patent Figure, 7A and 7B
14 represent the same data in Figure 3A and
15 3B in Chen?

16 A. Again, the underlying data looks
17 similar, but the grafts were apparently
18 redrawn. And the fact that there is
19 missing color again.

20 Q. Sure. All right. If you could
21 skip in the patent to Page 25, Figure 8A.

22 A. Uh-huh.

23 Q. And compare that in Chen to Figure
24 4, Figure 4A, would you agree that the
25 patent Figure 8A appears to be the same

1 data as Chen's Figure 4A?

2 A. As far as I can tell without the
3 color they look like it's the same
4 underlying data.

5 Q. All right. One more page, if you
6 turn to the page in the patent, Page 26
7 and Figure 8B and 8C. And if you can
8 compare that to Chen Figure 4B and 4, C
9 would you agree that the data in the
10 patent Figure 8B and 8C appear to be the
11 same data presented in Chen, Figure 4B and
12 4C?

13 A. As far as I can tell, it's very
14 difficult due to the reproduction quality
15 on 8B. It looks like it's the same, but
16 it's really hard to tell without the
17 color, but from a consistency standpoint,
18 it's probably representing the same thing;
19 but it's completely inverted and it's
20 black and white, and it's difficult to
21 tell.

22 Q. All right. In the patent if you
23 could please turn to Page 28. So here we
24 have Figure 9A in Exhibit 1073, if you
25 could compare Figure 91 in Exhibit 23 with

1 Chen Figure 5A, would you agree that the
2 data in Exhibit 1073 Figure 9A appear to
3 be the same data in Chen Figure 5A?

4 A. Yes. Absent the black and white
5 versus color, they look like they would be
6 the same underlying data.

7 Q. All right. If you could turn in
8 the patent to Page 30 of Exhibit 1073.
9 That's Figure 10A.

10 A. Okay.

11 Q. And then compare that if you can
12 with Figure 6A in Chen. And let me know
13 if you agree that the data presented in
14 the patent Figure 10A appear to be the
15 same as Figure 6A?

16 A. As I quickly look at those now, I
17 still have a challenge of Figure 6A due to
18 the color versus black and white, but they
19 look consistent.

20 Q. All right. So in the patent, if we
21 can go back to Exhibit 5. That's on Page
22 78. It begins on Column 48.

23 A. Page 78.

24 Q. Uh-huh.

25 A. Okay.

1 Q. In the sentence I read to you
2 earlier refers to Figure 20. This is Line
3 48. It references Figure 20.

4 A. Uh-huh.

5 Q. And it's in reference to code
6 words. Do you see that reference there?

7 A. Yep.

8 Q. Okay. Let's take a look at figure
9 20. Start with 20A. It's on Page 47.

10 A. Okay. Got it.

11 Q. Okay. Do you understand what is
12 depicted in Figure 20A, B, C and D?

13 A. A, B, I'm just looking at them all
14 to make sure.

15 Q. Uh-huh.

16 A. D. Okay. It says code book for
17 the 140 gene experiment, so a zero is an
18 off at that particular imaging multiplex
19 frame. A one would be an on. And so
20 these were representing the codes that
21 would be for the 140 gene experiment set.

22 Q. When you say off and on, are you
23 referring to florescence?

24 A. Yes. I'm referring to a
25 Florescence hybridization event that would

1 be a single molecule on signal. So it
2 would be an individual transcript. With
3 its florescence at that particular cycle.

4 Q. And if there is, in each -- there
5 is several columns here in Figure 20.

6 A. Uh-huh.

7 Q. Does each column represent a round
8 of readout probe hybridization?

9 A. Yes.

10 Q. Okay. And when we see a one in a
11 particular column, that indicates that
12 that particular RNA species fluoresced in
13 that round; is that correct?

14 A. That's correct.

15 Q. And if we see a zero in a
16 particular column, it means that that
17 particular RNA species did not flores in
18 that round; is that correct?

19 A. That is correct.

20 Q. Okay. And so if you went down a
21 single column. For example, the first
22 column and counted all of the ones does
23 that reflect the number of different RNA
24 species detected in that particular round?

25 A. Again, yes. So just to be clear,

1 they're taking an image. If that message
2 was in that image, and it was one of these
3 on here, there would be, wherever there is
4 a one it would show up. It doesn't mean
5 that all of these are in one image, but it
6 could be. I don't know if that answers
7 your question. So the answer is yes.
8 That one would indicate that that is an on
9 point. It doesn't mean it's the one on
10 here, but if it were in that frame some of
11 these that have ones on them may show up
12 as a spot in the image.

13 Q. I see. So it depends on which
14 frame you're viewing, as opposed, that
15 dictates the florescence you're going to
16 see.

17 A. Well, it's the first frame, so
18 that's not a variable. It's whether that
19 message was in that frame at all or one or
20 five or ten. So you don't know. There is
21 a potential for one of these messages to
22 show up in that frame.

23 Q. I see. And if that message were in
24 that frame and it's fluorescing, it would
25 be a one.

1 A. Yes, unless the exceptions occur
2 where there is some error in here. Of
3 course, this is where they would do the
4 correction.

5 Q. And when we're talking about within
6 a frame, what do you mean by frame when
7 you're saying that?

8 A. Well, it's one image taken at one
9 given location. So it's one image taken
10 at one location at one plane when I'm
11 talking about that.

12 Q. And so in any given round of
13 hybridization, is it fair to say, at least
14 in this experiment, they could detect up
15 to whatever the total number of ones is in
16 a given frame?

17 A. Up to, that many unique messenger
18 RNAs.

19 Q. Is it your opinion that this patent
20 performed 3D MERFISH experiments?

21 A. It is my opinion that she
22 explicitly stated that 2D and 3D spatial
23 information could be acquired.

24 Q. But is it your opinion that they
25 performed any 3D MERIFSH experiments in

1 this patent?

2 A. She basically taught that you
3 could. I have another opinion.

4 Q. I'm asking you about what they
5 disclosed. Are there any 3D MERFISH
6 experiments in this patent?

7 A. Okay. Again, to be clear, they
8 demonstrate 2D. And with all of their
9 other information, if you want the other
10 three-dimensional information, it can be
11 gotten. And it was basically explaining
12 to a POA that it could be possible.

13 So it was taught that 3D could be
14 done. She demonstrated in 2D, with one
15 particular example of 140 gene set; but I
16 will comment to you that if you go to Page
17 61, Column 14, Line 8, in some cases a
18 significant portion of the nucleic acid
19 within the cell may be studied. For
20 instance, in some cases enough of the RNA
21 present within a cell may be determined so
22 as to produce a partial or complete
23 transcript of a cell. In some cases at
24 least four types of MRAs are determined
25 within a cell. In some cases at least

1 three, at least four, at least seven, and
2 so forth.

3 So while she provides an example,
4 she teaches that you can actually do less.
5 And she certainly teaches that you can do
6 more. And because she did it in 2D, she
7 also teaches you can do it in 3D.

8 So, again, this is why there is
9 embodiments. This is why she teaches to
10 do these things. I'm just making the
11 statement to you.

12 That doesn't mean that a POSA
13 wouldn't have understood it. In fact, it
14 was contrary. They would have been
15 motivated and they would have had a
16 heightened probability of success, a
17 reasonable chance of success.

18 Q. Can you show me any 3D MERFISH data
19 in this patent?

20 A. Again, she taught that you could do
21 2D and 3D spatial information within the
22 patent.

23 Q. Can you show me any 3D MERFISH data
24 in this patent?

25 A. As a POSA it doesn't matter. She

1 did it in 2D. She described the 3D
2 experiment that she did, so they did the
3 3D using FISH. So this would have been
4 absolutely taught MERIFISH had been
5 motivated to do it. And they would have
6 had a reasonable chance of success of
7 achieving it. All's you've got to do is
8 focus to a different plane as she's
9 described. That's why we've been going
10 through all of these 3D techniques.

11 So simply because it's not there,
12 she described embodiments where you would.
13 And you could do less probes. You could
14 do more probes. It's explicitly stated.

15 Q. Which figure in this patent has 3D
16 MERFISH data?

17 A. As I told you, she is using 2D as
18 an example, but she teaches 3D.

19 Q. But you just agreed that there is
20 no 3D FISH data in the patent; correct?

21 A. Again, I understand that there is
22 flexibility in how we interpret the
23 claims. And she describes explicitly the
24 use of 3D. She uses 2D. I'm saying it's
25 not a big deal for a POSA to have been

1 motivated and with a level of expertise of
2 a POSA at that time to achieve 3D. I
3 didn't say there was 3D explicit examples,
4 but a lot of times in a patent as you can
5 understand that's what the different
6 embodiment are for. That's why they have
7 the specifications on here because they
8 can't do every experiment in a patent;
9 okay?

10 So 2D is there. Cells are more
11 than one layer thick. People would have
12 been motivated. Just because she didn't
13 have 3D doesn't mean someone wouldn't have
14 been motivated, in fact, they certainly
15 would have been.

16 Q. Do you agree that the experiments
17 presented in these figures are 2D?

18 A. So the experiment she describes
19 includes a 3D FISH experiment as a quality
20 control. The actual demonstrated images
21 happen to be of a 2D dataset, but she
22 describes determining positions outside of
23 it using traditional FISH. Again, which
24 would have been interpreted that that's
25 something that people would want to do.

1 Q. You're still not answering my
2 question, Dr. Czymmek. I'm asking you
3 whether you agree or not, yes or no, does
4 this patent have 3D MERFISH experiments?

5 A. Okay. Now, you just said it.
6 There is a difference between 3D MERFISH
7 experiments. She has done 3D FISH
8 experiments. She did not do a 3D MERFISH
9 experiment, but she taught to do it, and
10 she did 3D FISH experiments.

11 Again, as I qualify clearly, A POSA
12 would have been motivated to do this in
13 3D. And they would have had a reasonable
14 chance of success with all of the
15 technologies out there.

16 So I answered your question. I
17 said yes, but she also teaches it. So
18 just she doesn't teach it, the embodiments
19 and the specifications teach it. Again,
20 I've explained to you you can't do every
21 experiment to get it out the door.

22 And, by the way, she only showed
23 140. Does that mean I can't do 1,000? I
24 can't do 3? No. She teaches that. And
25 this is the point that Shroff was making.

1 I should use this patent as a
2 determination of what their thinking was.
3 I see examples of 3D spatial information.
4 And I see examples of much smaller and
5 much larger datasets.

6 Q. Do you have see any examples of 3D
7 MERFISH data?

8 A. I've already told you that she
9 doesn't include that. Just like she
10 doesn't include all the different
11 embodiments and specifications that are
12 possible.

13 Q. It's your opinion that this patent
14 discloses 3D FISH?

15 A. She uses 3D FISH as a quality
16 control, and explains that when you want
17 to improve accuracy, you can use any
18 optical sectioning technique that would
19 allow you to look at adjacent tiles and
20 adjacent focal planes.

21 So she teaches it. And she
22 actually does FISH in her experiment. She
23 doesn't show a picture of it, but she did
24 the work on it, so that experiment was
25 performed because it's a natural thing to

1 do when you have a cell and you want to do
2 a quality control.

3 Q. Where are you referring to where
4 you say she did a quality control 3D FISH
5 experiment?

6 A. This is a very large document. If
7 it's following along here, I mean, you
8 know, if you want to give me some time to
9 find that section on here; but it's
10 linking to this document. You're showing
11 all the overlap in the data. I just have
12 to go in here and dig for a while. It may
13 take some time. It's a long document.

14 Q. When you say linking to this
15 document, you mean linking to the Chen
16 paper?

17 A. Well, this patent is using a lot of
18 this data, so there is a linkage in here.
19 And that's exactly why Shroff said, well,
20 the patent prosecution history should be
21 relevant in what they were thinking.

22 And I'm explaining to you they were
23 thinking more than just this 141 probe
24 set. They explicitly stated they were
25 doing it in 3D. They explicitly stated

1 you could do down to three or many more,
2 in the thousands.

3 Q. And so when you're referring to the
4 3D FISH quality control experiment in the
5 patent, your understanding is that's the
6 same quality control validation test
7 that's disclosed in the Chen paper?

8 A. I would have to go look
9 word-for-word, but if she's transferring
10 this information, then she likely would
11 have put this experiment over on it. It's
12 just where it's buried in this document.
13 If that's good use of time, I'm happy to
14 go after it, but certainly the time of the
15 patent's priority date, it's already
16 listed here, anyways.

17 And she already disclosed 3D
18 spatial information as one of her
19 teachings. And she already disclosed
20 optical sectioning and adjacent focal
21 planes in her teachings.

22 Of all of these things that you
23 just find in each case. And you can't do
24 everything. And that's why you have your
25 specifications and embodiments.

1 Q. All right. If you could turn in
2 this patent to Page 87, Column 65.

3 A. Okay.

4 Q. Beginning on Line 28, Paragraph
5 says because cells were used in live
6 imaging. Do you see that?

7 A. Yes, I do.

8 Q. All right. Does this appear to be
9 the same validation test you were
10 referring to?

11 A. Yes. This seems to match up. And
12 it explicitly states in here that it was
13 found that only a small fraction, 15
14 percent. And it says in here RNA
15 molecules were outside the imaging range
16 of the fixed focal plane without Z
17 scanning. The measurements are also
18 confirmed that the exitary -- exitation
19 geometry eliminated to full depth cells.
20 Any optical sectioning technique could be
21 employed in the MERFISH to allow imaging
22 of the RNAs to all thicker cells or
23 tissues.

24 So, again, this implies and they
25 demonstrate you can do it in 3D. There

1 were still some that were on there if you
2 want to go back and see what she states in
3 her original paper. Perhaps that language
4 is in here. Oh, there we go. On Column
5 66, 27: It is noted that this number
6 counts for the majority, but not all RNA
7 molecules within a cell because a fraction
8 of the cell could be outside the imaging
9 area or focal depth. Tiling images of
10 adjacent area and adjacent focal planes
11 could be employed to improve the counting
12 accuracy.

13 So we're coming back to the same
14 thing that's being shown in both of them.
15 So now I see this consistently. In
16 addition, she was able to describe other
17 embodiments that allow you to do a lot
18 less and a lot more than a POSA would have
19 been motivated to do without having to say
20 I have to do MERFISH on 140 or more.

21 Q. But the embodiment was generating
22 data in the patent calling for the 3D
23 MERFISH data.

24 A. Right. Yeah. That's how patents
25 work. I think you understand that. They

1 can't do every possible example. Any
2 patent that I have written provides some
3 exemplary example. And then we expand it.
4 They're flexible.

5 Q. In Chen Exhibit 1003, Figure 2 on
6 Page 4, Figure 2A, what is your
7 understanding of what's depicted there in
8 Figure 2A on Chen?

9 A. Well, I will read the figure
10 legend. A is images of RNA molecules in
11 an IMR 90 cell after each hybridization
12 round, hyb 1 to hyb 16. The images after
13 photobleaching, for example bleach 1
14 demonstrate efficient removal of
15 florescent signals between hybridizations.

16 So this detects an image from hyb
17 1. The image they took after bleaching to
18 show that they have eliminated the signal.
19 Then they show the image from hyb 2. And
20 then use a cartoon of...to represent the
21 other iterations. And they show the final
22 hybridization at 16, which would
23 representative whatever molecules had an
24 on code in that particular scene.

25 Q. So in the image presented in the

1 hyb 1, how many different RNA molecules
2 are depicted there in that image? Do you
3 know?

4 A. I mean, it may be described in here
5 somewhere, but if you look at the figure
6 legend it says simultaneous measurement of
7 140 RNA species in single cell by use of
8 MERFISH with a 16 bit MHDA code.

9 I don't know if she's using the
10 same data for B. Okay. It looks like B
11 says: The localization of all detected
12 single molecules in the cell are colored
13 according to their measured binary words.

14 So this appears to be the same cell
15 as in A. So I couldn't tell you which
16 specific one. It's an on code in position
17 1. And with 140 th genes I couldn't tell
18 you just by a black and white image unless
19 you look at the whole series of 16 and
20 decode it.

21 Q. And would you your answer be the
22 same if you are looking at hyb 2 image
23 panel?

24 A. Correct. It's an image with spots.
25 It requires decoding to know what the full

1 length of the 16 image hybridization
2 scheme.

3 Q. And would your answer be the same
4 looking at hyb 16 in the panel there?

5 A. Yes. My answer would be the same.

6 Q. How many different species of RNA
7 molecules are imaged in a single round of
8 Chen's 140 RNA experiment, 140 gene
9 experiment?

10 A. Well, she goes for 140. If you
11 want we can go through it. I don't know,
12 maybe. We'd have to count the ones that
13 potentially be there; but, as I stated to
14 you, it doesn't mean that it's necessarily
15 there in a particular frame.

16 So my comment is less than 140 and
17 a lot less, but it depends if it was an
18 bid at that position of that frame.

19 Q. How many different species of RNA
20 molecules are imaged in a single round in
21 Chen's 2001 RNA experiment? Do you know?

22 A. Well, potentially 1,000, but, you
23 know, we're in the same situation where
24 you can't know specifically. I'm trying
25 to see if she actually has an image. Do

1 you see an image on here that she did
2 1,000? I know she talked about it. I'm
3 trying to remember because I see most of
4 her data showing the 140 set. Okay. They
5 did G measurements. There is Figure 5.
6 This is 1,001 RNA species. So it's Figure
7 5.

8 Again, I think there is a
9 supplement that we don't have that
10 actually would show the potential for them
11 to be there. You can see in the field of
12 view in one little small box region there
13 are 12 of them that they can
14 differentiate. Except for three of them
15 you can't see because they're dark at that
16 position.

17 Q. That's the 500 nanometer cut out?

18 A. Yes. The end set.

19 Q. The end set?

20 A. Yeah.

21 (Thereupon, a short recess in the proceedings was
22 had.)

23 Q. (By Mr. Holman) During the break,
24 Dr. Czymmek, did you speak to anyone or
25 speak with anyone about the substance of

1 your testimony today?

2 A. I did not.

3 Q. You are testifying in this IPR
4 proceeding as Bruker's technical expert;
5 is that correct?

6 A. That is correct.

7 Q. What is your educational
8 background?

9 A. I have a Bachelor's in Biology and
10 a Ph.D. in Botany and Pathology. And I
11 did a post doc after that. That's usually
12 at DuPont. So this is at the Center of
13 Research and Development, doing cell
14 biology.

15 Q. Do you have any educational degrees
16 if economics?

17 A. I read the Wall Street Journal, but
18 I have no formal degree. I have taken
19 ad-hoc business classes as an executive
20 when I was at Zeis, but no formal
21 economics degree.

22 Q. Do you have an educational degrees
23 in finance?

24 A. Not a degree.

25 Q. Do you have any educational degrees

1 in accounting?

2 A. Not a degree.

3 Q. Have you ever taken a CPA exam?

4 A. I have not taken a CPA exam.

5 Q. Do you consider yourself an expert
6 in economics?

7 A. I do not consider myself an expert
8 in economics.

9 Q. Do you consider yourself an expert
10 in accounting?

11 A. I do not consider myself an expert
12 in accounting.

13 Q. Do you consider yourself an expert
14 in finance?

15 A. I do not consider myself an expert
16 in finance.

17 MR. HOLMAN: All right. No further
18 questions. Pass the witness.

19 MR. WALTER: I don't have any
20 questions myself.

21 MR. HOLMAN: All right. This
22 deposition is over. Thank you for your
23 time.

24 MR. WALTER: We'll review it for
25 errors later.

1 MR. HOLMAN: We need it right away,
2 Monday.

3 (SIGNATURE NOT WAIVED.)
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REPORTER'S CERTIFICATE

State of Missouri)
County of St. Louis)

I, EILEEN J. BELL, a Certified
Court Reporter within and for the State of
Missouri, duly commissioned and qualified,
do hereby certify that the within named
witness, DR. KIRK CZYMMEK, was by me first
duly sworn to testify the truth, the whole
truth and nothing but the truth in the
cause aforesaid; that the testimony then
given by the above-referenced witness was
by me reduced to stenotype in the presence
of said witness; afterwards transcribed,
and that the foregoing is a true and
correct transcription of the testimony so
given by the above-referenced witness.

I do further certify that this
deposition was taken at the time and place
in the foregoing caption specified and was
completed without adjournment.

Eileen J. Bell

EILEEN J. BELL, CCR #833

1 Eileen J. Bell, CCR #833

2 April 21, 2025

3 Derek Walter, ESQ

4 JONES DAY

5 555 California Street

6 San Francisco, CA 94104

7 In Re: Before the US Patent Appeal Board v. Harvard
8 College

9 Dear Mr. Walter:

10 Please find enclosed your copy of the deposition of
11 DR. KIRK CZYMMEK, taken on April 17, 2025, in the
12 above-referenced case. Also enclosed is the original
13 signature page and errata sheets.

14 Please have Dr. Czymmek read your copy of the
15 transcript, indicate any changes and/or corrections
16 desired on the errata sheets, and sign the signature
17 page before a notary public.

18 Please return the errata sheets and notarized
19 signature page to Mr. Holman for filing prior to trial
20 date.

21 Thank you for your attention to this matter.

22 Sincerely,

23 *Eileen J. Bell*

24 Eileen J. Bell, CCR #833

25 Enclosures

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6 I, DR. KIRK CZYMMEK do hereby certify:

7 That I have read the foregoing

8 deposition;

9 That I have made such changes in form
10 and/or substance to the within deposition
11 as might be necessary to render the same
12 true and correct;

13 That having made such changes thereon,
14 I hereby subscribe my name to the
15 deposition.

16 I declare under penalty of perjury that
17 the foregoing is true and correct.

18

19

20 DR. KIRK CZYMMEK

21

22 Executed this day of

23 2025, at

24 Notary Public:

25 My Commission Expires:

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Date Taken: April 17, 2025

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