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5 UNITED STATES PATENT AND TRADEMARK OFFICE

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7 BEFORE THE PATENT TRIAL AND APPEAL BOARD

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9 BRUKER SPATIAL BIOLOGY, INC.,
10 Petitioner

11 v.

12 PRESIDENT AND FELLOWS OF HARVARD COLLEGE
13 and 10X GENOMICS, INC.,
14 Patent Owner

15 -----
16 Case IPR2024-00526
17 U.S. Patent No. 11,542,554
18 -----

19 DEPOSITION OF KIRK CZYMMEK, PH.D.
20 TAKEN ON BEHALF OF THE PATENT OWNER
21 NOVEMBER 26, 2024

22 (Starting time of the deposition: 8:03 a.m. CST)
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I N D E X

QUESTIONS BY:	PAGE
MS. KHANDURI	5
MR. WALTER	86

E X H I B I T S

EXHIBIT		PAGE
Exhibit 1002	Referenced prior exhibit -	23
	not marked during deposition	
Exhibit 1003	Referenced prior exhibit -	69
	not marked during deposition	
Exhibit 1004	Referenced prior exhibit -	86
	not marked during deposition	

(No exhibits will be attached to the deposition transcript.)

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BRUKER SPATIAL BIOLOGY, INC.,
Petitioner

v.

PRESIDENT AND FELLOWS OF HARVARD COLLEGE
and 10X GENOMICS, INC.,
Patent Owner

Case IPR2024-00526
U.S. Patent No. 11,542,554

DEPOSITION OF KIRK CZYMMEK, PH.D., produced,
sworn and examined on November 26, 2024, between the
hours of eight o'clock in the forenoon and twelve
o'clock noon of that day, at the Crowne Plaza Hotel,
11228 Lone Eagle Drive, Bridgeton, Missouri 63044,
before William L. DeVries, a Certified Court
Reporter (MO), Registered Diplomate Reporter, and
Certified Realtime Reporter, in a certain cause now
pending in the United States Patent and Trademark
Office, Before the Patent Trial and Appeal Board,
between BRUKER SPATIAL BIOLOGY, INC., Petitioner,
vs. President and Fellows of Harvard College and 10X
Genomics, Inc., Patent Owner; on behalf of the
Patent Owner.

A P P E A R A N C E S

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William L. DeVries, RDR/CRR
Missouri CCR #566

1 IT IS HEREBY STIPULATED AND AGREED by
2 and between counsel for the Petitioner and counsel
3 for the Patent Owner that this deposition may be
4 taken in shorthand by William L. DeVries, RDR/CRR, a
5 Certified Court Reporter and Certified Shorthand
6 Reporter, and afterwards transcribed into
7 typewriting; and the signature of the witness is
8 expressly reserved.

9 * * * * *

10 KIRK CZYMMEK, PH.D.,
11 of lawful age, produced, sworn and examined on
12 behalf of the Patent Owner, deposes and says:

13 (Starting time of the deposition: 8:03 a.m.)

14 COURT REPORTER: Do you swear or affirm
15 that the testimony you are about to give in this
16 proceeding will be the truth, the whole truth, and
17 nothing but the truth?

18 THE WITNESS: I do.

19 EXAMINATION

20 QUESTIONS BY MS. KHANDURI:

21 Q. Good morning, Dr. Czymmek.

22 A. Good morning.

23 Q. How are you doing?

24 A. Good.

25 Q. My name is Pratibha Khanduri, and I'm

1 with the law firm Sterne Kessler Goldstein & Fox. I
2 represent 10X Genomics and I'll be taking your
3 deposition today. I have --

4 MR. WALTER: You might want to speak up
5 just a little bit.

6 THE WITNESS: Okay.

7 Q. (By Ms. Khanduri) I have with me my
8 colleague David Holman, also from Sterne Kessler.
9 Could you please state your full name and place of
10 residence for the record?

11 A. My full name is Kirk James Czymmek,
12 C-Z-Y-M-M-E-K, and my place of residence is 603
13 Martin Pointe Court, Pointe with an E, Wildwood,
14 Missouri 63011.

15 Q. Thank you. Have you ever been deposed
16 before, Doctor?

17 A. Yes, I have.

18 Q. And when was that?

19 A. I was deposed about three years ago and
20 about ten years ago regarding alumina cases and I
21 don't have the exact dates. I don't know if it's in
22 my document here, but it was a while ago.

23 Q. So those were the only two times you
24 were deposed before?

25 A. Correct.

1 Q. And that was for the same case with
2 aluminum?

3 A. Well, they were different cases, but
4 they were alumina related.

5 Q. And were those district court
6 litigations?

7 A. I don't recall. I mean, we were in
8 Delaware for one of them in a trial.

9 Q. Okay. What was the subject matter of
10 your first deposition?

11 A. Basically it was the flow cells I was
12 measuring and taking measurements on the flow cells
13 and serving as an expert witness that the flow cells
14 did not violate -- did not infringe the patent.

15 Q. Okay. So you performed some
16 experiments using some flow cells that were at issue
17 and then you were giving your expert opinion on
18 those flow cells?

19 A. Correct. In the first case.

20 Q. Okay. And in the second instance what
21 was the subject matter?

22 A. Again, it was related to the alumina
23 products and the dyes they were using and the
24 wavelengths of dyes in the equipment that they --
25 the product that they had.

1 Q. And were you an expert witness for
2 alumina in that case, the second case?

3 A. Yes.

4 Q. What about the first case?

5 A. Yes.

6 Q. Both times you were an expert witness
7 for alumina?

8 A. Correct.

9 Q. Okay. Have you testified at trial?

10 A. Yes.

11 Q. And which cases?

12 A. Again, the second alumina case, yeah.

13 Q. And the subject matter was the same
14 regarding flow cells?

15 A. Well, again, it was the fluorescent
16 dyes and the equipment that they had, the
17 fluorescent wavelengths of dyes that they were
18 using.

19 Q. Okay. What kind of experiments did you
20 perform to test the flow cells for one of the
21 previous cases where you had been deposed?

22 A. I basically took a series of dyes that
23 are used in the products and used spectrophotometry
24 to measure the wavelengths and match them up with
25 the filters that they were using in the products.

1 Q. What flow cells did you use?

2 A. Again, in that particular case it
3 wasn't a flow cell. It was the dyes themselves that
4 I was measuring.

5 Q. I'm sorry.

6 A. And their spectrum. Yes. Flow cell
7 was the first case.

8 Q. Okay. So in the case where you were
9 measuring flow cells, what flow cells were you
10 looking at?

11 (Court reporter interruption.)

12 A. This was, like I said, over ten years
13 ago, so I don't remember the specific product number
14 at that point.

15 Q. (By Ms. Khanduri) Were they
16 commercially available flow cells?

17 A. Yes, they were.

18 Q. Were they Bioptechs FCS2 flow cells?

19 A. No, they were the alumina product.

20 Q. Okay.

21 A. But they're slides. They're slides in
22 which they have the lawn of spots that are on the
23 slides.

24 Q. Okay. Sounds good. Thank you. So,
25 Doctor, you've been sworn in today. You understand

1 that means that you must testify accurately and
2 honestly because you are under oath and you are
3 testifying under penalty of perjury. You understand
4 that?

5 A. Yes, I do.

6 Q. Okay. Also, we have our conversation
7 being transcribed today. So I would request you to
8 let me finish my question first before you start
9 answering and I will do the same. I'll wait for you
10 to -- I'll try my best to wait for you to complete
11 your answer and then I'll, you know, respond to it.
12 Sounds good?

13 A. Understood.

14 Q. Okay. The other thing is if you have
15 any questions about -- strike that.

16 If you do not understand any question
17 that I ask, I request you to ask me for
18 clarification or explanation rather than asking your
19 counsel. Do you understand that?

20 A. Understood.

21 Q. Thank you. And you'll agree to do
22 that?

23 A. I agree to do that.

24 Q. Okay. Thanks. During the deposition
25 you are not permitted to speak with anyone about the

1 substance of your testimony, including during the
2 breaks. You understand that, right?

3 A. Understood.

4 Q. And you agree to do that?

5 A. I agree to do that.

6 Q. Thanks. We'll take breaks at regular
7 intervals, but if you would like a break just ask
8 me. The only thing I would ask is for you to answer
9 the question if there's a question pending before
10 taking a break. Sounds good?

11 A. Understood.

12 Q. Your counsel may object to some of my
13 questions, but if your counsel objects to my
14 questions you must still answer my questions unless
15 your counsel tells you not to do that. Do you
16 understand that?

17 A. I understand that.

18 Q. Okay. Thanks. Do you have -- I see
19 you have a document in front of you. Is that your
20 declaration that you submitted in this case?

21 A. That is my unmarked declaration.

22 Q. Okay. Thank you. Do you have any
23 other notes with you?

24 A. No.

25 Q. Okay. Do you understand why you're

1 being deposited today?

2 A. I do.

3 Q. And what's your understanding?

4 A. My understanding is that
5 NanoString/Bruker is defending a patent infringement
6 from 10X.

7 Q. Okay.

8 A. And I'm serving as an expert witness
9 that that is not the case.

10 Q. Okay. So you said you are -- so you
11 said your understanding is that NanoString/Bruker is
12 defending a patent -- defending a patent
13 infringement from 10X?

14 A. Well, okay. Again, I use this in broad
15 terms.

16 Q. Okay.

17 A. NanoString is -- basically had an IPR
18 review and basically making the position that it's
19 not -- these claims by 10X are not patentable
20 because they're obvious among other reasons, and so
21 I'm basically providing my expert witness on a
22 number of these claims.

23 Q. So would it be fair to say you're
24 providing your opinions for NanoString, which is now
25 Bruker, regarding whether the claims of the patent

1 at issue in this proceeding is not -- are not
2 patentable; is that fair?

3 A. Again, I don't know if there's any
4 double negatives in there, sorry. I'm just trying
5 to make sure I heard the question.

6 Q. Okay. So could you please again tell
7 me what's your understanding why you are here today?

8 A. Again, there were patent infringement
9 claims against NanoString/Bruker and I am -- looked
10 at those claims and provided my expert opinion on
11 whether they were valid or obvious.

12 Q. Okay. So you understand that patent
13 infringement issue is not -- is not a part of this
14 proceeding, right, the proceeding for which you are
15 being deposed today?

16 A. Okay. Can you repeat the question?

17 Q. My question is do you understand that
18 patent infringement issue is not part of the
19 proceeding for which you are being deposed today?
20 Do you understand that?

21 A. What do you mean by patent infringement
22 issue?

23 Q. So you mentioned in your answer that
24 there were patent infringement claims against
25 NanoString/Bruker and you looked at those claims to

1 provide your expert opinion on whether those claims
2 were valid or obvious.

3 A. Okay.

4 Q. So my question simply is you understand
5 that the patent infringement aspect is not part of
6 this proceeding today. You understand that?

7 A. Okay. To be clear, I'm not a lawyer.

8 Q. Okay.

9 A. So -- okay. I have the guidance -- the
10 differentiation between what you're saying. If -- I
11 made my statement, if you're telling me this is a
12 separate -- separate from what I made my statement,
13 then I believe as I stand here now and I understand
14 it I could accept that, but --

15 Q. Okay. But you agree that you provided
16 some opinions on some claims, whether those claims
17 were patentable or obvious, and you submitted a
18 declaration regarding that. You understand that?

19 A. Correct.

20 Q. And you are being deposed on that
21 declaration?

22 A. Yes, I am.

23 Q. Okay. Do you understand that the
24 proceeding for which we are sitting here today is
25 called an inter partes review?

1 A. Yes, I do.

2 Q. What is your understanding of an inter
3 partes review?

4 A. Again, an inter partes review is
5 basically a patent was claimed and NanoString/Bruker
6 is challenging those claims.

7 Q. Okay.

8 A. And the board is reviewing whether --
9 these claims, something was missed based on its
10 prior approval.

11 Q. Okay. Thanks. When did NanoString
12 first contact you for this IPR?

13 A. It would have been last year sometime.
14 I think spring, summer, but I don't remember the
15 exact date.

16 Q. Had you -- did you -- strike that.
17 Had you -- strike that.

18 Did you know about any patent disputes
19 between 10X Genomics and NanoString before you were
20 contacted about this IPR?

21 A. I did not.

22 Q. Who contacted you for your -- for your
23 involvement in this IPR?

24 A. Weil contacted me.

25 Q. Do you recall a specific person who

1 contacted you?

2 A. Derek contacted me.

3 Q. Were you aware of 10X Genomics before
4 Derek contacted you?

5 A. Yes.

6 Q. And how did you come to know about 10X
7 Genomics?

8 A. So my laboratory is an imaging center.
9 I had NSF funding, spatial omics and arrays, using
10 arrays, and I was aware of 10X had products that
11 were different than what our research was funded
12 for, but would do something along those lines.

13 Q. So would it be fair to say you haven't
14 used 10X Genomics products?

15 A. I have personally not used 10X
16 products.

17 Q. Are there 10X Genomics products in the
18 imaging products you mentioned?

19 A. There are not 10X Genomics products in
20 my imaging center.

21 Q. So what imaging products do you have at
22 your imaging center?

23 A. Do you want specific manufacturers and
24 models or a general overview of the technologies?

25 Q. Just manufacturers -- just the name of

1 the manufacturers would be fine.

2 A. Okay. I have an Elyra 7
3 super-resolution microscope from Zeiss. I have a
4 Thermo Fisher hydra plasma focused ion beam scanning
5 electron microscope equipped with cryo from Thermo
6 Scientific.

7 I have a Talos 120 TEM transmission
8 electron microscope from Thermo Scientific. Both of
9 the hydra and the Talos are cryo equipped. I have a
10 Axio Zoom from Zeiss, which is a macro microscope.
11 I have a Nikon upright microscope equipped with
12 digital cameras.

13 I have a Leica SP8 white light confocal
14 microscope. I have a Zeiss combi laser capture
15 microdissection system. Those are the major
16 microscopes that I have in my center.

17 Q. Okay. Thank you. So you do not have
18 any NanoString products?

19 A. I do not.

20 Q. You do not have any Bruker products?

21 A. Double-checking because there's
22 peripheral equipment. I do not have any Bruker
23 products either.

24 Q. Have you used NanoString products
25 before?

1 A. I have not used NanoString products
2 before.

3 Q. What about Bruker?

4 A. So I was a global vice president in a
5 company called Zeiss. My -- I had an applications
6 teams around the world. Bruker made elemental --
7 EDS or elemental dispersive spectroscopy equipment
8 which were attached to scanning electron microscopes
9 to do elemental analysis. And so during that time I
10 would have had exposure to Bruker as well as other
11 manufacturers who made EDS equipment.

12 Q. Did you use any of those Bruker --
13 strike that.

14 Did you use any of those Bruker
15 equipments?

16 A. Not personally, but my teams did.

17 Q. Aside from serving as an expert witness
18 in this IPR, do you have any other professional
19 relationship with NanoString?

20 A. I do not.

21 Q. What about Bruker?

22 A. I do not.

23 Q. No research funding?

24 A. No. As I sit here, I know they've
25 approached me -- this is from a salesperson

1 perspective, about using imaging-based mass spec,
2 but I'm not pursuing that. It's been quite some
3 time since I've had contact with them.

4 Q. And in the past would it be fair to say
5 you have not had any professional relationship with
6 Bruker or NanoString other than this involvement --
7 other than involvement in this IPR?

8 A. Again, I was a global vice president
9 heading the applications team. So I would have had
10 interactions with Bruker global or sales or local
11 salespeople who would have put their EDS equipment
12 on our instruments to request loans or to support
13 our team in sales transactions. Different
14 technology.

15 Q. Okay.

16 A. This is years ago. I haven't -- it's
17 been greater than five years since I had that
18 interaction.

19 Q. Okay. Do you own any stocks in either
20 Bruker or NanoString?

21 A. Not that I'm aware of. I have
22 basically funds that are target date-based funds and
23 whether they hold it or not I have no knowledge.

24 Q. Okay. Thanks. During your work in
25 this IPR have you communicated with anyone other

1 than who is not -- who is a lawyer?

2 A. No.

3 Q. Are you being compensated for your
4 testimony in this case?

5 A. Yes, I am.

6 Q. And what's your billing rate?

7 A. \$350 per hour.

8 Q. Have you submitted any invoices for
9 your work in this IPR?

10 A. I have.

11 Q. Could you tell me the total amount that
12 you have invoiced so far?

13 A. I don't remember an exact amount. I
14 know that in the fall might have been around -- I
15 don't know, 15 -- this is -- I want to be accurate
16 here, but I don't remember the exact amount.

17 It's usually five to 10,000 at a time
18 depending on how long and how intense we were
19 working on the documents for a period of weeks.

20 Somewhere between, I don't know, maybe 20 and
21 50,000. Sorry for the broad number. I just don't
22 know. I didn't go through records beforehand.

23 Q. So are you saying your -- are you
24 saying the total amount that you have billed so far
25 is within 50,000?

1 A. Less than 50,000 for sure.

2 Q. What did you do to prepare for this
3 deposition today?

4 A. I reviewed all of my documents on hand.
5 I reviewed as many of the exhibits again beforehand
6 again, and I looked at the patent owner's positions
7 and Waller's deposition.

8 Q. I think you said you reviewed Waller's
9 deposition. I assume you mean Waller's declaration?

10 A. Declaration. You're correct. There
11 was no deposition. Thank you for clarifying. My
12 apologies.

13 Q. As part of your review, did you review
14 your declaration in this case?

15 A. Yes.

16 Q. What other documents did you review?

17 A. Again, the exhibits. I can't say that
18 I read all of them cover to cover again in the last
19 few weeks, but I certainly did at one point over the
20 last year or so that I've been involved.

21 I reviewed Waller's declaration, the
22 patent owner's I guess rebuttals. I had another
23 response to the patent owner -- sorry, I don't have
24 the term for their particular documents which they
25 were objecting to evidence. And then I had a

1 response. So --

2 Q. Did you recall reviewing decision by
3 the patent and trial board?

4 A. Oh, yes. Yes. I did review that.

5 Q. Who did you meet with in preparation of
6 your deposition?

7 A. Derek.

8 Q. Anyone else?

9 A. No.

10 Q. How many meetings did you guys have?

11 A. It's probably maybe about four by Zoom
12 for about an hour and then yesterday we had a
13 face-to-face.

14 Q. Okay. For how long yesterday?

15 A. About seven or eight hours.

16 (Court reporter interruption.)

17 Q. (By Ms. Khanduri) So approximately
18 20 hours total?

19 A. About that maybe.

20 Q. Okay.

21 A. Maybe plus or minus.

22 Q. So Dr. Czymmek, you already have your
23 declaration with you. I'm going to hand your
24 counsel a copy of the declaration.

25 (Court reporter interruption.)

1 Q. (By Ms. Khanduri) So Dr. Czymmek you
2 have your declaration that you submitted in this
3 IPR, which has been marked Exhibit 1002. Correct?

4 A. Correct.

5 Q. And you recognize this document, right,
6 of course?

7 A. Yes, I do.

8 Q. Let's turn to page 172, which is the
9 last page of your declaration. Is this your
10 signature on page 172 of the exhibit?

11 A. Yes, it is.

12 Q. And did you sign it on January 24,
13 2024?

14 A. Correct.

15 Q. In preparing this declaration did you
16 read all the exhibits that are cited in the
17 declaration?

18 A. Yes, I did.

19 Q. Did you rely on any other documents to
20 form your opinions in this declaration other than
21 the ones that are already cited in your declaration?

22 A. No, I did not rely on any other
23 documents.

24 (WHEREIN, a recess was taken.)

25 Q. (By Ms. Khanduri) So, Doctor, before

1 the break we were looking at your declaration and
2 you testified that you did not rely on any other
3 documents to form your opinions in this declaration
4 other than the ones that are already cited in your
5 declaration, right?

6 A. Correct.

7 Q. So if a document was important for your
8 opinions you would have cited it. Would that be
9 fair to say?

10 A. So the answer is yes, if it was
11 important I would have cited it. However, due to
12 the number of claims that need to be covered there
13 was, you know, other documents out there, but we
14 kept it as tight as we could. But if it was
15 important I would have included it, but there were
16 others that weren't included.

17 Q. Does any specific document come to mind
18 that you could have included but did not include?

19 A. No. I think at this point based on my
20 declaration I picked sufficient documents to make my
21 arguments.

22 Q. Approximately how many hours did you
23 spend to prepare your declaration?

24 A. It was over a three-month period and I
25 would say, you know, two to three weeks of effort.

1 We can translate that into 40 hours, I don't know,
2 120 plus or minus. I'm just ballparking here. It
3 would be in my billable hours, but I didn't check
4 those before I came.

5 Q. So you said you can translate that into
6 40 hours. Then you mentioned 120 plus or minus.

7 A. You're asking me to be precise on
8 spending three months and remembering all of my
9 hours, and I'm just telling you I don't remember the
10 exact amount. My total billable hours was under
11 50,000, like I mentioned.

12 It was probably closer to 20 or 30
13 maximum. So we can do a calculation on that. I'm
14 just trying to be honest with you. I don't have an
15 exact number in my head, but it was not a few hours,
16 but it was significant amount to put this document
17 together.

18 Q. Okay. So within 120 hours plus minus?

19 A. Again, probably. I can only tell you
20 that this is an estimate based on my feeling of the
21 period of time and it was not like it was three
22 specific days. It was hours in review as time
23 permitted.

24 Q. Okay. Did you meet with anyone to
25 prepare your declaration?

1 A. Not physically. I had some Zoom calls
2 with our counsel that I was working with.

3 Q. So other than your counsel sitting with
4 you today, did you meet with anyone else?

5 A. There were one or two other lawyers
6 from the firm who were early on involved in the
7 declaration.

8 Q. Do you recall their names?

9 A. Well, one was Wes, but I think his last
10 name is Derrick so I get you guys mixed up a teeny
11 bit. And there was another lawyer that I just don't
12 remember his name at the time that was -- sorry. He
13 was Asian. That's what I remember, but I don't
14 remember his name just because it's been a long -- I
15 don't know, maybe it's close to a year since I
16 interacted with him.

17 Q. Did you meet with anyone who was not a
18 lawyer while preparing your declaration?

19 A. No.

20 Q. And you said the last time you reviewed
21 your declaration was to prepare for the deposition
22 today?

23 A. Correct.

24 Q. Is there anything you would like to
25 correct in your declaration?

1 A. Not that I can think of as I stand
2 here.

3 Q. So you still stand by your declaration?

4 A. Yes, I still stand by my declaration.

5 Q. Doctor, you have a Ph.D. in botany and
6 plant pathology; is that right?

7 A. Correct.

8 Q. Where are you currently employed?

9 A. I am currently employed at the Donald
10 Danforth Plant Science Center, which is in
11 St. Louis.

12 Q. And what is the nature of your
13 employment at the plant science center?

14 A. I am the director of the Advanced
15 Bioimaging Laboratory and I'm a principal
16 investigator.

17 Q. So you conduct scientific research as
18 part of your employment at the plant center?

19 A. That is correct.

20 Q. And what's the nature of your research?

21 A. My personal research is related to the
22 mission of our center, which is to improve crops and
23 food for the human condition. So it can range from
24 anything in which a plant interacts with microbes
25 and/or its environment and/or the soil and/or the

1 air.

2 And so typically my research is looking
3 at cellular tissue and subcellular localization of
4 molecules that will help scientists understand the
5 particular biology or scientific question.

6 Q. Do you use microscopy tools as part of
7 your research?

8 A. Yes, as director of the Advanced
9 Bioimaging Laboratory I also listed to you a number
10 of the microscopes, those are specific microscopes.
11 I didn't talk about all of the supporting equipment,
12 but those are specific microscopes that I use.

13 Q. So in your mind microscopy tools is a
14 broader group than microscopes?

15 A. Okay. I'm using the word microscopy
16 tools just because, for example, a focused ion beam
17 scanning electron microscope uses ions to ablate or
18 remove samples of materials rather than physical
19 cutting as used in an ion -- well, it is a physical
20 cutting, but it's using a plasma ion beam.

21 But I also have equipment that would
22 help prepare a sample to get into those microscopes
23 with high fidelity, such as a high-pressure freezer,
24 a plunge freezer, a microwave processor, an ultra
25 microtome for sectioning, a vibratome for

1 sectioning. Does that make sense? I just want to
2 make sure.

3 Q. I think so. So I think what you're
4 saying is that microscopy tools include microscopes
5 plus tools that one can use to prepare samples, for
6 example, and other peripheral aspects of performing
7 microscopy I guess?

8 A. Correct. In order to prepare a sample
9 to be in the microscope there will be different
10 techniques that I have to use to make the -- for
11 example, the probes accessible to the tissue, which
12 would be sectioning or to prepare it for one
13 modality or another.

14 Q. And would it be fair to say you also
15 use microscopes as part of your scientific research
16 at the plant center?

17 A. Yes. Daily.

18 Q. Do you have any relationship with Saint
19 Louis University?

20 A. I have an affiliated faculty position
21 with Saint Louis University.

22 Q. Okay. And do you perform any
23 scientific research as part of your relationship
24 with Saint Louis University?

25 A. So there are principal investigators at

1 the Danforth Center who have faculty appointments at
2 Saint Louis University. I oftentimes will have
3 undergraduates or graduate students do internships
4 in my center doing my research. I currently do not
5 have a specific project with a Saint Louis
6 University scientist on their work.

7 Q. Okay. Thank you. Doctor, do you have
8 experience imaging biological samples?

9 A. Many decades of experience, yes.

10 Q. And what about imaging single molecules
11 in biological samples?

12 A. Many years of experience, yes.

13 Q. Could you give me some idea or some
14 example where you have used imaging -- strike that.

15 Can you give me an example where you
16 imaged single molecules in biological samples as
17 part of your research?

18 A. I can give you several, but I use
19 hybridization chain reaction, for example, to look
20 at single messenger RNA molecules in plant tissues.
21 That's published in bio archives and is currently in
22 revision.

23 If you look a little further back in my
24 history I use single-molecule localization
25 microscopy in yeast against certain fluorescent

1 proteins. That was, again, probably 15 years ago.

2 Just to give you an example.

3 So when I was at the University of
4 Delaware I ran and directed the Delaware
5 Biotechnology Institute Bioimaging Center where I
6 also had an a Elyra system, an earlier generation
7 that did single-molecule localization microscopy.

8 Q. So you have significant experience in
9 microscopy as well as single-molecule imaging?

10 A. Yes.

11 Q. Do you know an imaging technique called
12 MERFISH, M-E-R-F-I-S-H?

13 A. Yes, I'm familiar with MERFISH.

14 Q. Do you have experience using MERFISH?

15 A. I have not personally used MERFISH.

16 Q. We talked about NanoString's products
17 before. Have you used -- strike that. Would it be
18 fair to say you have not used CosMx before?

19 A. It would be fair to say that I have
20 never used CosMx before.

21 Q. Have you heard of CosMx before you got
22 involved in this IPR?

23 A. I had only heard of it as a spatial
24 omics platform.

25 Q. Do you have any impressions of CosMx

1 from your colleagues?

2 A. I do not. I'm not sure if my specific
3 colleagues have used a CosMx system.

4 Q. What about Xenium?

5 A. So you're referring to the 10X
6 platform?

7 Q. Yes. 10X's Xenium platform.

8 A. And what is your question?

9 Q. My question is do you have experience
10 using 10X's Xenium platform?

11 A. I have not used the 10X Xenium
12 platform.

13 Q. Okay. Have you had any feedback
14 regarding 10X's Xenium platform from your
15 colleagues?

16 A. So I believe one of my colleagues used
17 it, but was unsuccessful in getting a result, but to
18 be clear, most of the work I would be doing in
19 spatial omics on these platforms is plants and these
20 equipments typically are more geared towards
21 biomedical as their primary oftentimes. So at this
22 point it's very minimal to none and I was not asked
23 to opine on their designs or the platforms.

24 Q. Okay. Another question, have you had
25 any feedback regarding NanoString, now Bruker's

1 CosMx platform from your colleagues?

2 A. Again, the answer is no, and I want to
3 preface that by saying that the work that we're
4 doing is that we're building our own arrays and so
5 we're trying to actually get our own technology to
6 be working, so we're just aware of it because it's
7 another spatial omics.

8 Q. Doctor, would it be fair to say you
9 have experience with 3D imaging of single molecules
10 in biological samples?

11 A. Yes, I do.

12 Q. Did you perform 3D imaging of single
13 molecules in biological samples before getting
14 involved in this IPR?

15 A. Yes, I did. Well, as I mentioned, I
16 used hybridization chain reaction so I use my
17 super-resolution microscope to do that, and because
18 my tissues have more than one dimension I take
19 volumes of stacks through them looking at the single
20 molecules.

21 Q. Do they have three dimensions?

22 A. Almost every cell does.

23 Q. Did you perform 3D imaging of single
24 molecules in biological samples before November
25 2015?

1 A. Yes, absolutely.

2 Q. Okay. Have you developed any systems
3 for 3D imaging in biological samples?

4 A. So you're asking me if I developed a
5 technology specifically to do 3D imaging?

6 Q. That's right.

7 A. So the answer is no, but I qualify that
8 is that I'm an applications person, number one, and
9 as an applications person I apply these technologies
10 and I tend to be involved in I would say an early
11 adopter.

12 And number two is in my role at Zeiss
13 as a global vice president of the applications
14 centers oftentimes I would interface with their
15 development teams and my team would be doing testing
16 of software and hardware that would implement these
17 things sometimes.

18 I don't want to make that as I'm
19 directly involved in an R&D group that's building
20 these things, but I understand it. When I was an
21 applications scientist in Noran Instruments I was
22 part of the team that was designing the software,
23 the hardware, the emission filters and so forth for
24 products called the Odyssey and the OZ.

25 So I have experience doing development

1 of products, either peripherally or part of the
2 team. I apologize that was a little bit longer. If
3 I need to reframe anything for you, let me know.

4 Q. Yeah, thank you. It's not a big deal.

5 So just so I understand, I asked you if
6 you have developed any systems for 3D imaging in
7 biological samples, and you started out by saying
8 no, and you emphasized that you are more involved in
9 application, that you were an application scientist,
10 but then towards the end you mentioned you have
11 experience doing development of products either
12 peripherally or part of the team. So I'm not fully
13 clear.

14 A. Okay. I think you -- was your question
15 specific to single molecule systems? I'm trying to
16 remember. I apologize. I want to get it right for
17 you.

18 Q. Yes. So let me ask the question again.
19 Have you developed any systems for 3D imaging in
20 biological samples?

21 A. Okay. So then I will revert back to
22 probably the most direct example is when I was an
23 applications scientist at Noran Instruments I worked
24 with the engineers and the software and hardware
25 people to develop the OZ, which is a high-speed

1 confocal microscope that could image at 480 frames
2 per second.

3 Q. And how were you involved in developing
4 the high-speed confocal microscope that you just
5 mentioned?

6 A. So Noran Instruments at that time had a
7 confocal division and I was an applications
8 scientist and it was a small company, so I would be
9 involved with the engineers and beta testing.

10 I also helped design the specifications
11 for emission filters for the dyes that would have
12 been on that system. And I worked regularly with
13 the engineers as they beta tested it and they would
14 design it, failure testing, creating 3D stacks,
15 using deconvolution with the 3D stacks with imaging
16 processing people.

17 So it was pretty broad, but everybody
18 who built the system, it's not just the engineer who
19 can design the parts in CAD. It's the people
20 assembling it together, it's the people doing the
21 code, it's the people testing it, it's the people
22 providing specifications for the emission pathway
23 which I was involved with.

24 Q. So one aspect of your involvement was
25 to do beta testing of the system that you were

1 developing?

2 A. Well, I guess I would call it alpha
3 testing because it was before that. It was before
4 anybody else, a customer would have seen it and this
5 was in the early nineties.

6 Q. Okay. So your role in -- one of your
7 roles in developing the high-speed confocal
8 microscope we've been talking about was to do alpha
9 testing of the system?

10 A. Again, the product was from concept
11 to -- you know, I was specifying, for example, the
12 emission filter tests. I was doing any testing
13 while it was early looking like a frame in a room to
14 the point where, you know, the customer looking,
15 covers were on it and so forth. So it was through
16 development process --

17 Q. Okay.

18 A. -- when it was attached physically to a
19 microscope. But again, I helped design the
20 specifications for the emission filters that were
21 used in the technology, so I would call that even
22 before alpha if you want to say that.

23 Q. So my apologies, Doctor. I'm not fully
24 understanding. In your last answer you said when it
25 was physically -- strike that.

1 You said when it was physically
2 attached to a microscope. What was physically
3 attached to a microscope?

4 A. Okay. So almost all of these
5 technologies have a base underlying platform, which
6 is a chassis that holds an optic and focusing
7 product. So when you make a confocal microscope
8 back then, many of them were add-ons to an existing
9 microscope.

10 So you could take this box that was a
11 high-speed confocal, was called the OZ, and you
12 could attach it to a Nikon, you could attach it to
13 an Olympus, you could attach it to Zeiss.

14 So I couldn't do anything till that box
15 that did high-speed imaging was interfaced with the
16 particular microscope. That's when I actually did
17 the alpha and beta testing and did Z stacks. Prior
18 to that I had provided specifications for the
19 emission pathway and the filters that would allow
20 common dyes to be used.

21 Q. Okay. Thank you.

22 A. I mean, this is digging back in my
23 history here a little bit, so --

24 Q. I understand. Thanks. So just so I
25 understand it properly --

1 A. Uh-huh.

2 Q. -- you talked about a box that you
3 attached to the microscope. Is that correct?

4 A. The box -- it was confocal, right, and
5 that box had lasers attached to it and computer
6 control attached to it and any peripheral that would
7 allow it to take -- which would -- actually a linear
8 encoded Z motor onto the focus drive and so forth.
9 So it was a little bit more than that. There was
10 basically a computer control system with it.

11 Q. Okay. Did you design the computing
12 system as part of your development process?

13 A. I -- okay. I want to make sure you
14 finish your statement. So the answer is no, I do
15 not design computer systems.

16 Q. Okay.

17 A. An engineer designs them. I would act
18 as an end user to break it and make sure that they
19 designed it and make sure that it was robust after
20 they integrated everything and made sure it was
21 working properly.

22 Q. Okay.

23 A. With minimal to no bugs I guess is the
24 word.

25 Q. So did you design optical system?

1 A. No. I designed specifications for the
2 emission pathway, but the optical system is designed
3 by the physicist that was an optical expert.

4 Q. I get it. Thank you.

5 A. All right. Again, I'm applications,
6 but the optical folks don't know the dyes and the
7 application side so this is where you interface it.
8 It's a team that does these things.

9 Q. Okay. Thank you. So similar question,
10 Doctor, but now in the context of individual
11 molecules. Have you developed any imaging systems
12 for determining three-dimensional position of
13 individual biomolecules in a tissue sample?

14 A. I have not developed a system, but I
15 didn't need to develop a system because they existed
16 and I used them accordingly.

17 Q. And was this before 2015?

18 A. Yes. I was using a Zeiss Elyra 7
19 super-resolution molecule that was a single-molecule
20 imaging system. To be clear, there's a difference
21 between single floor for imaging system and a
22 single-molecule imaging system.

23 And the nice thing about hybridization
24 is you can decorate them with lots of fluorophores,
25 which means you can see them with standard

1 microscopes as well, okay? So when you use the word
2 single molecule, if it's decorated with 10, 20, 30
3 fluorophores you can see those readily with many
4 technologies.

5 Q. Let me understand your answer.

6 A. Okay.

7 Q. So you're saying that determining 3D
8 position of an individual molecule in fluorescent
9 microscopy would be different compared to
10 nonfluorescent microscopy? Is that --

11 A. I didn't say anything like that, so I
12 apologize if that somehow came across that way.

13 Q. Okay. Okay. Okay. Doctor, do you
14 have an understanding of the term Z stacking in the
15 context of imaging?

16 A. Yes, I do.

17 Q. And could you tell me what your
18 understanding is?

19 A. Well, from an imaging standpoint
20 wherever the objective lens is focused is a single
21 plane. It has a depth of field to it. There can be
22 interfering or contaminating signals around that
23 depth of field, but to simply change the Z position
24 either by a focus knob or through Z stacking where
25 it's controlled by computer, you can create a

1 Z stack, which is an accumulation of adjacent Z
2 planes. Typically done at a regular interval.

3 Q. Okay. So then changing the Z position
4 by focus knob is different from Z stacking. Is that
5 correct?

6 A. No, it's the same thing.

7 Q. What about optical sectioning, do you
8 have an understanding of the term optical sectioning
9 in the context of imaging?

10 A. I do.

11 Q. Could you tell me what that is?

12 A. So optical sectioning is often used
13 where a technique allows you to minimize or reduce
14 out-of-focus information that will lower contrast
15 and resolution of an image. And if applying
16 Z stacking or Z positioning you will get a stack or
17 series of images adjacent and adjacent planes that
18 are high contrast and high resolution and they can
19 be put together and made into a 3-dimensional image
20 or dataset, confocal microscopy being one of the
21 most obvious because it uses a pinhole to reject
22 out-of-focus light.

23 Light microscopy will actually just do
24 exudation only in a very thin plane. It's a
25 different strategy, but optical sectioning is also

1 going to be done through deconvolution where you
2 mathematically reassign the light. All of those are
3 known in the art and context of this patent.

4 Q. So you mention out-of-focus
5 information. Is that the background noise you're
6 talking about?

7 A. Background noise is a pretty broad
8 term. Out-of-focus information could be background,
9 but also background can be nonspecific binding of a
10 probe within the focal plane. It can also be
11 autofluorescence in the tissue.

12 So optical sectioning will not get rid
13 of the things that are part of the tissue, but it
14 could get rid of out-of-focus information. Again,
15 depending on the illumination geometry of the
16 microscope.

17 Q. Okay. Thanks. Do you have an
18 understanding of the term point spread function in
19 the context of imaging?

20 A. I do.

21 Q. Would you please tell me what that is?

22 A. So in reference to a microscope and I'm
23 going to use an example here, if you put a small
24 sub-resolution bead -- and I'm going to, again, give
25 simply an example. Fluorescent bead of around

1 100 nanometers for a typical microscope.

2 That bead will have a spread to it
3 that's related to defraction. So this is what's
4 limiting the resolution of the light microscope, and
5 every microscope has an optical transfer function
6 which depends on the objective lens and so forth.

7 The aberrations as it's looking through
8 the sample. So point spread function basically
9 looks like an hourglass or football shape in the
10 Z-axis, but it also has these defraction patterns
11 which cause an actual round object to look
12 differently. Again, typically an hourglass or
13 football shaped is how it's referred to in three
14 dimensions.

15 Q. So would you say that point spread
16 function is the amount of blurriness of a signal?

17 A. The point spread function will
18 contribute to the blurriness in a signal, but also
19 scattering of light, out-of-focus light and so
20 forth. If you have a bad point spread function it
21 will make things blurry for sure, but I wouldn't
22 call -- as I sit here and think about it now, I
23 wouldn't think that's the only thing limiting
24 blurriness, but it would impact if you have a bad
25 point spread function.

1 Q. So just to be clear, you're saying that
2 if you have a bad point spread function it would
3 impact the blurriness?

4 A. It could make it worse, but you could
5 still have a good point spread function, and if
6 you're trying to resolve beyond the limits of a
7 particular defraction limit of light and the
8 wavelengths you're using and you're not using
9 specialized techniques like special resolution or
10 deconvolution, you know, you have this fundamental
11 physical limit.

12 Q. Okay. So does point spread function
13 reflect microscope's resolution?

14 A. So it's related to resolution.
15 Resolution uses different criteria called Nyquist or
16 Rayleigh criteria, where it's the ability to
17 distinguish two adjacent points from each other. So
18 for example, if you had a low-magnification
19 objective lens, it inherently forms a bigger spot in
20 the sample. The --

21 (Court reporter interruption.)

22 A. The numerical aperture of an objective
23 lens defines its resolution power, and so the higher
24 the numerical aperture the smaller spot it can form,
25 and therefore it determines its resolving power.

1 However, it also matters on what
2 detector configuration you have. So if you only --
3 you have to have enough spots in the imaging, you
4 need to be able to take advantage of the resolution
5 of an objective lens.

6 So just because I have a point spread
7 function of a high NA lens doesn't mean I'm
8 realizing it and you need to match your imaging
9 system -- detector system to take advantage of that
10 if you want full resolution.

11 I'm sorry, it's a little bit long. I
12 can repeat any section, but it's never simple. It
13 was one of these, well, yes, but, okay? There's
14 other factors involved in getting resolution. And
15 of course, signal-to-noise, which I didn't get into.

16 Q. Okay. So let's talk about
17 signal-to-noise ratio I guess you were talking
18 about, right?

19 A. Uh-huh. Yes, I guess we call it
20 signal-to-noise ratio in general.

21 Q. Okay. Could you tell me what that is,
22 signal-to-noise ratio and how that -- strike that.

23 Could you tell me what signal-to-noise
24 ratio is in the context of imaging?

25 A. Well, in the end if I have signal

1 coming from my sample, and I'm just going to kind of
2 keep this in simple terms, if I image very, very
3 quickly, have a lot of shot noise or scatter noise
4 or detector noise or electronic noise in the image,
5 so something that may be actually smooth with a
6 certain intensity, if I image very quickly I have
7 noise over top of it. And you can calculate the
8 signal-to-noise of an image, meaning if I take --
9 integrate longer and collect more signal the noise
10 would actually become reduced.

11 So it's about quality factor of the
12 image in which you can interpret structures. So in
13 the context of a spot or bead if I image very
14 quickly, I may have a noisy image and it may be
15 harder for me to be certain where my object is.

16 But if I integrate the signal longer or
17 make sure that my signal is stronger, has higher
18 intensity, I can improve the signal over this noise,
19 electronic noise or background that is inside the
20 sample.

21 Q. So then would you say that
22 signal-to-noise ratio is an important consideration
23 in imaging?

24 A. So the answer is yes. It's an
25 important consideration. Doesn't mean every

1 day-to-day that all of my users who take microscopes
2 every day consider it, but it is an important
3 consideration for quality of image and particularly
4 doing any analysis for sure.

5 Q. What about point spread function, is
6 that an important consideration for imaging?

7 A. It depends on the question you're
8 trying to ask. So the answer is knowing the point
9 spread function of the instrument is critical if
10 you're doing mathematical deconvolution, for
11 example, although they can, you know, make estimates
12 for that, but my comment is they're factors that
13 play a role.

14 If you use the word critical it's
15 important, and they need to be considered, but a lot
16 of imaging can be done and still get the result you
17 want without everything being perfect.

18 Q. Doctor, a little bit ago you mentioned
19 that one needs to map the detector system to take
20 advantage of -- strike that.

21 So going back to signal-to-noise ratio,
22 Doctor, what is the noise in signal-to-noise ratio?

23 A. Again, noise is typically electronic
24 noise inside -- in the system. Sometimes it could
25 be background signals in the light path and it could

1 be nonspecific binding. If you wanted to think of
2 it generally sometimes people refer to it's not the
3 specific signal that I'm looking for.

4 Q. So would signals from planes above and
5 below the focal plane that you are imaging also
6 contribute to noise then?

7 A. So if it's background information
8 that's not part of your sample it's signal. It's
9 signal in a different location. Typically I like to
10 look at noise as being from the speed and detector
11 of the image. I would just call that out-of-focus
12 signal. And again, you can use that information
13 three deconvolution, and I don't think they would
14 call that noise, for example.

15 MS. KHANDURI: Okay. Let's take a
16 break.

17 (WHEREIN, a recess was taken from
18 9:12 a.m. to 9:20 a.m.)

19 Q. (By Ms. Khanduri) So before the break,
20 Doctor, we were talking about signal-to-noise ratio.

21 A. Uh-huh.

22 Q. Does the number of target analytes in
23 your sample that you're looking at impact
24 signal-to-noise ratio?

25 A. So I would ask for a clarification on

1 target analyte. If you're referring to the number
2 of molecules in the image or the number of
3 fluorophores, is the analyte the fluorophore you're
4 referring to, so the probe?

5 Q. Yeah, thank you. I'll ask the question
6 again. Does the number of signals -- strike that.

7 Does the number of fluorophores in the
8 sample impact signal-to-noise ratio?

9 A. The answer would be yes, it can. The
10 more fluorophores there are per target object the
11 better the signal-to-noise. However, there's a risk
12 that oftentimes background can also be elevated in
13 certain situations as well, but in general if I were
14 to design an experiment I would put more
15 fluorophores to improve signal-to-noise.

16 Q. And then same question, but now for
17 number of molecules. Does the number of molecules
18 in the sample impact signal-to-noise ratio?

19 A. So if you're referring to number of
20 molecules meaning if I had 1,000 molecules versus
21 five molecules and the 1,000 molecules are closely
22 overlapping, that's a different -- that's a
23 resolution issue.

24 But if each of those thousand molecules
25 has the same number of -- I guess if I use your word

1 analytes or fluorophores in them, signal-to-noise
2 for that particular point or spot should be the
3 same.

4 But if you have too many in a field of
5 view you have a different problem, and that is
6 solving them as individual entities. I would not
7 call that signal-to-noise problem.

8 Q. So would it be fair to say if the
9 density of molecules increases in a sample then
10 resolution becomes a problem?

11 A. Meaning if you want to see the
12 individual objects and be able to count them, the
13 higher the density or if the density is too high
14 they may overlap. There still are ways to tell the
15 difference, but if there can be a point where you
16 have basically a uniform lawn of the molecules
17 overlapping a microscope would need a different
18 strategy to resolve.

19 Q. So let me understand. So as the
20 density of the target molecules in the sample
21 increases, resolution becomes more challenging?

22 A. Again, the resolution of the microscope
23 will be fixed in your detector. However, resolving
24 individual entities, if they're closely spaced,
25 needs to be considered. It doesn't mean it's

1 unsolvable, that's exactly what single-molecule
2 microscopy does. You only activate a subpopulation
3 of the total molecules to be able to differentiate
4 them from each other.

5 Q. Okay. So then as the density of the
6 target molecules in the sample increases, then
7 resolving individual molecules become difficult?

8 A. In some instances there are strategies
9 to have it. You just need a different strategy to
10 deal with it if it arises.

11 Q. What about sample thickness, does
12 sample thickness have an impact on signal-to-noise
13 ratio?

14 A. If you're using a widefield microscope,
15 if you have a thick sample you'll have more
16 background from adjacent focal planes. If you went
17 optical sectioning -- again, your reference was to
18 signal-to-noise; is that correct?

19 Q. That's right.

20 A. Using optical sectioning, you can have
21 a thick section and that can be okay. If you
22 properly set up your experiment in your optic so
23 that you match the objective lens with the media
24 that it's looking to inside of the sample, doesn't
25 have to be an issue, but it's something that needs

1 to be considered.

2 Q. So are you saying that you -- strike
3 that.

4 Are you saying that the objective lens
5 must be matched with the media?

6 A. The best practice is to match it with
7 the media, but for example, some techniques require
8 a mismatch when you're looking at things near the
9 cover slip. It doesn't need to be perfectly
10 matched. It depends on where you want to image to.

11 Q. Okay. And what are we matching?

12 A. Refractive index of the sample and its
13 matrix and the refractive index of the immersion
14 media of the objective lens are two things that are
15 commonly considered.

16 Q. Okay. So it's important to match the
17 refractive index of the objective lens and the media
18 for imaging?

19 A. For the best performance, but I would
20 tell you in the real world there are instances where
21 it doesn't have to be a perfect match and you can
22 get a suitable result. It's not an absolute. It's
23 just a strategy.

24 Q. So what happens when the refractive
25 index of the objective lens does not match with the

1 refractive index of the sample?

2 A. You get what's called spherical
3 aberration, where the point spread function will
4 become distorted or asymmetrical and therefore it
5 will affect -- again, normally these effects are
6 minimal near the cover slip.

7 But the bigger the mismatch the deeper
8 you go, it can have an impact depending on the
9 difference between the -- how -- the refractive
10 index is. So you can get very close, you can have
11 identical, you can have not quite as close, but you
12 can still find usable conditions depending on
13 thickness of the tissue and its optical properties.

14 Q. So would it be fair to say if the
15 refractive index of the objective lens does not
16 match that of the sample, the image could lack
17 clarity?

18 A. Again, it depends. I work with plant
19 samples all the time. I can use an oil objective
20 with those plant samples near the cover slip and I
21 can get better clarity than I could with a water
22 lens which is designed to look deeper.

23 It depends on what question you're
24 trying to solve. I would not use an oil lens to
25 look 300 microns through a plant unless I had done

1 something to the plant to make its refractive index
2 match the oil, okay? It depends. There's no
3 absolute case on here. It's best practice and the
4 question you're trying to ask.

5 Q. So going back to signal density,
6 Doctor, we were talking about how signal density
7 impacts the resolution of individual molecules in
8 the sample.

9 A. Uh-huh.

10 Q. Would it be fair to say that in your
11 opinion if the signal density increases then the
12 resolution of individual molecules decreases?

13 A. If you don't do something about it, but
14 theoretically it could happen. But again, there are
15 strategies like single-molecule localization where
16 you would only turn out a subset of those molecules
17 or you could use a technique like expansion
18 microscopy, which will allow the distance between
19 molecules to be spread.

20 Even though they're the same there,
21 they have a certain density, but they're just
22 expanded over a longer range. So my comment is yes,
23 but depending on what your ultimate goal is there
24 are strategies to deal with that.

25 Q. Is it important to consider signal --

1 strike that.

2 Is it important to consider density of
3 molecules that need to be resolved for imaging --
4 strike that.

5 Is it important to consider the density
6 of molecules when imaging a sample?

7 A. It depends on what you want to achieve.
8 Sometimes it could be. Sometimes it doesn't matter.
9 Sometimes you want to see them nice and dense and
10 contiguous and overlapping. For example,
11 microtubules is commonly looked at that way.

12 Easier to interpret than a bunch of
13 molecules, but that's just an example. But I could
14 see instances where it would be important and
15 there's many instances where it wouldn't be
16 important, but not always important.

17 Q. Does signal density become important
18 when you're performing 3D imaging of a sample?

19 A. I think my answer is similar to my
20 previous one. It depends on what you're trying to
21 achieve. If you're trying to count single molecules
22 you want to pay attention to that and make sure that
23 your labeling strategy is such that you can count
24 your single molecules.

25 Q. What about -- what about when you're

1 determining 3-dimensional position of individual
2 molecules in a sample, in that context does the
3 density of the target molecules become important?

4 A. So in the same way that it would be for
5 2D. So if it's -- again, by the way, I want you to
6 think about 3D as several 2D images, okay? So --
7 but they're just in adjacent planes above or below
8 each other.

9 So if the density matters in 2D, it
10 will also matter in 3D for a particular experiment.
11 So normally you may design your experiment to
12 control that if it's important or if it's expected.

13 Q. So you say normally you may design your
14 experiment to control that if it's important or if
15 it's expected. Do you mean that one can design an
16 experiment to control resolution if high signal --
17 high-target molecule density is expected?

18 A. Could you repeat that?

19 Q. Sure. I'll do that. So you said so
20 normally you may design your experiment to control
21 that if it's important or if it's expected. I'm
22 just trying to understand what that is and what it's
23 is in that statement.

24 A. Okay. In the end we're talking about a
25 defraction-limited spot that is formed by an

1 objective lens, and I'm just giving you an example.

2 A spot using visible light can be around 200 to
3 250 nanometers without doing any other special
4 mathematical or super-resolution techniques. So in
5 that spot there can be -- clearly it's the size of
6 bacterium actually if you look at it as 3D point
7 spread function.

8 (Court reporter interruption.)

9 A. So a lot of biology we wouldn't be able
10 to resolve all the individual molecules inside of
11 that spot. But if that spot has one messenger RNA,
12 for example, with a hundred or more fluorophores on
13 it, it will look the size of that spot.

14 And if the next messenger RNA is a
15 little further away but beyond the defraction limit,
16 you can distinguish them as two, okay? So normally
17 they will magnify on the camera so that one spot
18 will have multiple pixels so they can -- will be
19 able to tell the difference between two that are
20 adjacent to each other.

21 So again, there are strategies. A lot
22 of messenger RNAs are sparse. They're distributed
23 through the cell. Some could be in clusters.
24 Again, it depends on the question of whether you
25 expect that that would be true.

1 If you're looking at a high-density
2 area or you're trying to look at many, many
3 messages, then there's a strategy of, well, I don't
4 look at them all at the same time, right? I find
5 another way.

6 Q. Okay. But if your goal is to look at a
7 large number of target molecules in one round of
8 imaging, then the density of molecules becomes
9 important, right?

10 A. Then what becomes important?

11 Q. The density of the molecules becomes
12 important.

13 A. You have to think about it, but if
14 you're doing one round of one messenger RNA, you
15 know, there's very -- that may be the exception
16 rather than the rule of how messenger RNA works, but
17 -- as I think about now what I understand. But I
18 think the comment is, is that many instances it
19 doesn't matter and some instances it could matter.
20 I think that's what I'd like to say.

21 Q. My question, though, is if your goal is
22 to image a lot of RNAs at the same time, would the
23 density of the RNAs become important in that context
24 for resolution?

25 A. It could. But biologically

1 practically, is it? That's my question. I'm
2 telling you that in many cases it's not. I didn't
3 want to say it's one or the other. It could be
4 important for some questions. So that's what I
5 could say.

6 But the reality is when you look at
7 messenger RNA in a cell of one particular species,
8 they may be near each other in certain regions, but
9 they're not solid images. They're spots across the
10 cell. The cell keeps them distributed because they
11 need to be done in a local way.

12 There may be instances where it's
13 higher. There are biological instances in that
14 place and that time I would consider, but I wouldn't
15 have it as a blanket rule based on what the reality
16 of that biology is that we see in the literature.

17 Q. Okay. You mentioned numerical aperture
18 a bit ago in one of your answers. Could you explain
19 what a numerical aperture of a lens is?

20 A. So there is a calculation which is
21 numerical aperture equals sine times alpha and alpha
22 is the angle of light, it's half the cone of light
23 basically. They use this angle that the light
24 enters the pupil of the objective lens.

25 So an objective lens that has a large

1 collecting angle -- and again, they take this half
2 angle on here, it will have a large numerical
3 aperture, which means it has a higher resolving
4 power and a higher light gathering power.

5 A lens that has a long working distance
6 and a short collection angle will have a lower
7 numerical aperture. For example, an air objective
8 lens is typically under one.

9 If it's a water objective it's around
10 one. If it's an oil objective depending on the
11 objective lens and its properties it will be closer
12 to 1.4 plus or minus.

13 Q. And then numerical aperture is also
14 called NA?

15 A. I mean, that's the shorthand that you
16 would see in the literature, correct.

17 Q. What is considered a high numerical
18 aperture?

19 A. I mean, it depends for the class of
20 objective lens. I'm sorry, I'm just being clear. A
21 high NA air lens would be .75, for example, .8. A
22 high water objective would be around 1.2.

23 The highest of them all could be 1.4
24 and above. I have objectives that are 1.46. I
25 think there's even diamond lenses that are much

1 higher than that. So for the purposes of, you know,
2 putting an anchor point for you, oil objectives will
3 have higher NAs than water objectives will have
4 higher NAs than air objectives.

5 Q. Okay. I think my question was slightly
6 different. I apologize --

7 A. Okay.

8 Q. -- if I didn't convey what I wanted to
9 ask. So what I was trying to ask is what number NA
10 is considered high?

11 A. I think I gave you the answer.

12 Q. Okay.

13 A. It depends on the class of objective
14 lens. I would say a high NA air lens and a high NA
15 water, and I said as you think of all three of those
16 collectively oil would have a higher numerical
17 aperture.

18 Q. Okay.

19 A. Okay. 1.4 is common for some
20 techniques, but 1.3 is still high. 1.2 is high for
21 a water objective lens, but it's less than an oil.

22 Q. So for air objective lenses an NA of
23 .75 or higher is --

24 A. Point nine, yeah. It's -- once you --
25 it's a refractive index related, so the refractive

1 index air is part of that consideration, but an air
2 objective lens .75, .9. I've seen some very short
3 working distance lenses that can do that.

4 Q. Okay. So then for air objective lenses
5 .75 --

6 A. I mean, I'm just giving you a number.
7 I have a .8 20X objective lens which I consider a
8 high for that objective lens, okay? I know some
9 that are .9 that are not used for material science
10 that are expensive, but you can get them. A high is
11 just a funny word. It's kind of vague in many
12 respects, right? It's not an absolute. It depends
13 on what you're trying to do.

14 Q. So if in the field a POSA would say
15 high -- high NA air lens, what would your
16 understanding be?

17 A. I would be thinking it was more like .8
18 or .9 and not .2.

19 Q. Okay. How about an oil objective lens,
20 if a POSA would say a high-oil objective lens, what
21 would your understanding be?

22 A. I'll just rephrase that. I think you
23 mean a high NA oil objective lens?

24 Q. Yeah, let me ask the question again.

25 A. I want to make sure I clarify.

1 Q. Let me ask the question again. For oil
2 objective lens, if a POSA says high NA, what would
3 your understanding be?

4 A. For high numerical aperture 63 or 100X
5 lens, 1.4 or 1.46 would both be considered high.

6 Q. And then how about water lens, water
7 objective, for a water objective lens, if a POSA
8 were to say high NA lens, what would your
9 understanding be?

10 A. It depends if it's a dipping lens or
11 water immersion lens.

12 Q. Okay. So for a water immersion lens,
13 if a POSA were to say that the lens is -- has high
14 NA, what would your understanding be?

15 A. It would be around 1.1 or 1.2 common
16 water immersion objective lenses.

17 Q. And then same question for water
18 dipping lens, if a POSA were to say that the lens
19 has high NA, what would your understanding be?

20 A. I would say somewhere around one.
21 That's -- that's a bracket, right? I mean, it's not
22 an absolute.

23 Q. What's the difference between a water
24 immersion lens and had a water dipping lens?

25 A. There's a few things. Water immersion

1 lenses are typically cover slip corrected. So a
2 cover slip needs between that objective lens and the
3 sample. They tend to be far more color corrected.
4 They tend to have shorter working distances. This
5 is just in general.

6 Dipping lenses are designed to be
7 immersed oftentimes in an aqueous and/or salt
8 solution and do not require a cover slip. In fact,
9 they're designed to not use a cover slip.

10 Oftentimes they're in upright
11 microscopes, but you can use any of these lenses on
12 upright or inverted microscopes. You just have to
13 do it in a certain way.

14 Q. Why would a POSA choose to use a high
15 NA lens?

16 A. Because they're trying to achieve
17 resolution and more signal potentially. Oftentimes
18 these high NA lenses are much better corrected for
19 spherical and color aberrations as well. Oftentimes
20 lower NA lenses have fewer corrections. There could
21 be several reasons, but these are the common ones
22 off the top of mind.

23 Q. What about a low NA lens, why would a
24 POSA choose a low NA lens?

25 A. Because they're looking for an overview

1 of their sample, a larger perspective to do
2 multiscale imaging or it's sufficient to answer the
3 question, meaning they have a bright sample that
4 doesn't need to have perfect optical sectioning, the
5 perspective they get from seeing a larger field of
6 view is sufficient and you don't have to clean it up
7 because it's air.

8 So you don't have to mess with oil or
9 water. Sometimes it's a convenience factor. The
10 other reason they use it is to locate a target of
11 interest because it's faster to look at this whole
12 room than it is to look here and then search for it.

13 Finally, and this is not a
14 comprehensive list, the air lenses that are low NA
15 tend to have longer working distances, so it may be
16 that they can get some clearance that they need to
17 be able to image.

18 Q. So in your answer you mention optical
19 sectioning. Would it be correct to say that a low
20 NA lens is not good for optical sectioning?

21 A. No, you can still optically section it.
22 I don't remember explicitly saying that in that way,
23 but I would say that the lower the numerical
24 aperture the thicker the optical slice.

25 Again, if I have to go and look a long

1 distance, not taking a 1001-micron sections, instead
2 I can take 110-micron sections helps in the speed of
3 the processing or the ability to cover large
4 distances.

5 Q. Okay. Doctor, do you have an
6 understanding of the term drift in the context of
7 imaging?

8 A. I do.

9 Q. Could you tell me what your
10 understanding is?

11 A. Drift is the movement of your object of
12 interest during the time frame in which you're
13 acquiring data. There are many causes of drift.
14 Number one cause I would argue is probably thermal
15 drift, meaning a difference between the temperature
16 of your objective, the temperature of your
17 microscope, the temperature of your sample.

18 There's also mechanical drift. The
19 device or object like the stage can have drift.
20 There's drift due to fluids moving through your
21 sample, which can cause movement. So there's --
22 just giving you a few samples of where drift is
23 involved.

24 Ultimately what it means is that your
25 plane of interest may leave or move and if you're

1 going back around, for example, and doing an
2 automated experiment you need to make sure that you
3 can get back to the same place with as much
4 precision as possible.

5 Q. So what role does drift play in
6 imaging?

7 A. Well, as I just mentioned a few moments
8 ago the drift rates can be quite high even with a
9 small temperature gradient, for example, between
10 your sample and the objective lens.

11 So if that gradient exists there's
12 movement. So it means that your target of interest
13 goes out of focus or to a different focal plane
14 of -- that you're not interested in.

15 Q. So what happens when the target of
16 interest goes out of focus as a result of drift?

17 A. So first of all, there are remedies for
18 drift, providing temperature stability, providing
19 mechanical stability, making sure that your sample
20 is in a fixed position using high-quality components
21 that are more precise in there.

22 But if you don't have those remedies,
23 you have to -- you would typically want to scan
24 quickly and make sure that you still encompass your
25 area of interest. If you have those remedies then

1 you try to implement them so that you can maintain
2 the precision that you're going after with your
3 target image.

4 Q. And were these remedies available in
5 2015?

6 A. Yes, because I used them on my own
7 research before then.

8 Q. Does image acquisition time have an
9 impact on drift?

10 A. Image acquisition time doesn't have an
11 impact on drift, but drift has an impact on image
12 acquisition time. The drift is there, so it may be
13 important that I would try to reduce image
14 acquisition time, for example, but ultimately I
15 would actually just apply a out-of-focus remedy
16 to -- when it's Z drift specifically, for example.

17 Q. You talked about MERFISH earlier today.

18 A. Uh-huh.

19 Q. And you provided your opinions on
20 MERFISH in your declaration, correct?

21 A. Correct.

22 Q. I will hand you, Doctor, a document
23 that has been marked Exhibit 1003. Do you recognize
24 this document, Exhibit 1003, Doctor?

25 A. Yes, I do.

1 Q. And you provided opinions on this
2 document in your declaration, correct?

3 A. Yes, I did.

4 Q. And you called this document Zhuang,
5 Z-H-U-A-N-G, in your declaration, correct?

6 A. That is correct, although Chen is the
7 primary author.

8 Q. Okay. So if I say Chen, would you
9 understand that I'm referring to this document,
10 which is Exhibit 1003?

11 A. Yes. I'm thinking out loud if
12 there's -- Chen had other articles that are
13 exhibits, but I do understand for the context of
14 what we're talking now, yes.

15 Q. Okay. So Chen describes the technique
16 MERFISH, correct?

17 A. That's correct.

18 Q. And MERFISH stands for multiplexed
19 error-robust fluorescence in situ hybridization,
20 correct?

21 A. That is correct.

22 Q. What is your understanding of the term
23 multiplexed in MERFISH?

24 A. It means that they collected multiple
25 images in series enable -- allowing them to decode

1 the FISH signal in this particular case. Multiplex
2 is typically multiple rounds of probing in general.

3 Q. How was MERFISH different from prior
4 FISH techniques?

5 A. In prior FISH techniques they typically
6 used just FISH, which they would code a messenger
7 RNA with a single color and capture that information
8 in 2D and 3D. So essentially they were limited in
9 the number of messenger RNAs that they could see in
10 a particular cell or tissue.

11 MS. KHANDURI: Okay. Let's take a
12 break.

13 (WHEREIN, a recess was taken from
14 9:58 a.m. to 10:11 a.m.)

15 Q. (By Ms. Khanduri) Before the break,
16 Doctor, we were talking about MERFISH, and I was
17 asking you how MERFISH is different from prior FISH
18 techniques, so let me ask you this: How is MERFISH
19 different from smFISH?

20 A. Single-molecule FISH?

21 Q. That's right.

22 A. Well, in general, I mean, this is a
23 single-molecule technique except for it has this
24 encoding strategy to it. So in many respects in
25 single-molecule FISH they're looking at

1 single-messenger RNAs as individuals.

2 But again, as I mentioned before the
3 break they're limited because they're not
4 multiplexed, okay? So in general you might call
5 single-molecule FISH, you decorate each messenger
6 RNA with a color, and they're typically doing them
7 in two or three dimensions. And -- while MERFISH
8 has this encoding scheme that allows you to look at
9 hundreds or thousands of them.

10 Q. So would it be correct to say that
11 MERFISH images substantially higher number of RNA
12 species compared to prior smFISH techniques?

13 A. Yes, it has the potential for that and
14 she demonstrates to some extent I think it's 100
15 something and then she went to a thousand with
16 nonerror code correction if I recall. So that's
17 more than the handfuls that you might be able to do
18 with color alone without encoding.

19 Q. Okay. And how was MERFISH different
20 from the prior SeqFISH technique?

21 A. Well, SeqFISH is basically using a
22 multicolor strategy, but it's multiplexed. So in
23 the case of the Cai patent involved here, they would
24 have four-color channels and they would hybridize
25 and decorate one messenger RNA with one color and

1 then they would strip it, remove it, deactivate it,
2 whatever.

3 Well, this particular case they would
4 strip it and then they would come in with a second
5 color and then they would do a third color as well
6 and so then you could have multiple populations
7 based on the number of fluorophores and number of
8 colors you're working with, you could amplify the
9 potential number of messenger RNAs.

10 So it's just a different strategy.
11 They didn't have necessarily error correction,
12 but because you would hybridize and go back to the
13 original hybridization than at least the one example
14 that they provided in their patent, you could match
15 those up and confirm.

16 So again, it's based on number of
17 fluorophores and the number of colors and you can
18 scale it based on that. They weren't necessarily
19 using a 16-bit or 14-bit strategy in their
20 multiplexing, but you could.

21 Q. So would it be fair to say then that
22 MERFISH images substantially higher number of RNA
23 species compared to prior SeqFISH techniques?

24 A. Maybe demonstrated, but in principle if
25 you look at the Cai patent you could do more than

1 they were actually performed. So in principle they
2 could also do thousands, many thousands, but without
3 the error correction in the same way. So there are
4 tradeoffs. I consider them analogous.

5 Q. Okay. So you -- in your previous
6 answer you talked about SeqFISH and you mentioned
7 that -- in your previous answer in response to my
8 question on SeqFISH you mention there were several
9 rounds of imaging; is that right?

10 A. Yes. Based on the Cai patent they were
11 multiplexed, correct. Through an automation process
12 is basically what they disclosed would be an
13 embodiment.

14 Q. Okay. You discuss Bioptechs FCS2 flow
15 chamber in your declaration, correct?

16 A. Yes, I did.

17 Q. Why would a POSA use a Bioptechs FCS2
18 flow chamber in their imaging strategy?

19 A. To introduce flow and to have
20 temperature control.

21 Q. Why would a POSA use Bioptechs FCS2
22 flow chamber for imaging biological samples?

23 A. There are multiple reasons. Again, if
24 you want to have your specimen at a certain
25 temperature or temperatures you could control it

1 precisely with the FCS2 and their objective heater
2 because of either the chemistry or the biological
3 functions of the cells dependent on that control.

4 Q. Does FCS2 flow chamber have an
5 objective heater?

6 A. If you don't mind, I can refer to my
7 declaration?

8 Q. Sure.

9 A. Just take me a moment to find, go to
10 page 110, Exhibit 1015.017.

11 (Court reporter interruption.)

12 A. Okay. So if you look at this figure
13 showing the assemblage of the Biopetechs FCS2 and the
14 objective heater showing it's characterized by
15 sophisticated temperature control, high-volume
16 perfusion rates, and compactability with standard
17 microscope techniques. So these were coupled
18 together to maintain temperature.

19 Q. (By Ms. Khanduri) But the objective
20 heater is not part of FCS2 flow chamber, correct?

21 A. The objective heater can be
22 independently used. The Chen 2015 article used the
23 objective heater and the Biopetechs FCS2, so this is
24 exactly how I would expect them to configure it.

25 Q. So are you testifying that Chen 2015

1 article in its setup used objective heater as part
2 of FCS2 flow chamber?

3 A. They used it with their microscope
4 configuration. It specifically says that they used
5 it, objective heater at 37 degrees and they used the
6 Bioprotechs FCS2 in their methods.

7 Q. Okay. So objective heater in Chen's
8 imaging system was not part of FCS2 flow chamber,
9 correct?

10 A. They're both from Bioprotechs. They were
11 used in this experiment, okay? So you can purchase
12 them separately, but they use them both and that's
13 the expected use. We had this big discussion a few
14 minutes ago just to make sure that it's clear about
15 drift.

16 And if you have that temperature at
17 37 degrees you want to match these things and so you
18 would use a Bioprotechs flow cell, which number one
19 has the advantage you can move the reagents and
20 control those reagents moving through. Number two
21 is she specified a temperature of 37 degrees, which
22 required these components to be working together.

23 Q. In your answer you mentioned she
24 specified --

25 A. When I say she, I said Chen. Maybe I

1 should not be gender specific on this, okay? I
2 apologize.

3 Q. Okay. So is your testimony again that
4 in Chen's system the objective heater was part of
5 FCS2 flow chamber?

6 A. You're trying to make these out like
7 you buy them as one unit. I've already stated that
8 the FCS2 is coupled, just like this drawing, from
9 the way she described it in her materials and
10 methods.

11 Q. Doctor, I just want to be clear. So is
12 your testimony then that the FCS2 flow chamber has
13 objective heater as part of its arrangement?

14 A. They each have their own part number,
15 but the MERFISH protocol as specified in her
16 experiment used -- and I quote, the objective was
17 heated to 37 degrees with the Biopetechs objective
18 heater, okay? And the samples cover slip was --

19 (Court reporter interruption.)

20 A. -- assembled into a Biopetechs FCS2 flow
21 chamber, and the flow -- and I'll finish the
22 sentence. And the flow through this chamber was
23 controlled via home-built fluidic system composed of
24 three computer-controlled valves, so forth.

25 That is on 1003.011 on the bottom of

1 the middle column in the top of the third column.

2 So they have their own unique part, but she combined
3 them in a way a POSA would understand and be
4 motivated to do to maintain the temperature of
5 37 degrees for these experiments.

6 Q. (By Ms. Khanduri) So just so I
7 understand your testimony, is your opinion that
8 Chen's system had objective heater as part of
9 Bioprotechs FCS2 flow chamber?

10 A. She combined them together based on her
11 materials and methods.

12 Q. So then the answer is I think, and
13 correct me if I'm wrong, that the FCS2 flow chamber
14 from Bioprotechs did not have objective heater as its
15 component, correct?

16 A. If you buy the parts you can buy them
17 separately, but they are coupled to -- by a person
18 who is ordinary skill in the art. I owned one. I
19 used them. I used them together when I wanted to
20 maintain temperature of my sample.

21 Q. Are you testifying that the objective
22 heater heated the FCS2 flow chamber?

23 A. The objective heater as we specify in
24 our declaration is optically coupled through the oil
25 to the specimen chamber, and it is a huge heat sink.

1 So the answer is yes, it had an effect on it.

2 Remember there's an objective lens, has
3 a very short working distance and has an oil there.
4 And I would -- I mean, if you bear with me I can go
5 to the Biotech's which actually describe how if you
6 don't heat the objective lens you have gradients
7 that cause issues and also make sure it ensures that
8 your chemistry is correct.

9 Q. Okay. So your testimony is that the
10 objective heater in Chen's system is coupled to FCS2
11 flow chamber, correct?

12 A. The objective heater set at 37 degrees
13 is coupled through oil to the chamber right where
14 the cells and tissue are nearby. Thermally coupled.
15 Otherwise you wouldn't need an objective heater.

16 Q. Would it be fair to say that because it
17 is called an objective heater it is heating the
18 objective?

19 A. It is heating the objective, but in
20 addition because it is coupled through the oil it is
21 also heating the cells and the tissue or whatever is
22 in the chamber.

23 Q. Why would a POA use FCS2 flow chamber
24 for imaging live cells?

25 A. For imaging live cells? Just to be

1 clear, that's different. Imaging live cells, some
2 cells require specific temperatures to be
3 biologically or physiologically relevant.

4 However, when you're not imaging live
5 cells a flow chamber can allow the chemistry to be
6 at the temperature that you need it to be to either
7 speed up the interaction or to reduce nonspecific
8 finding.

9 So we can talk about live cells, but
10 it's also understood that this chamber is just a
11 flow cell with temperature control and you can look
12 at living and fixed cells with it.

13 I apologize. I had one more. It's not
14 just about temperature control. It's about having
15 the ability to perfuse fluids and liquids of the
16 required composition in a laminar flow that is more
17 uniform across the sample. So that's why the flow
18 cell is a flow cell. It just has temperature
19 control as well.

20 Q. Okay. So let me ask you the question
21 again. Why would a POA use FCS2 flow chamber for
22 imaging biological samples?

23 A. They would image it because of the flow
24 cell capacity and the temperature control capacity.
25 And it conveniently assembles together on cover

1 slips. It's very straightforward to use.

2 You have a lot of flexibility in how
3 you can design your experiment and chemistry and
4 solutions that need to move through the system. And
5 more importantly you maintain the temperature with
6 higher precision than other types of strategies.

7 Q. And the temperature control apparatus
8 in FCS2 flow chamber increases the temperature of
9 the flow chamber?

10 A. You have -- you have control over the
11 temperature on it, so you can increase it. There is
12 a range. I don't recall the range right now. And
13 importantly it allows very precise local control so
14 that you can not have to heat massive amounts of
15 reagent.

16 You can do that all locally right in
17 the dish. It's one of the advantages of it. One of
18 the other advantages of it. It was the de facto
19 temperature-controlling microfluidics stage for many
20 biologists. That's why I owned them and used them
21 in my own laboratory on experiments.

22 Q. What is a widefield imaging, Doctor?

23 A. So widefield imaging is generally where
24 you illuminate the entire sample or much of the
25 sample as opposed to scanning it with a single

1 point, for example, like a confocal microscope is a
2 laser scanning microscope which will scan point by
3 point and we're only illuminating a small portion of
4 the sample at a time, and widefield illumination
5 typically the whole sample is illuminated.

6 However, the widefield can be modified
7 to do a technique called oblique illumination where
8 you bring the laser light source up on one side of
9 the objective and hit a certain angle.

10 If it's a critical angle it will, like
11 total internal reflection in fiber-optics, it will
12 illuminate only at the cover slip. If you do a
13 noncritical angle nearby you can shoot obliquely up
14 through. It's still part of the widefield -- still
15 considered a part of the widefield strategy.

16 Q. Okay. And when is widefield imaging
17 used?

18 A. I mean, daily, it's the bread and
19 butter. Widefield tends to be simpler
20 configurations of the instruments because you don't
21 have to scan the sample. Many things can be done by
22 widefield. I do it every day, okay?

23 It happens in my laboratory every day.
24 I might not be at the microscope every day on a
25 widefield microscope, but it's a bread and butter

1 tool, basic fundamental tool in most live cell or
2 biology imaging labs.

3 Q. Would you say that widefield imaging
4 has a poorer axial resolution compared to natural
5 resolution?

6 A. Let me again clarify. You can take
7 general widefield without optical sectioning. The
8 objective focal plane is fixed. However, you get
9 the out-of-focus light that's coming through the
10 sample.

11 So in general if you do a Z stack of a
12 widefield image of a thick tissue without
13 confocality or any other strategy it will be
14 typically less. If you use oblique illumination you
15 are still rejecting out-of-focus planes. For
16 example, in the case of the MERFISH.

17 And so you still get, you know, some
18 ability to not degrade it completely as you would in
19 full widefield. So my comment is widefield can be,
20 but there are again strategies like deconvolution
21 and so forth.

22 I want to be cautious of my, for
23 example, my Elyra 7 is a super-resolution microscope
24 and I can scatter it with a pattern of spots from
25 those widefield lasers and I can get high-resolution

1 data out of it. So it depends.

2 If you just want a word that says
3 widefield in general, the assumption might be if you
4 just took it out of the box and put it on the
5 microscope stage, it will be less than an optical
6 sectioning technique if you weren't doing a more
7 specific modality that would try to correct for
8 that.

9 Q. So to understand, you're saying in
10 general widefield imaging has a lower -- strike
11 that.

12 In general, widefield imaging has a
13 poorer axial resolution than natural resolution?

14 A. If the widefield technology does not
15 have an optical sectioning strategy and you have
16 thick tissues, theoretically the resolution could be
17 the same, but you can have other strategies to
18 improve it. Like I said, using confocality or
19 deconvolution. It's usually the lowest cost
20 implementation without having to scan and do other
21 things.

22 Q. Okay. In your answer you mentioned
23 that widefield imaging has the lowest cost
24 implementation without having to scan and do other
25 things.

1 A. I think I said the word usually, but --
2 okay. If I did say usually --

3 Q. Let me say that again.

4 A. Okay.

5 Q. In your previous answer you said
6 widefield imaging usually has the lowest cost
7 implementation without having to scan and do other
8 things. What do you mean by that?

9 A. Again, for super-resolution microscopy
10 where you have to do structured illumination or
11 using light sheet, again, you need lasers coming in
12 from a different angle and so forth, they become a
13 little bit more complex, but you know, oftentimes a
14 widefield microscope, again, is just light source
15 coming in. It's just simpler because you're not
16 scanning, okay?

17 MS. KHANDURI: Okay. Let's take a
18 break. I don't expect much more, so let's take a
19 break.

20 MR. WALTER: Okay.

21 (WHEREIN, a recess was taken from
22 10:39 a.m. to 11:00 a.m.)

23 Q. (By Ms. Khanduri) Doctor, did you know
24 Xiaowei Zhuang, the author on Chen publication
25 before your involvement in this IPR?

1 A. No, I never met her.

2 Q. Do you have any relationship with
3 Dr. Zhuang?

4 A. I do not.

5 Q. Did you -- did you know Long Cai, who
6 is one of the inventors on the Cai patent, which is
7 Exhibit 1004, before your involvement in this IPR?

8 A. No. I never met him and in both cases
9 I know of their work, but I have not known them
10 personally and do not know them.

11 Q. Do you have any relationship with
12 Dr. Cai?

13 A. No.

14 Q. During the breaks today, Doctor, did
15 you speak with anyone about the substance of your
16 testimony today?

17 A. I did not.

18 MS. KHANDURI: Thank you. I don't have
19 any more questions. We'll pass the witness.

20 MR. WALTER: Okay. I just have a few
21 quick questions.

22 EXAMINATION

23 QUESTIONS BY MR. WALTER:

24 Q. Do you recall you were asked some
25 questions today, Dr. Czymmek, about the Bioprotechs

1 FCS flow cell?

2 A. Yes, I do.

3 Q. Was that the flow cell that was used in
4 the Chen paper, Exhibit 1003?

5 A. Yes, it is.

6 Q. What is your understanding as to
7 whether the Bioptechs FCS2 flow cell that was used
8 in the Chen paper?

9 (Court reporter interruption.)

10 Q. (By Mr. Walter) What is your
11 understanding as to whether the Bioptechs FCS2 flow
12 cell that was used in the Chen paper was a heated
13 version of the flow cell or something else?

14 A. Okay. So you got that? So at a later
15 citation by the Zhuang lab at this point, in fact it
16 was a Su citation, was it 2020 from the same lab
17 they specify the part number for the heated version
18 of the Bioptechs and the one that was provided as an
19 alternative is nonheated is a very different part
20 number. So it's the same one.

21 Q. Okay. And do you remember what exhibit
22 that was?

23 A. 2007 or 9. I have to see it in front
24 of me. If I had the exhibit list with Su that's
25 what I would be looking for. I just don't have -- I

1 apologize. I know it's 2007, 8 or 9. I apologize.

2 I'm just going by visual memory of the screen.

3 MR. WALTER: Okay. Very good. Thank
4 you. I don't have anything else.

5 MS. KHANDURI: Okay. Let's take a
6 break, five-minute break. Thank you.

7 MR. WALTER: Okay.

8 (WHEREIN, a recess was taken from
9 11:04 a.m. to 11:08 a.m.)

10 MS. KHANDURI: Okay. Back on record.
11 I don't have any more questions, Doctor. Thank you
12 for your time.

13 COURT REPORTER: Signature is reserved?

14 MR. WALTER: Yeah.

15 (Ending time of the deposition: 11:08 a.m.)
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CERTIFICATE OF REPORTER

I, the undersigned Certified Court Reporter holding a valid and current license issued by the State of Missouri, do hereby certify:

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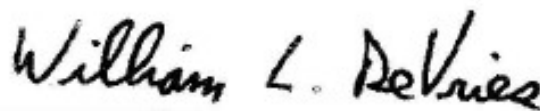
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---	---	---

AGREED 5:1 air 28:1 61:7,21 62:4,14,22 63:1,4,15 66:7,14 allowing 70:25 alpha 37:2,8,22 38:17 60:21 alternative 87:19 alumina 6:20 7:4,22 8:2,7,12 9:19 aluminum 7:2 amount 20:11,13,16,24 25:10,16 44:16 amounts 81:14 amplify 73:8 analogous 74:4 analysis 18:9 48:4 analyte 50:1,3 analytes 49:22 51:1 anchor 62:2 and/or 27:25 65:7 angle 60:22,23 61:1,2,6 82:9,10,13 85:12 answering 10:9 answers 60:18 aperture 45:22,24 60:17,19,21 61:3, 7,13,18 62:17 64:4 66:24 apologies 21:12 37:23 apologize 35:2,16 41:12 62:6 77:2 80:13 88:1 apparatus 81:7 application 35:9 40:7 applications 18:5 19:9 34:8,9,13,21 35:23 36:7 40:5 apply 34:9 69:15 applying 42:15 appointments 30:1 approached 18:25 approval 15:10 approximately 22:17 24:22 aqueous 65:7 archives 30:21 area 59:2 68:25 argue 67:14	arguments 24:21 arises 52:10 arrangement 77:13 arrays 16:9,10 33:4 art 43:3 78:18 article 75:22 76:1 articles 70:12 Asian 26:13 aspect 14:5 36:24 aspects 29:6 assemblage 75:13 assembled 77:20 assembles 80:25 assembling 36:20 assume 21:9 assumption 84:3 asymmetrical 54:4 attach 38:12,13 attached 18:8 37:18 38:2,3 39:3,5,6 attention 56:22 author 70:7 85:24 autofluorescence 43:11 automated 68:2 automation 74:11 aware 16:3,10 19:21 33:6 axial 83:4 84:13 Axio 17:10 B back 30:23 35:21 38:8,22 48:21 55:5 68:1,3 73:12 88:10 background 43:5,7,8,9 47:19 48:25 49:7 50:12 52:16 bacterium 58:6 bad 44:20,24 45:2 ballparking 25:2 base 38:5 based 15:9 24:19 25:20 60:15 73:7, 16,18 74:10 78:10	basic 83:1 basically 7:11 8:22 12:17,18,21 15:5 19:22 39:10 44:8 51:16 60:23 72:21 74:12 bead 43:24,25 44:2 47:13 beam 17:4 28:16,20 bear 79:4 behalf 5:12 beta 36:9,13,25 38:17 big 35:4 76:13 bigger 45:19 54:7 billable 25:3,10 billed 20:24 billing 20:6 binding 43:9 49:1 bio 30:21 Bioimaging 27:15 28:9 31:5 biological 30:8,11,16 33:10,13,24 34:3 35:7,20 60:13 74:22 75:2 80:22 biologically 59:25 80:3 biologists 81:20 biology 28:5 58:9 60:16 83:2 biomedical 32:21 biomolecules 40:13 Bioprotechs 9:18 74:14,17,21 75:13, 23 76:6,10,18 77:17,20 78:9,14 79:5 86:25 87:7,11,18 Biotechnology 31:5 bit 6:5 26:11 35:2 38:23 39:9 46:11 48:18 60:18 85:13 blanket 60:15 blurriness 44:16,18,24 45:3 blurry 44:21 board 15:8 22:3 botany 27:5 bottom 77:25 box 38:10,14 39:2,4,5 84:4 bracket 64:21 bread 82:18,25 break 11:7,10 24:1 39:18 49:16,19 71:12,15 72:3 85:18,19 88:6
--	---	---

breaks 11:2,6 86:14 bright 66:3 bring 82:8 broad 12:14 20:21 36:17 43:7 broader 28:14 Bruker 12:25 17:20,22 18:3,6,10,12, 14,21 19:6,10,20 Bruker's 32:25 bugs 39:23 building 33:4 34:19 built 36:18 bunch 56:12 butter 82:19,25 buy 77:7 78:16 C C-Z-Y-M-M-E-K 6:12 CAD 36:19 Cai 72:23 73:25 74:10 86:5,6,12 calculate 47:7 calculation 25:13 60:20 call 37:2,21 44:22 46:19 49:11,14 51:7 72:4 called 14:25 18:5 31:11 34:24 38:11 45:15 54:2 61:14 70:4 79:17 82:7 calls 26:1 camera 58:17 cameras 17:12 capacity 80:24 capture 17:14 71:7 case 7:1,19 8:2,4,12 9:2,7,8 11:20 12:9 20:4 21:14 55:3 71:1 72:23 73:3 83:16 cases 6:20 7:3 8:11,21 60:2 86:8 cautious 83:22 cell 9:3,6 33:22 58:23 60:7,10 71:10 76:18 80:11,18,24 83:1 87:1,3,7,12, 13 cells 7:11,12,13,16,18 8:14,20 9:1,9, 16,18 75:3 79:14,21,24,25 80:1,2,5,9, 12	cellular 28:3 center 16:8,20,22 17:16 27:10,13,18, 22 29:16 30:1,4 31:5 centers 34:14 Certified 5:5 chain 30:19 33:16 challenging 15:6 51:21 chamber 74:15,18,22 75:4,20 76:2,8 77:5,12,21,22 78:9,13,22,25 79:11, 13,22,23 80:5,10,21 81:8,9 change 41:23 changing 42:3 channels 72:24 characterized 75:14 chassis 38:6 check 25:3 chemistry 75:2 79:8 80:5 81:3 Chen 70:6,8,12,15 75:22,25 76:25 85:24 87:4,8,12 Chen's 76:7 77:4 78:8 79:10 choose 65:14,24 citation 87:15,16 cited 23:16,21 24:4,8,11 claimed 15:5 claims 12:19,22,25 13:9,10,24,25 14:1,16 15:6,9 24:12 clarification 10:18 49:25 clarify 63:25 83:6 clarifying 21:11 clarity 54:17,21 class 61:19 62:13 clean 66:6 clear 14:7 32:18 35:13 40:20 45:1 61:20 76:14 77:11 80:1 clearance 66:16 close 26:15 54:10,11 closely 50:21 51:24 closer 25:12 61:11 clusters 58:23 code 36:21 71:6 72:16 colleague 6:8	colleagues 32:1,3,15,16 33:1 collect 47:9 collected 70:24 collecting 61:1 collection 61:6 collectively 62:16 color 65:3,19 71:7 72:6,18,25 73:5 colors 73:8,17 column 78:1 combi 17:14 combined 78:2,10 comment 48:12 55:22 59:18 83:19 commercially 9:16 common 38:20 62:19 64:15 65:21 commonly 53:15 56:11 communicated 19:25 compactability 75:16 company 18:5 36:8 compared 41:9 72:12 73:23 83:4 compensated 20:3 complete 10:10 completely 83:18 complex 85:13 component 78:15 components 68:20 76:22 composed 77:23 composition 80:16 comprehensive 66:14 computer 39:5,10,15 41:25 computer-controlled 77:24 computing 39:11 concept 37:10 condition 27:23 conditions 54:12 conduct 27:17 cone 60:22 configuration 46:2 76:4 configurations 82:20
---	--	--

configure 75:24 confirm 73:15 confocal 17:13 36:1,4,7 37:7 38:7,11 39:4 42:20 82:1 confocality 83:13 84:18 consideration 47:22,25 48:3,6 63:1 considered 48:15 51:25 53:1,15 61:17 62:10 64:5 82:15 contact 15:12 19:3 contacted 15:20,22,24 16:1,2,4 contaminating 41:22 context 40:10 41:15 42:9 43:3,19 46:24 47:13 57:2 59:23 67:6 70:13 contiguous 56:10 contrast 42:14,18 contribute 44:18 49:6 control 39:6,10 57:12,14,16,20 74:20,25 75:3,15 76:20 80:11,14,19, 24 81:7,10,13 controlled 41:25 77:23 convenience 66:9 conveniently 80:25 conversation 10:6 convey 62:8 copy 22:24 correct 6:25 7:19 8:8 14:19 21:10 23:3,4,14 24:6 26:23,25 27:7,19 29:8 39:3 42:5 52:18 61:16 66:19 69:20,21 70:2,5,6,16,17,20,21 72:10 74:11,15 75:20 76:9 78:13,15 79:8,11 84:7 corrected 65:1,3,18 correction 72:16 73:11 74:3 corrections 65:20 Cosmx 31:18,20,21,25 32:3 33:1 cost 84:19,23 85:6 counsel 5:2 10:19 11:12,13,15 22:24 26:2,3 count 51:12 56:21,23 coupled 75:17 77:8 78:17,24 79:10, 13,14,20 court 5:5,14 6:13 7:5 9:11 22:16,25 45:21 58:8 75:11 77:19 87:9 88:13 cover 21:18 53:9 54:6,20 65:1,2,8,9	67:3 77:18 80:25 82:12 covered 24:12 covers 37:15 create 41:25 creating 36:14 criteria 45:15,16 critical 48:9,14 82:10 crops 27:22 cryo 17:5,9 customer 37:4,14 cutting 28:19,20 Czymmek 5:10,21 6:11 22:22 23:1 86:25 D daily 29:17 82:18 Danforth 27:10 30:1 data 67:13 84:1 dataset 42:20 date 15:15 date-based 19:22 dates 6:21 David 6:8 day 48:2 82:22,23,24 day-to-day 48:1 days 25:22 de 81:18 deactivate 73:1 deal 35:4 52:10 55:24 decades 30:9 decision 22:2 declaration 11:20,21 14:18,21 21:9, 10,14,21 22:23,24 23:2,9,15,17,20,21 24:1,3,5,20,23 25:25 26:7,18,21,25 27:3,4 69:20 70:2,5 74:15 75:7 78:24 decode 70:25 deconvolution 36:15 43:1 45:10 48:10 49:13 83:20 84:19 decorate 40:24 72:5,25 decorated 41:2	decreases 55:12 deeper 54:7,22 defending 12:5,12 defines 45:23 defraction 44:3,10 45:7 58:15 defraction-limited 57:25 degrade 83:18 degrees 76:5,17,21 77:17 78:5 79:12 Delaware 7:8 31:4 demonstrated 73:24 demonstrates 72:14 dense 56:9 density 51:9,13,20 52:5 55:5,6,11,21 56:2,5,17 57:3,9,17 59:8,11,23 dependent 75:3 depending 20:18 43:15 54:8,12 55:23 61:10 depends 44:6 48:7 53:10 54:18,23 55:2 56:7,20 58:24 61:19 62:13 63:12 64:10 84:1 deposed 6:15,19,24 8:21 12:1 13:15, 19 14:20 deposes 5:12 deposition 5:3,13 6:3 7:10 10:24 21:3,7,9,11 22:6 26:21 88:15 depth 41:21,23 Derek 16:2,4 22:7 Derrick 26:10 describe 79:5 describes 70:15 design 36:10,14,19 37:19 39:11,15, 25 50:14 57:11,13,15,20 81:3 designed 39:19 40:1,2 54:22 65:6,9 designing 34:22 designs 32:23 39:17 detector 46:2,9 47:4 48:19 49:10 51:23 determines 45:25 determining 40:12 41:7 57:1 develop 35:25 40:15 developed 34:2,4 35:6,19 40:11,14
---	---	--

developing 36:3 37:1,7 development 34:15,25 35:11 37:16 39:12 device 67:19 Devries 5:4 diamond 61:25 difference 40:20 51:15 54:9 58:19 64:23 67:15 differentiate 52:3 differentiation 14:10 differently 44:12 difficult 52:7 digging 38:22 digital 17:12 dimension 33:18 dimensions 33:21 44:14 72:7 dipping 64:10,18,24 65:6 direct 35:22 directed 31:4 directly 34:19 director 27:14 28:8 disclosed 74:12 discuss 74:14 discussion 76:13 dish 81:17 dispersive 18:7 disputes 15:18 distance 55:18 61:5 63:3 67:1 79:3 distances 65:4 66:15 67:4 distinguish 45:17 58:16 distorted 54:4 distributed 58:22 60:10 district 7:5 division 36:7 Doctor 6:16 9:25 23:25 27:5 30:7 33:8 37:23 40:10 41:13 48:18,22 49:20 55:6 67:5 69:22,24 71:16 77:11 81:22 85:23 86:14 88:11 document 6:22 11:19 23:5 24:7,17 25:16 69:22,24 70:2,4,9 documents 20:19 21:4,16,24 23:19,	23 24:3,13,20 Donald 27:9 double 13:4 Double-checking 17:21 drawing 77:8 drift 67:6,11,13,15,18,19,20,22 68:5, 8,16,18 69:9,11,12,16 76:15 drive 39:8 due 24:11 67:20 dyes 7:23,24 8:16,17,22 9:3 36:11 38:20 40:6 E earlier 31:6 69:17 early 26:6 34:10 37:5,13 Easier 56:12 EDS 18:7,11 19:11 effect 79:1 effects 54:5 effort 24:25 electron 17:5,8 18:8 28:17 electronic 47:4,19 48:23 elemental 18:6,7,9 elevated 50:12 Elyra 17:2 31:6 40:18 83:23 embodiment 74:13 emission 34:23 36:11,22 37:12,20 38:19 40:2 emphasized 35:8 employed 27:8,9 employment 27:13,18 enable 70:25 encoded 39:8 encoding 71:24 72:8,18 encompass 68:24 end 35:10 39:18 46:25 57:24 ending 88:15 engineer 36:18 39:17 engineers 35:24 36:9,13	ensures 79:7 enters 60:24 entire 81:24 entities 51:6,24 environment 27:25 equals 60:21 equipment 7:24 8:16 17:22 18:7,11 19:11 28:11,21 equipments 18:15 32:20 equipped 17:5,9,11 error 73:11 74:3 error-robust 70:19 essentially 71:8 estimate 25:20 estimates 48:11 evidence 21:25 exact 6:21 15:15 20:13,16 25:10,15 EXAMINATION 5:19 86:22 examined 5:11 exception 59:15 exhibit 23:3,10 69:23,24 70:10 75:10 86:7 87:4,21,24 exhibits 21:5,17 23:16 70:13 existed 40:15 existing 38:8 exists 68:11 expanded 55:22 expansion 55:17 expect 58:25 75:24 85:18 expected 57:12,15,17,21 76:13 expensive 63:10 experience 30:8,9,12 31:8,14 32:9 33:9 34:25 35:11 experiment 50:14 52:22 57:10,11, 14,16,20 68:2 76:11 77:16 81:3 experiments 7:16 8:19 78:5 81:21 expert 7:13,17 8:1,6 12:8,21 13:10 14:1 18:17 40:3 explain 60:18 explanation 10:18
--	--	--

explicitly 66:22 exposure 18:10 expressly 5:8 extent 72:14 exudation 42:24 F face-to-face 22:13 fact 65:8 87:15 facto 81:18 factor 47:11 66:9 factors 46:14 48:12 faculty 29:20 30:1 failure 36:14 fair 12:23 13:2 16:13 19:4 24:9 29:14 31:18,19 33:8 51:8 54:14 55:10 73:21 79:16 fall 20:14 familiar 31:13 faster 66:11 FCS 87:1 FCS2 9:18 74:14,17,21 75:1,4,13,20, 23 76:2,6,8 77:5,8,12,20 78:9,13,22 79:10,23 80:21 81:8 87:7,11 feedback 32:13,25 feeling 25:20 fewer 65:20 fiber-optics 82:11 fidelity 28:23 field 41:21,23 51:4 63:14 66:5 figure 75:12 filter 37:12 filters 8:25 34:23 36:11 37:20 38:19 Finally 66:13 find 54:12 59:4 75:9 finding 80:8 fine 17:1 finish 10:8 39:14 77:21 firm 6:1 26:6 FISH 71:1,4,5,6,17,20,25 72:5	Fisher 17:4 five-minute 88:6 fixed 51:23 68:20 80:12 83:8 flexibility 81:2 floor 40:21 flow 7:11,12,13,16,18 8:14,20 9:1,3, 6,9,16,18 74:14,18,19,22 75:4,20 76:2,8,18 77:5,12,20,21,22 78:9,13, 22 79:11,23 80:5,11,16,17,18,21,23 81:8,9 87:1,3,7,11,13 fluidic 77:23 fluids 67:20 80:15 fluorescence 70:19 fluorescent 8:15,17 30:25 41:8 43:25 fluorophore 50:3 fluorophores 40:24 41:3 50:3,7,10, 15 51:1 58:12 73:7,17 focal 43:10 49:5 52:16 68:13 83:8 focus 39:8 41:24 42:4 68:13,16 focused 17:4 28:16 41:20 focusing 38:6 folks 40:6 food 27:23 football 44:9,13 form 23:20 24:3 45:24 formed 57:25 forms 45:19 four-color 72:24 Fox 6:1 frame 37:13 67:12 frames 36:1 freezer 28:23,24 front 11:19 87:23 full 6:9,11 46:10 83:19 fully 35:12 37:23 function 43:18 44:5,8,16,17,20,25 45:2,5,12 46:7 48:5,9 54:3 58:7 functions 75:3 fundamental 45:10 83:1 funded 16:11	funding 16:9 18:23 funds 19:22 funny 63:11 G gathering 61:4 gave 62:11 geared 32:20 gender 77:1 general 16:24 46:20 50:13 65:5 71:2, 22 72:4 83:7,11 84:3,10,12 generally 49:2 81:23 generation 31:6 Genomics 6:2 15:19 16:3,7,14,17,19 geometry 43:15 give 5:15 30:13,15,18 31:2 43:24 giving 7:17 58:1 63:6 67:22 global 18:4 19:8,10 34:13 goal 55:23 59:6,21 Goldstein 6:1 good 5:21,22,24 9:24 10:12 11:10 45:5 66:20 88:3 gradient 68:9,11 gradients 79:6 graduate 30:3 greater 19:17 group 28:14 34:19 guess 21:22 29:7 37:2 39:23 46:17, 19 50:25 guidance 14:9 guys 22:10 26:10 H half 60:22 61:1 hand 21:4 22:23 69:22 handfuls 72:17 happen 55:14 harder 47:15 hardware 34:16,23 35:24
---	---	---

head 25:15 heading 19:9 heard 13:5 31:21,23 heat 78:25 79:6 81:14 heated 77:17 78:22 87:12,17 heater 75:1,5,14,20,21,23 76:1,5,7 77:4,13,18 78:8,14,22,23 79:10,12,15,17 heating 79:17,19,21 helped 36:10 37:19 helps 67:2 high 28:23 42:18 46:7 51:13 57:16 61:17,21,22 62:10,14,20 63:8,10,15,23 64:2,4,5,8,13,19 65:14,18 68:8 high-density 59:1 high-oil 63:20 high-pressure 28:23 high-quality 68:20 high-resolution 83:25 high-speed 35:25 36:4 37:7 38:11,15 high-target 57:17 high-volume 75:15 higher 45:23 47:17 51:13 60:13 61:3,4 62:1,3,4,16,23 72:11 73:22 81:6 highest 61:23 history 30:24 38:23 hit 82:9 hold 19:23 holds 38:6 Holman 6:8 home-built 77:23 honest 25:14 honestly 10:2 hour 20:7 22:12 hourglass 44:9,12 hours 22:15,18 24:22 25:1,3,6,9,10,15,18,22 huge 78:25 human 27:23 hundred 58:12	hundreds 72:9 hybridization 30:19 33:16 40:23 70:19 73:13 hybridize 72:24 73:12 hydra 17:4,9 I idea 30:13 identical 54:11 illuminate 81:24 82:12 illuminated 82:5 illuminating 82:3 illumination 43:15 82:4,7 83:14 85:10 image 36:1 42:15,19 47:2,4,6,8,12,13,14 48:3 49:11 50:2 53:10 54:16 59:22 66:17 69:3,8,10,11,13 80:23 83:12 imaged 30:16 images 42:17 57:6 60:9 70:25 72:11 73:22 imaging 16:8,18,20,21,22 30:8,10,14 31:9,11 33:9,12,23 34:3,5 35:6,19 36:15 38:15 40:11,20,21,22 41:15,19 42:9 43:19 46:3,8,24 47:23 48:6,16 49:5 53:18 56:3,6,18 59:8 66:2 67:7 68:6 74:9,18,22 76:8 79:24,25 80:1,4,22 81:22,23 82:16 83:2,3 84:10,12,23 85:6 imaging-based 19:1 immersed 65:7 immersion 53:13 64:11,12,16,24,25 impact 44:24 45:3 49:23 50:8,18 52:12 54:8 69:9,11 impacts 55:7 implement 34:16 69:1 implementation 84:20,24 85:7 important 24:7,11,15 47:22,25 48:2,6,15 53:16 55:25 56:2,5,14,16,17 57:3,12,14,21 59:9,10,12,23 60:4 69:13 importantly 81:5,13 impressions 31:25 improve 27:22 47:18 50:15 84:18	include 24:18 29:4 included 24:15,16,18 including 11:1 increase 81:11 increases 51:9,21 52:6 55:11 81:8 independently 75:22 index 53:12,13,17,25 54:1,10,15 55:1 62:25 63:1 individual 40:10,13 41:8 51:6,12,24 52:7 55:7,12 57:1 58:10 individuals 72:1 information 42:14 43:5,8,14 49:7,12 71:7 infringe 7:14 infringement 12:5,13 13:8,13,18,21,24 14:5 inherently 45:19 inside 47:19 48:24 52:24 58:10 instance 7:20 instances 52:8 53:20 56:14,15 59:18,19 60:12,13 Institute 31:5 instrument 48:9 instruments 19:12 34:21 35:23 36:6 82:20 integrate 47:9,16 integrated 39:20 intense 20:18 intensity 47:6,18 inter 14:25 15:2,4 interacted 26:16 interaction 19:18 80:7 interactions 19:10 interacts 27:24 interest 66:11 67:12,25 68:12,16,25 interested 68:14 interface 34:14 40:7 interfaced 38:15 interfering 41:22 internal 82:11 internships 30:3
--	---	--

interpret 47:12 56:12 interruption 9:11 22:16,25 45:21 58:8 75:11 77:19 87:9 interval 42:2 intervals 11:7 introduce 74:19 inventors 86:6 inverted 65:12 investigator 27:16 investigators 29:25 invoiced 20:12 invoices 20:8 involved 21:20 26:6 31:22 33:14 34:10,19 35:8 36:3,9,23 46:14 67:23 72:23 involvement 15:23 19:6,7 36:24 85:25 86:7 ion 17:4 28:16,19,20 ions 28:17 IPR 12:17 15:12,20,23 18:18 19:7,25 20:9 23:3 31:22 33:14 85:25 86:7 issue 7:16 13:1,13,18,22 50:23 52:25 issues 79:7 J James 6:11 January 23:12 K Kessler 6:1,8 Khanduri 5:20,25 6:7 9:15 22:17 23:1,25 49:15,19 71:11,15 75:19 78:6 85:17,23 86:18 88:5,10 kind 8:19 47:1 63:11 Kirk 5:10 6:11 knob 41:24 42:4 knowing 48:8 knowledge 19:23 L lab 87:15,16	labeling 56:23 laboratory 16:8 27:15 28:9 81:21 82:23 labs 83:2 lack 54:16 laminar 80:16 large 59:7 60:25 61:2 67:3 larger 66:1,5 laser 17:14 82:2,8 lasers 39:5 83:25 85:11 law 6:1 lawful 5:11 lawn 9:22 51:16 lawyer 14:7 20:1 26:11,18 lawyers 26:5 leave 67:25 Leica 17:13 lens 41:20 44:6 45:19,23 46:5,7 52:23 53:4,14,17,25 54:15,22,24 58:1 60:19,24,25 61:5,8,11,20,21 62:14,21 63:2,7,8,15,19,20,23 64:2,5,6,7,8,10, 11,12,13,18,24 65:2,15,23,24 66:20 68:10 79:2,6 lenses 61:25 62:22 63:3,4 64:16 65:1,6,11,18,20 66:14 light 17:13 42:22,23 43:2 44:4,19 45:7 48:25 58:2 60:22,23 61:4 82:8 83:9 85:11,14 limit 45:7,11 58:15 limited 71:8 72:3 limiting 44:4,23 limits 45:6 linear 39:7 lines 16:12 liquids 80:15 list 66:14 87:24 listed 28:9 literature 60:16 61:16 litigations 7:6 live 79:24,25 80:1,4,9 83:1 living 80:12 loans 19:12	local 19:10 60:11 81:13 localization 28:3 30:24 31:7 55:15 locally 81:16 locate 66:10 location 49:9 long 20:18 22:14 26:14 46:11 61:5 66:25 86:5 longer 35:2 47:9,16 55:22 66:15 looked 13:9,25 21:6 56:11 lot 47:3 48:15 58:9,21 59:22 81:2 lots 40:24 loud 70:11 Louis 27:11 29:19,21,24 30:2,5 low 65:23,24 66:14,19 low-magnification 45:18 lower 42:14 61:6 65:20 66:23 84:10 lowest 84:19,23 85:6 M M-E-R-F-I-S-H 31:12 macro 17:10 made 14:11,12 18:6,11 39:20 42:19 magnify 58:17 maintain 69:1 75:18 78:4,20 81:5 major 17:15 make 13:5 24:20 29:1,2,10 34:18 38:7 39:13,18,19 44:21 45:4 47:17 48:11 55:1 56:22 63:25 68:2,24 76:14 77:6 79:7 making 12:18 68:19 manufacturers 16:23,25 17:1 18:11 map 48:19 marked 23:3 69:23 Martin 6:13 mass 19:1 massive 81:14 match 8:24 46:8 52:23 53:6,16,21,25 54:16 55:2 73:14 76:17 matched 53:5,10 matching 53:11
--	--	--

material 63:9 materials 28:18 77:9 78:11 mathematical 48:10 58:4 mathematically 43:2 matrix 53:13 matter 7:9,21 8:13 56:8 57:10 59:19 matters 46:1 57:9 maximum 25:13 meaning 47:8 50:20 51:11 66:3 67:15 means 10:1 40:25 61:3 67:24 68:12 70:24 measure 8:24 measurements 7:12 measuring 7:12 9:4,9 mechanical 67:18 68:19 media 52:23 53:5,7,14,17 meet 22:5 25:24 26:4,17 meetings 22:10 memory 88:2 mention 43:4 66:18 74:8 mentioned 13:23 16:18 25:6,11 33:15 35:10 36:5 48:18 60:17 68:7 72:2 74:6 76:23 84:22 MERFISH 31:12,13,14,15 69:17,20 70:16,18,23 71:3,16,17,18 72:7,11,19 73:22 77:15 83:16 mess 66:8 messages 59:3 messenger 30:20 58:11,14,22 59:14,16 60:7 71:6,9 72:5,25 73:9 met 86:1,8 methods 76:6 77:10 78:11 microbes 27:24 microdissection 17:15 microfluidics 81:19 microns 54:25 microscope 17:3,5,8,10,11,14 28:17 29:9 33:17 36:1,4 37:8,19 38:2,3,7,9,16 39:3 43:16,22 44:1,4,5 51:17,22 52:14 67:17 75:17 76:3 82:1,2,24,25 83:23 84:5 85:14	microscope's 45:13 microscopes 17:16 18:8 28:10,12,14,22 29:4,15 41:1 48:1 65:11,12 microscopy 28:6,13,15 29:4,7 30:25 31:7,9 41:9,10 42:20,23 52:2 55:18 85:9 microtome 28:25 microtubules 56:11 microwave 28:24 middle 78:1 mind 24:17 28:13 65:22 75:6 minimal 32:22 39:23 54:6 minimize 42:13 minus 22:21 25:2,6,18 61:12 minutes 76:14 mismatch 53:8 54:7 missed 15:9 mission 27:22 Missouri 6:14 mixed 26:10 modality 29:13 84:7 models 16:24 modified 82:6 molecule 35:15 40:19 41:2,8 57:17 molecules 28:4 30:10,16,20 33:9,13,20,24 40:11 50:2,17,20,21,24 51:9,16,20 52:3,6,7 55:7,12,16,19 56:3,6,13,21,24 57:2,3 58:10 59:7,8,11 moment 75:9 moments 68:7 months 25:8 morning 5:21,22 motivated 78:4 motor 39:8 move 67:25 76:19 81:4 movement 67:11,21 68:12 moving 67:20 76:20 multicolor 72:22 multiple 58:18 70:24 71:2 73:6 74:23 Multiplex 71:1	multiplexed 70:18,23 72:4,22 74:11 multiplexing 73:20 multiscale 66:2 N NA 46:7 61:14,21 62:9,14,22 63:15,23 64:2,8,14,19 65:15,18,20,23,24 66:14,20 names 26:8 nanometers 44:1 58:3 Nanostring 12:17,24 15:11,19 17:18,24 18:1,19 19:6,20 32:25 Nanostring's 31:16 Nanostring/bruker 12:5,11 13:9,25 15:5 NAS 62:3,4 natural 83:4 84:13 nature 27:12,20 nearby 79:14 82:13 necessarily 73:11,18 negatives 13:4 nice 40:23 56:9 Nikon 17:11 38:12 nineties 37:5 noise 43:5,7 47:3,4,7,9,18,19 48:22,23,24 49:6,10,14 noisy 47:14 noncritical 82:13 nonerror 72:16 nonfluorescent 41:10 nonheated 87:19 nonspecific 43:9 49:1 80:7 Noran 34:21 35:23 36:6 notes 11:23 November 33:24 NSF 16:9 number 9:13 12:22 20:21 24:12 25:15 28:9 34:8,12 49:22 50:1,2,6,7,17,19,25 59:7 62:9 63:6 67:14 71:9 72:11 73:7,9,16,17,22 76:18,20 77:14 87:17,20
--	---	---

numerical 45:22,24 60:17,19,21 61:2,7,13,17 62:16 64:4 66:23 Nyquist 45:15 O oath 10:2 object 11:12 44:11 47:15 50:10 67:11,19 objecting 21:25 objective 41:20 44:6 45:19,22 46:5 52:23 53:4,14,17,25 54:15,19 58:1 60:24,25 61:7,9,10,11,20,22 62:13, 21,22 63:2,4,7,8,19,20,23 64:2,7,16 65:2 67:16 68:10 75:1,5,14,19,21,23 76:1,5,7 77:4,13,16,17 78:8,14,21,23 79:2,6,10,12,15,17,18,19 82:9 83:8 objectives 61:24 62:2,3,4 objects 11:13 51:12 oblique 82:7 83:14 obliquely 82:13 obvious 12:20 13:11 14:2,17 42:21 Odyssey 34:24 oftentimes 30:2 32:21 34:14 50:12 65:7,10,17,19 85:13 oil 54:19,24 55:2 61:10 62:2,16,21 63:19,23 64:1 66:8 78:24 79:3,13,20 Olympus 38:13 omics 16:9 31:24 32:19 33:7 opine 32:23 opinion 7:17 13:10 14:1 55:11 78:7 opinions 12:24 14:16 23:20 24:3,8 69:19 70:1 opposed 81:25 optic 38:6 52:22 optical 39:25 40:2,3,6 42:7,8,12,25 43:12 44:5 52:17,20 54:13 66:4,18, 20,24 83:7 84:5,15 optically 66:21 78:24 order 29:8 ordinary 78:18 original 73:13 out-of-focus 42:14,22 43:4,8,14 44:19 49:11 69:15 83:9,15	overlap 51:14 overlapping 50:22 51:17 56:10 overview 16:24 65:25 owned 78:18 81:20 owner 5:3,12 21:23 owner's 21:6,22 OZ 34:24 35:25 38:11 P paper 87:4,8,12 part 13:13,18 14:5 21:13 27:18 28:6 29:15,23 30:17 34:22 35:1,12 39:12 43:13 49:8 63:1 75:20 76:1,8 77:4,13, 14 78:2,8 82:14,15 87:17,19 partes 14:25 15:3,4 parts 36:19 78:16 pass 86:19 past 19:4 patent 5:3,12 7:14 12:5,12,25 13:8, 12,18,21,24 14:5 15:5,18 21:6,22,23 22:3 43:3 72:23 73:14,25 74:10 86:6 patentable 12:19 13:2 14:17 path 48:25 pathology 27:6 pathway 36:22 38:19 40:2 pattern 83:24 patterns 44:10 pay 56:22 penalty 10:3 pending 11:9 people 35:25 36:16,19,20,21 49:2 perfect 48:17 53:21 66:4 perfectly 53:9 perform 8:20 29:22 33:12,23 performance 53:19 performed 7:15 74:1 performing 29:6 56:18 perfuse 80:15 perfusion 75:16 period 20:19 24:24 25:21	peripheral 17:22 29:6 39:6 peripherally 35:1,12 perjury 10:3 permitted 10:25 25:23 person 15:25 34:8,9 78:17 personal 27:21 personally 16:15 18:16 31:15 86:10 perspective 19:1 66:1,5 Petitioner 5:2 Ph.d. 5:10 27:5 physical 28:18,19 45:11 physically 26:1 37:18,25 38:1,2 physicist 40:3 physiologically 80:3 picked 24:20 pinhole 42:21 pixels 58:18 place 6:9,12 60:14 68:3 plane 41:21 42:24 43:10 49:5 67:25 68:13 83:8 planes 42:2,17 49:4 52:16 57:7 83:15 plant 27:6,10,13,18,24 29:16 30:20 54:18,20,25 55:1 plants 32:19 plasma 17:4 28:20 platform 31:24 32:6,7,10,12,14 33:1 38:5 platforms 32:19,23 play 48:13 68:5 plunge 28:24 point 9:14 21:19 24:19 32:22 37:14 43:18 44:8,15,17,20,25 45:2,5,12 46:6 48:5,8 51:2,15 54:3 58:6 62:2,24 82:1,2,3 87:15 Pointe 6:13 points 45:17 poorer 83:4 84:13 populations 73:6 portion 82:3 POSA 63:14,20 64:2,7,13,18 65:14, 24 74:17,21 78:3 79:23 80:21
--	--	---

position 12:18 29:20 40:12 41:8,23 42:3 57:1 68:20 positioning 42:16 positions 21:6 potential 72:13 73:9 potentially 65:17 power 45:23,25 61:4 practically 60:1 practice 53:6 55:3 Pratibha 5:25 precise 25:7 68:21 81:13 precisely 75:1 precision 68:4 69:2 81:6 preface 33:3 preparation 22:5 prepare 21:2 24:23 25:25 26:21 28:22 29:5,8,12 preparing 23:15 26:18 president 18:4 19:8 34:13 pretty 36:17 43:7 previous 8:21 56:20 74:5,7 85:5 primary 32:21 70:7 principal 27:15 29:25 principle 73:24 74:1 prior 15:10 38:17 71:3,5,17 72:12,20 73:23 probe 43:10 50:4 probes 29:11 probing 71:2 problem 51:5,7,10 proceeding 5:16 13:1,14,19 14:6,24 process 37:16 39:12 74:11 processing 36:16 67:3 processor 28:24 produced 5:11 product 7:25 9:13,19 37:10 38:7 products 7:23 8:23,25 16:10,14,16, 17,18,19,21 17:18,20,23,24 18:1 31:16 34:24 35:1,11 professional 18:18 19:5	project 30:5 properly 38:25 39:21 52:22 properties 54:13 61:11 proteins 31:1 protocol 77:15 provide 14:1 provided 13:10 14:15 38:18 69:19 70:1 73:14 87:18 providing 12:21,24 36:22 68:18 publication 85:24 published 30:21 pupil 60:24 purchase 76:11 purposes 62:1 pursuing 19:2 put 19:11 25:16 42:19 43:23 50:14 84:4 putting 62:2 Q quality 34:7 quality 47:11 48:3 question 10:8,16 11:9 13:5,16,17 14:4 28:5 32:8,9,24 35:14,18 40:9 48:7 50:5,16 54:23 55:4 58:24 59:21 60:1 62:5 63:24 64:1,17 66:3 74:8 80:20 questions 5:20 10:15 11:13,14 60:4 86:19,21,23,25 88:11 quick 86:21 quickly 47:3,6,14 68:24 quote 77:16 R R&d 34:19 ran 31:4 range 27:23 55:22 81:12 rate 20:6 rates 68:8 75:16 ratio 46:17,20,22,24 47:22 48:21,22 49:20,24 50:8,18 52:13	Rayleigh 45:16 RDR/CRR 5:4 reaction 30:19 33:16 read 21:18 23:16 readily 41:3 reagent 81:15 reagents 76:19,20 real 53:20 reality 60:6,15 realizing 46:8 reason 66:10 reasons 12:20 65:21 74:23 reassign 43:2 rebuttals 21:22 recall 7:7 15:25 22:2 26:8 72:16 81:12 86:24 recess 23:24 49:17 71:13 85:21 88:8 recognize 23:5 69:23 record 6:10 88:10 records 20:22 reduce 42:13 69:13 80:7 reduced 47:10 refer 49:2 75:6 reference 43:22 52:17 referred 44:13 referring 32:5 50:1,4,19 70:9 reflect 45:13 reflection 82:11 refractive 53:12,13,17,24 54:1,9,15 55:1 62:25 reframe 35:3 regions 60:8 regular 11:6 42:2 regularly 36:12 reject 42:21 rejecting 83:15 related 7:4,22 27:21 44:3 45:14 62:25 relationship 18:19 19:5 29:18,23 86:2,11
--	--	---

relevant 80:3 rely 23:19,22 24:2 remedies 68:17,22,25 69:4 remedy 69:15 remember 9:13 15:14 20:13,16 25:9 26:12,13,14 35:16 66:22 79:2 87:21 remembering 25:8 remove 28:18 73:1 repeat 13:16 46:12 57:18 rephrase 63:22 reporter 5:5,6,14 9:11 22:16,25 45:21 58:8 75:11 77:19 87:9 88:13 represent 6:2 request 10:7,17 19:12 require 53:7 65:8 80:2 required 76:22 80:16 research 16:11 18:23 27:17,20,21 28:2,7 29:15,23 30:4,17 69:7 reserved 5:8 88:13 residence 6:10,12 resolution 42:15,18 44:4 45:9,13,14, 15,23 46:4,10,14 50:23 51:10,21,22 55:7,12 57:16 59:24 65:17 83:4,5 84:13,16 resolve 45:6 51:18 58:10 resolved 56:3 resolving 45:25 51:23 52:7 61:3 respects 63:12 71:24 respond 10:11 response 21:23 22:1 74:7 result 32:17 48:16 53:22 68:16 revert 35:21 review 12:18 14:25 15:3,4 21:13,16 22:4 25:22 reviewed 21:4,5,8,21 26:20 reviewing 15:8 22:2 revision 30:22 rid 43:12,14 risk 50:11 RNA 30:20 58:11,14 59:14,16 60:7 71:7 72:6,11,25 73:22	RNAS 58:22 59:22,23 71:9 72:1 73:9 robust 39:19 role 34:12 37:6 48:13 68:5 roles 37:7 room 37:13 66:12 round 44:11 59:7,14 rounds 71:2 74:9 rule 59:16 60:15 S Saint 29:18,21,24 30:2,5 sales 19:10,13 salespeople 19:11 salesperson 18:25 salt 65:7 sample 28:22 29:8 40:13 44:8 45:20 47:1,20 49:8,23 50:8,18 51:9,20 52:6, 11,12,15,24 53:12 54:1,16 55:8 56:6, 18 57:2 65:3 66:1,3 67:17,21 68:10, 19 78:20 80:17 81:24,25 82:4,5,21 83:10 samples 28:18 29:5 30:8,11,16 33:10,13,24 34:3 35:7,20 54:19,20 67:22 74:22 77:18 80:22 scale 73:18 scan 68:23 82:2,21 84:20,24 85:7 scanning 17:4 18:8 28:17 81:25 82:2 85:16 scatter 47:3 83:24 scattering 44:19 scheme 72:8 science 27:10,13 63:9 scientific 17:6,8 27:17 28:5 29:15,23 scientist 30:6 34:21 35:9,23 36:8 scientists 28:4 screen 88:2 search 66:12 section 46:12 52:21 66:21 sectioning 28:25 29:1,12 42:7,8,12, 25 43:12 52:17,20 66:4,19,20 83:7 84:6,15 sections 67:1,2	sense 29:1 sentence 77:22 separate 14:12 separately 76:12 78:17 Seqfish 72:20,21 73:23 74:6,8 series 8:22 42:17 70:25 serving 7:13 12:8 18:17 set 52:22 79:12 setup 76:1 shape 44:9 shaped 44:13 sheet 85:11 shoot 82:13 short 61:6 63:2 79:3 shorter 65:4 shorthand 5:4,5 61:15 shot 47:3 showing 75:13,14 side 40:7 82:8 sign 23:12 signal 44:16,18 46:25 47:9,16,17,18 49:3,8,9,12 55:5,6,11,25 56:17 57:16 65:17 71:1 signal-to-noise 46:15,17,20,22,23 47:8,22 48:21,22 49:20,24 50:8,11, 15,18 51:1,7 52:12,18 signals 41:22 48:25 49:4 50:6 signature 5:7 23:10 88:13 significant 25:16 31:8 similar 40:9 56:19 simple 46:12 47:2 simpler 82:19 85:15 simply 14:4 41:23 43:25 sine 60:21 single 30:10,16,20 33:9,12,19,23 35:15 40:21 41:2,20 56:21,24 71:7 81:25 single-messenger 72:1 single-molecule 30:24 31:7,9 40:19,22 52:1 55:15 71:20,23,25 72:5 sink 78:25
--	--	---

sit 18:24 44:22 sitting 14:24 26:3 situ 70:19 situations 50:13 size 58:5,13 skill 78:18 slice 66:24 slides 9:21,23 slightly 62:5 slip 53:9 54:6,20 65:1,2,8,9 77:18 82:12 slips 81:1 small 36:8 43:23 68:9 82:3 smaller 45:24 smfish 71:19 72:12 smooth 47:5 software 34:16,22 35:24 soil 27:25 solid 60:9 solution 65:8 solutions 81:4 solve 54:24 solving 51:6 sophisticated 75:15 Sounds 9:24 10:12 11:10 source 82:8 85:14 SP8 17:13 spaced 51:24 sparse 58:22 spatial 16:9 31:23 32:19 33:7 speak 6:4 10:25 86:15 spec 19:1 special 45:9 58:3 specialized 45:9 species 60:7 72:12 73:23 specific 9:13 15:25 16:23 24:17 25:22 28:10,12 30:5 32:2 35:15 49:3 77:1 80:2 84:7 specifically 34:5 69:16 76:4 specifications 36:10,22 37:20	38:18 40:1 specimen 74:24 78:25 spectrophotometry 8:23 spectroscopy 18:7 spectrum 9:6 speed 49:10 67:2 80:7 spend 24:23 spending 25:8 spherical 54:2 65:19 spot 45:19,24 47:13 51:2 57:25 58:2, 5,11,13,17 spots 9:22 46:3 60:9 83:24 spread 43:18 44:2,8,15,17,20,25 45:2,5,12 46:6 48:5,9 54:3 55:19 58:7 spring 15:14 St 27:11 stability 68:18,19 stack 42:1,16 83:11 stacking 41:14,24 42:4,16 stacks 33:19 36:14,15 38:17 stage 67:19 81:19 84:5 stand 14:13 27:1,3,4 standard 40:25 75:16 standpoint 41:19 stands 70:18 start 10:8 started 35:7 starting 5:13 state 6:9 stated 77:7 statement 14:11,12 39:14 57:23 Sterne 6:1,8 STIPULATED 5:1 stocks 19:19 straightforward 81:1 strategies 52:8 55:15,24 58:21 81:6 83:20 84:17 strategy 42:25 51:18 52:9 53:23 56:23 59:3 71:24 72:22 73:10,19 74:18 82:15 83:13 84:15	strike 10:15 15:16,17 18:13 30:14 31:17 37:25 46:22 48:20 50:6 53:2 56:1,4 84:10 strip 73:1,4 stronger 47:17 structured 85:10 structures 47:12 students 30:3 Su 87:16,24 sub-resolution 43:24 subcellular 28:3 subject 7:9,21 8:13 submitted 11:20 14:17 20:8 23:2 subpopulation 52:2 subset 55:16 substance 11:1 86:15 substantially 72:11 73:22 sufficient 24:20 66:2,6 suitable 53:22 summer 15:14 super-resolution 17:3 33:17 40:19 58:4 83:23 85:9 support 19:12 supporting 28:11 swear 5:14 sworn 5:11 9:25 system 17:15 31:6 32:3 36:12,18,25 37:9 39:10,12,25 40:2,14,15,20,21,22 46:9 48:19,24 76:8 77:4,23 78:8 79:10 81:4 systems 34:2 35:6,15,19 39:15 40:11 T taking 6:2 7:12 11:10 67:1 talk 28:11 46:16 80:9 talked 31:16 39:2 69:17 74:6 talking 37:8 43:6 46:17 49:20 55:6 57:24 70:14 71:16 Talos 17:7,9 target 19:22 49:22 50:1,10 51:20 52:6 57:3 59:7 66:10 68:12,15 69:3
--	---	--

team 19:9,13 34:15,22 35:2,12 40:8 teams 18:6,16 34:15 technique 31:11 42:13 55:17 70:15 71:23 72:20 82:7 84:6 techniques 29:10 45:9 53:7 58:4 62:20 71:4,5,18 72:12 73:23 75:17 technologies 16:24 34:9 38:5 41:4 technology 19:14 33:5 34:5 37:21 84:14 teeny 26:10 telling 14:11 25:9 60:2 tells 11:15 TEM 17:7 temperature 67:15,16,17 68:9,18 74:20,25 75:15,18 76:16,21 78:4,20 80:6,11,14,18,24 81:5,7,8,11 temperature-controlling 81:19 temperatures 74:25 80:2 ten 6:20 9:12 tend 34:10 65:3,4 66:15 term 21:24 41:14 42:8 43:8,18 67:6 70:22 terms 12:15 47:2 test 8:20 tested 36:13 testified 8:9 24:2 testify 10:1 testifying 10:3 75:25 78:21 testimony 5:15 11:1 20:4 77:3,12 78:7 79:9 86:16 testing 34:15 36:9,14,21,25 37:3,9, 12 38:17 tests 37:12 theoretically 55:14 84:16 thermal 67:14 Thermally 79:14 Thermo 17:4,5,8 thick 52:15,21 83:12 84:16 thicker 66:24 thickness 52:11,12 54:13 thin 42:24	thing 10:14 11:8 40:23 42:6 44:23 things 34:17,20 40:8 43:13 44:21 53:8,14 64:25 76:17 82:21 84:21,25 85:8 thinking 63:17 70:11 thousand 50:24 72:15 thousands 72:9 74:2 three-dimensional 40:12 three-month 24:24 tight 24:14 till 38:14 time 5:13 18:9 19:3 20:17 25:21,22 26:12,20 36:6 54:19 59:4,22 60:14 67:12 69:8,10,12,14 82:4 88:12,15 times 6:23 8:6 60:21 tissue 28:3 29:11 40:13 43:11,13 54:13 71:10 79:14,21 83:12 tissues 30:20 33:18 84:16 today 6:3 9:25 10:7 12:1 13:7,15,19 14:6,24 21:3 26:4,22 69:17 86:14,16, 25 tool 83:1 tools 28:6,13,16 29:4,5 top 47:7 65:22 78:1 total 20:11,24 22:18 25:10 52:3 82:11 tradeoffs 74:4 transactions 19:13 transcribed 5:6 10:7 transfer 44:5 translate 25:1,5 transmission 17:7 trial 7:8 8:9 22:3 true 58:25 truth 5:16,17 turn 23:8 55:16 types 81:6 typewriting 5:7 typical 44:1 typically 28:2 32:20 42:2 44:12 48:23 49:9 61:8 65:1 68:23 71:2,5 72:6 82:5 83:14	U Uh-huh 39:1 46:19 49:21 55:9 69:18 ultimate 55:23 ultimately 67:24 69:14 ultra 28:24 undergraduates 30:3 underlying 38:5 understand 9:25 10:3,16,19 11:2, 16,17,25 13:12,17,20 14:4,6,13,18,23 28:4 34:20 35:5 38:24,25 41:5 51:19 57:22 59:17 70:9,13 78:3,7 84:9 understanding 12:3,4,11 13:7 15:2 37:24 41:14,18 42:8 43:18 63:16,21 64:3,9,14,19 67:6,10 70:22 87:6,11 understood 10:13,20 11:3,11 80:10 uniform 51:16 80:17 unique 78:2 unit 77:7 University 29:19,21,24 30:2,6 31:3 unmarked 11:21 unsolvable 52:1 unsuccessful 32:17 upright 17:11 65:10,12 usable 54:12 user 39:18 users 48:1 V vague 63:11 valid 13:11 14:2 valves 77:24 version 87:13,17 versus 50:20 vibratome 28:25 vice 18:4 19:8 34:13 view 51:5 66:6 violate 7:14 visible 58:2 visual 88:2
--	---	---

volumes 33:19

W

wait 10:9,10

Waller's 21:7,8,9,21

Walter 6:4 85:20 86:20,23 87:10
88:3,7,14

wanted 49:1 62:8 78:19

water 54:21 61:9,22 62:3,15,21 64:6,
7,11,12,16,17,23,24,25 66:9

wavelengths 7:24 8:17,24 45:8

ways 51:14

weeks 20:19 21:19 24:25

Weil 15:24

Wes 26:9

white 17:13

widefield 52:14 81:22,23 82:4,6,14,
15,16,19,22,25 83:3,7,12,19,25 84:3,
10,12,14,23 85:6,14

Wildwood 6:13

William 5:4

word 28:15 39:24 41:1 48:14 50:25
63:11 84:2 85:1

work 19:24 20:9 30:6 32:18 33:3
54:18 86:9

worked 35:23 36:12

working 20:19 26:2 33:6 39:21 61:5
63:3 65:4 66:15 73:8 76:22 79:3

works 59:16

world 18:6 53:20

worse 45:4

wrong 78:13

X

Xenium 32:4,7,10,11,14

Xiaowei 85:24

Y

year 15:13 21:20 26:15

years 6:19,20 9:12 19:16,17 30:12
31:1

yeast 30:25

yesterday 22:12,14

Z

Z-AXIS 44:10

Z-H-U-A-N-G 70:5

Zeiss 17:3,10,14 18:5 34:12 38:13
40:18

Zhuang 70:4 85:24 86:3 87:15

Zoom 17:10 22:11 26:1