

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

3 -----
4 GE HEALTHCARE, LTD.,

5 Petitioner,

6 v.

7 JOHNS HOPKINS UNIVERSITY,

8 Patent Owner.

9 Case No. PGR2025-00059

10 U.S. Patent No. 12,115,233

11 -----
12
13 DEPOSITION OF BRIAN MATTHEW ZEGLIS, PH.D.

14 Washington, D.C.

15 Wednesday, March 11, 2026

16 9:06 a.m.

17
18
19
20 Job No.: 620746

21 Pages 1 - 214

22 Reported By: Joan V. Cain

1 Deposition of BRIAN MATTHEW ZEGLIS, PH.D.,
2 held at the law offices of:

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17 Pursuant to Agreement, before Joan V. Cain,
18 Court Reporter and Notary Public in and for the
19 District of Columbia.
20
21
22

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By Dr. Partington	11

E X H I B I T S

(Attached to the Transcript.)

DEPOSITION DEPOSITION EXHIBITS	PAGE
EXHIBIT 2018 Errata to the Declaration of Brian Zeglis, Ph.D., 7/13/25	16
EXHIBIT 2019 Article: Radiopharmaceuticals for Imaging in Oncology with Special Emphasis on Positron-Emitting Agents, by Zeglis, et al.	120

E X H I B I T S C O N T I N U E D

(Attached to the Transcript.)

DEPOSITION	DEPOSITION EXHIBITS	PAGE
EXHIBIT 2020	Journal of Medical Chemistry Article: Identification of Selective and Potent Inhibitors of Fibroblast Activation Protein and Prolyl Oligopeptidase, by Poplawski, et al.	138
EXHIBIT 2021	Excerpted Pages 7 and 8 of Patent Application Publication No. US 2010/0098633 Annotated by Dr. Zeglis	183
EXHIBIT 2022	Excerpted Pages 12 to 14 of Patent Application Publication No. US 2010/0098633 Annotated by Dr. Zeglis	187

E X H I B I T S C O N T I N U E D

PREVIOUSLY MARKED EXHIBITS REFERENCED

EXHIBIT 1001	U.S. Patent No. 12,115,233	55
EXHIBIT 1003	Declaration of Brian Zeglis, Ph.D., 7/13/25	15
EXHIBIT 1004	Patent Application Publication No. US 2010/0098633 A1	159
EXHIBIT 1005	Patent Application Publication No. US 2012/0009121 A1	157
EXHIBIT 1006	Journal of Medical Chemistry Article: Extended Structure - Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2- cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP), by Jansen, et al.	152

E X H I B I T S C O N T I N U E D

PREVIOUSLY MARKED EXHIBITS	REFERENCED
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EXHIBIT 1007	American Chemical Society	136
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Article: Selective
Inhibitors of Fibroblast
Activation Protein (FAP)
with a (4-Quinolinoyl)
-Glycyl-2-Cyanopyrrolidine
Scaffold, by Jansen, et al.

EXHIBIT 1008	Molecules' Article:	159
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Evaluation of the
Radiolabeled Boronic
Acid-Based FAP Inhibitor
MIP-1232 for
Atherosclerotic Plaque
Imaging, by Meletta, et al.

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PREVIOUSLY MARKED EXHIBITS	REFERENCED
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EXHIBIT 1010	The Royal Society of	114
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Chemistry Article: A

Practical Guide to the

Construction of

Radiometallated

Bioconjugates for Positron

Emission Tomography

EXHIBIT 1044	Patent Application	132
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Publication No. US

2014/0357650 A1

EXHIBIT 2003	Royal Society of Chemistry	128
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Article: Selective

Inhibitors of Fibroblast

Activation Protein (FAP)

with a Xanthine Scaffold,

by Jansen, et al.

Transcript of Brian Zeglis, Ph.D.
Conducted on March 11, 2026

11

P R O C E E D I N G S

- - -

9:06 a.m., EDT

March 11, 2026

- - -

Whereupon,

BRIAN MATTHEW ZEGLIS, PH.D.,

having been duly sworn under penalties of perjury by
the Notary Public, was examined and did testify as
follows:

EXAMINATION BY COUNSEL FOR PATENT OWNER

09:06:57

BY DR. PARTINGTON:

09:06:57

Q Good morning, Dr. Zeglis.

09:06:57

A Good morning.

09:06:59

Q My name is Olga Partington with Sterne,
Kessler. Could you please state and --

09:06:59

09:07:01

MR. KUSHAN: Sorry. Sorry. Appearances?

09:07:08

DR. PARTINGTON: She has them.

09:07:10

THE COURT REPORTER: I do have appearances
noted.

09:07:10

09:07:15

MR. KUSHAN: You already have them?

09:07:15

Go ahead. Go ahead.

09:07:15

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Transcript of Brian Zeglis, Ph.D.
Conducted on March 11, 2026

12

1	BY DR. PARTINGTON:	09:07:15
2	Q Could you please spell and state your name	09:07:15
3	for the record.	09:07:18
4	A Brian, B-R-I-A-N, Matthew, M-A-T-T-H-E-W,	09:07:18
5	Zeglis, Z-E-G-L-I-S.	09:07:26
6	Q And what is your address?	09:07:34
7	A 180 East End Avenue, Apartment 5E, New	09:07:36
8	York, New York 10128.	09:07:44
9	Q Have you ever been deposed before, Doctor?	09:07:48
10	A No.	09:07:50
11	Q All right. Since you've never been deposed	09:07:54
12	before, I'm going to go over some ground rules. I'm	09:07:56
13	sure counsel explained some of them to you as well,	09:07:59
14	but I just want to make sure we're on the same page.	09:08:02
15	So I will be asking you some questions, and	09:08:05
16	your counsel may object. Now, it is important for	09:08:07
17	the court reporter that we don't speak over each	09:08:09
18	other, so please let me finish my question, and --	09:08:12
19	before you start answering and let -- give your	09:08:17
20	counsel opportunity to object before you start	09:08:21
21	answering as well.	09:08:23
22	Is that okay?	09:08:24

1	A	Yes.	09:08:24
2	Q	Great.	09:08:25
3		Now, also, court reporter cannot take down	09:08:25
4		nonverbal answers, like, you know, head nods or	09:08:28
5		mm-hmm, so please verbalize all of your answers.	09:08:32
6		Okay?	09:08:36
7	A	I understand.	09:08:36
8	Q	Thank you.	09:08:37
9		Sometimes your counsel may object to my	09:08:38
10		question. You still have to answer it, however,	09:08:41
11		unless your counsel instructs you not to answer.	09:08:45
12		Would you agree to do that?	09:08:48
13	A	I agree.	09:08:52
14	Q	Thank you.	09:08:53
15		Okay. So if at any point you need a break,	09:08:54
16		please let me know. We're going to keep track of it	09:08:59
17		and I'm going to try to break every hour or so, but	09:09:01
18		if you need a break, let me know. The only thing	09:09:03
19		that I ask is that if there's a question pending,	09:09:06
20		that you answer the question before you ask for a	09:09:08
21		break.	09:09:11
22		Is that all right?	09:09:12

1	A	Of course.	09:09:12
2	Q	If I ask you a question that you don't	09:09:13
3		understand, please ask for further clarifications,	09:09:15
4		because if you answer the question, I'm going to	09:09:19
5		assume that you understood it. Okay?	09:09:22
6	A	Okay.	09:09:24
7	Q	Now, the Patent Office rules require that	09:09:29
8		during the deposition today you do not discuss the	09:09:32
9		substance of your deposition with your counsel until	09:09:36
10		after the deposition.	09:09:41
11		Will you agree to abide by those rules?	09:09:42
12	A	I agree.	09:09:44
13	Q	Do you understand that you're here under	09:09:47
14		oath and under penalty of perjury?	09:09:49
15	A	I understand.	09:09:51
16	Q	Do you understand that you're here to	09:09:53
17		testify truthfully and accurately?	09:09:55
18	A	I understand.	09:09:58
19	Q	Is there any reason you cannot give	09:10:00
20		truthful testimony today?	09:10:02
21	A	There is no reason.	09:10:04
22	Q	Are you taking any medication or have any	09:10:06

1	medical conditions that would preclude you from	09:10:10
2	testifying truthfully today?	09:10:12
3	A No, I am not.	09:10:14
4	Q I see you brought something with you. Is	09:10:17
5	that your declaration?	09:10:21
6	A This is my declaration.	09:10:22
7	Q Counsel, will you represent that this is	09:10:24
8	the true and complete copy of Dr. Zeglis's	09:10:26
9	declaration submitted in these proceedings?	09:10:28
10	MR. KUSHAN: Yes.	09:10:32
11	DR. PARTINGTON: Thank you.	09:10:36
12	BY DR. PARTINGTON:	09:10:36
13	Q Doctor, what did you do to prepare for your	09:10:37
14	deposition today?	09:10:38
15	A There are two errata to the -- to the	09:10:39
16	declaration that might be worth submitting, I think,	09:10:45
17	at this point or later.	09:10:51
18	Q Sure. Let me see it.	09:10:52
19	Do you have multiple copies of them?	09:10:53
20	A Just this copy. I can read them to you or	09:10:55
21	just hand them to you.	09:10:58
22	MR. KUSHAN: We have additional copies.	09:11:00

1	THE WITNESS: Oh, additional copies.	09:11:01
2	DR. PARTINGTON: Thank you. So we probably	09:11:12
3	want to mark this as an exhibit.	09:11:15
4	Do you know what your next exhibit is?	09:11:22
5	MR. KUSHAN: I think we can locate that.	09:11:24
6	DR. ELLISON: We can make it our exhibit.	09:11:27
7	DR. PARTINGTON: Okay. Let's do	09:11:30
8	Exhibit 2018, please.	09:11:33
9	- - -	09:11:33
10	(Deposition Exhibit 2018 was marked	09:11:33
11	for identification.)	09:11:33
12	- - -	09:11:42
13	BY DR. PARTINGTON:	09:11:42
14	Q Is there anything on this errata that you	09:11:45
15	would like to specifically address right now?	09:11:48
16	A Sure. So paragraph 253. It says -- it	09:11:53
17	originally read: "Three of the six formulae include	09:11:58
18	a benzamide group structure, but the remainder do	09:12:02
19	not." The correction is that it should read: "Two	09:12:06
20	of the six formulae include a benzamide group, but	09:12:09
21	the reminder do not." That's a typographical error,	09:12:12
22	and in footnote 2 --	09:12:16

1	Q	Okay. I'm sorry. I'm going to stop you.	09:12:20
2		Oh, 2. I see that. I just wanted to make sure I	09:12:20
3		understand what the issue was.	09:12:20
4		Okay. Please go on.	09:12:22
5	A	And then, in footnote 241, it starts: "As	09:12:23
6		I noted in paragraph 171121" --	09:12:26
7	Q	Mm-hmm.	09:12:26
8	A	-- "Dr. Pomper stated that a compound with	09:12:29
9		a molecular weight below 1,500 Da would be a 'low	09:12:31
10		molecular weight [sic] compound,'" and now it should	09:12:37
11		read: "As I noted in paragraph 171, Dr. Pomper	09:12:41
12		stated..." and that's another typographical error.	09:12:44
13	Q	I see. Thank you.	09:12:47
14		All right. So let me go back to my	09:12:49
15		question then.	09:12:50
16		What did you do to prepare for your	09:12:51
17		deposition today?	09:12:53
18	A	I read the declaration several times. I	09:12:53
19		read several papers several times, and I discussed	09:12:58
20		the deposition with the lawyers.	09:13:02
21	Q	Okay. So let's start with which papers did	09:13:06
22		you read?	09:13:08

1	A	I read every exhibit that is listed in --	09:13:09
2		listed in the exhibits here while I was reading.	09:13:19
3	Q	Are you referring to --	09:13:22
4	A	I --	09:13:22
5	Q	-- Appendix C of your declaration?	09:13:23
6	A	Appendix C.	09:13:39
7	Q	Okay.	09:13:40
8		You mentioned that you met with counsel.	09:13:43
9		Who did you meet with?	09:13:44
10	A	Jeff Kushan, Amit Bhatla, and Ethan	09:13:48
11		Arrington --	09:13:58
12	Q	How many times did you meet with them in	09:13:58
13		preparation for your --	09:14:00
14	A	-- and also Lauren Katzeff.	09:13:57
15	Q	How many times did you meet in preparation	09:13:59
16		for your deposition today?	09:14:01
17	A	In person or --	09:14:01
18	Q	Let's start --	09:14:01
19	A	-- in aggregate?	09:14:02
20	Q	Let's start with in person.	09:14:04
21	A	Four times.	09:14:06
22	Q	Okay. And you've had multiple -- or strike	09:14:07

1	that.	09:14:08
2	Did you have online conversations with your	09:14:10
3	counsel in preparation for this deposition?	09:14:12
4	A Yes.	09:14:14
5	Q How many times?	09:14:15
6	A Several.	09:14:16
7	Q How long would you say, in aggregate, did	09:14:23
8	you spend meeting with counsel in preparation for	09:14:25
9	your deposition today?	09:14:28
10	A In person, approximately 25 to 30 hours.	09:14:36
11	Via telecommunications, that's a harder question to	09:14:50
12	answer because it goes back more finite instances,	09:14:56
13	but five to ten hours.	09:14:59
14	Q Okay. And how long would you say, in	09:15:03
15	aggregate, did you spend on your own preparing for	09:15:05
16	your deposition today?	09:15:07
17	A Does that question include reading the	09:15:14
18	literature?	09:15:17
19	Q It -- that question includes anything that	09:15:20
20	you would consider preparing for this deposition.	09:15:22
21	A Between 50 and 100 hours.	09:15:29
22	Q Now let me ask you a question about this	09:15:39

1 errata sheet. When did you discover the errors in
2 your declaration?

3 A Over the last two days.

4 Q And how did you discover those errors?

5 A During deposition training, looking at the
6 structures, and looking at the footnotes.

7 Q Did you discover them yourself, or did your
8 counsel point you to them?

9 A The first one I discovered myself. The
10 second one counsel and I both discovered.

11 Q Did you talk to anyone besides counsel
12 regarding the substance of your deposition today?

13 A No.

14 Q So you stated that you reviewed every
15 exhibit that is cited in Appendix C of your
16 declaration in preparation for your deposition
17 today.

18 Did you review any documents not mentioned
19 in your declaration?

20 A Only documents that I read within the
21 context of my job, which are other -- I mean, there
22 are other papers about optical PET and SPECT imaging

09:15:42

09:15:48

09:15:51

09:15:52

09:15:55

09:15:59

09:16:05

09:16:07

09:16:13

09:16:16

09:16:27

09:16:29

09:16:33

09:16:44

09:16:48

09:16:53

09:16:57

09:16:57

09:17:01

09:17:11

09:17:14

09:17:19

1 agents that I read daily. So none specifically

09:17:25

2 vis-~~?~~-vis the dep- -- deposition.

09:17:31

3 Q Okay.

09:17:33

4 A But I read five to ten papers a day.

09:17:33

5 Q Yeah, my question was specific to your --
6 in preparation for your deposition today, did you
7 review anything else outside of what's listed in
8 your declaration?

09:17:37

09:17:41

09:17:44

09:17:47

9 A Over time, I may have looked at abstracts
10 on papers on PubMed that are -- that relate to the
11 topic at hand, but that are not necessarily in the
12 declaration, just in the course of being interested
13 in things.

09:17:48

09:17:56

09:18:01

09:18:05

09:18:07

14 Q Do you remember what they were?

09:18:08

15 A No. There's too long of a time and too
16 much.

09:18:08

09:18:12

17 Q Is it fair to say that because you did not
18 include those abstracts in your declaration you did
19 not find them important for making your conclusions
20 that are described in your declaration?

09:18:12

09:18:16

09:18:20

09:18:26

21 A I'm not sure that's fair to say. They may
22 have made redundant points that are covered by other

09:18:30

09:18:32

1 exhibits that are -- that I used in the declaration.

09:18:38

2 So to wit, if one paper I used in the
3 declaration said gallium-68 is a good PET imaging
4 agent, I have looked at other papers that also say
5 gallium-68 is a good radionuclide that I would not
6 have felt compelled to put in the declaration
7 because it is a redundant point.

09:18:46

09:18:50

09:18:56

09:18:59

09:19:03

09:19:06

8 Q So let me make sure I understand. The only
9 reason you would not have included a reference in
10 your declaration is because it provided information
11 that is already found in something -- some other
12 reference that is cited in your declaration,
13 correct?

09:19:09

09:19:12

09:19:16

09:19:21

09:19:26

09:19:28

14 A Or if I read the paper after the
15 declaration was finalized.

09:19:28

09:19:32

16 Q Were there documents -- were there papers
17 that you read after the declaration was finalized
18 that you would deem to be important for your
19 opinion?

09:19:36

09:19:38

09:19:42

09:19:47

20 A None that I can think of right here and
21 now.

09:19:50

09:19:52

22 Q Okay. So we already discussed that you

09:19:59

1	have your declaration in front of you. This is a	09:20:05
2	declaration that you submitted in case	09:20:09
3	PGR2025-00059, correct?	09:20:16
4	A Correct.	09:20:18
5	Q I'm going to refer to this case as, like,	09:20:18
6	"this case" or, "these proceedings."	09:20:22
7	Will you understand that I'm talking about	09:20:25
8	the case PGR2025-00059?	09:20:26
9	A I understand.	09:20:31
10	Q And the patent that is involved in this	09:20:34
11	case is U.S. Patent No. 12,115,233, correct?	09:20:36
12	A Correct.	09:20:42
13	Q And I'm going to refer to this as the '233	09:20:43
14	patent or the challenged patent, and will you	09:20:47
15	understand that that's the patent I'm referring to?	09:20:50
16	A Sure.	09:20:54
17	Q Now, if you could just turn to page 215 of	09:20:59
18	your declaration, please.	09:21:02
19	A (Witness complied.)	09:21:27
20	Q It is signed and dated on July 13th, 2025,	09:21:27
21	correct?	09:21:31
22	A 7/13/2025, yes.	09:21:33

1	Q	And that is your signature on this page?	09:21:37
2	A	That is my signature.	09:21:39
3	Q	And all opinions that you're offering today	09:21:43
4		are contained in this declaration, correct?	09:21:46
5	A	The declaration represents my opinions on	09:21:51
6		this issue, but you might ask me a question in which	09:21:54
7		I express an opinion that is not contained in this,	09:21:59
8		so I can't forecast that all my opinions expressed	09:22:02
9		today will be contained in this. But the	09:22:06
10		declaration contains my opinions.	09:22:08
11	Q	I understand.	09:22:10
12		When were you first approached to provide	09:22:18
13		testimony in this case?	09:22:21
14	A	It's a long time ago, but either late --	09:22:30
15		very late 2024 or early 2025.	09:22:32
16	Q	And who approached you?	09:22:37
17	A	Again, it's a long time ago, but I think	09:22:39
18		Jeff Kushan.	09:22:44
19	Q	Okay. Counsel for GE, correct?	09:22:45
20	A	No (indicating.)	09:22:49
21	Q	Counsel for GE.	09:22:50
22	A	Oh, yes.	09:22:51

1	Q	How long did you spend preparing your	09:22:52
2		declaration, Doctor?	09:22:59
3	A	It was prepared over several months. From	09:23:06
4		the initial discussions up until July 13th, 2025,	09:23:10
5		and -- do you mean in terms of the time frame or	09:23:18
6		number of hours?	09:23:21
7	Q	Number of hours, please.	09:23:22
8	A	Between 50 and a hundred.	09:23:34
9	Q	Did you perform any literature searches in	09:23:37
10		preparing your declaration?	09:23:42
11	A	Yes.	09:23:43
12	Q	What did you search?	09:23:43
13	A	I can't remember every single one of my	09:23:47
14		literature searches, obviously, but, presumably, I	09:23:50
15		would have searched, gating the search to the	09:23:57
16		pre-2017 period, fibroblast activation protein, FAP,	09:24:02
17		FAP inhibitor, PET imaging, SPECT imaging, optical	09:24:09
18		imaging, in vitro optical imaging. Terms generally	09:24:17
19		like that.	09:24:26
20		But, again, I can't possibly remember every	09:24:27
21		single literature search I've ever done.	09:24:29
22	Q	Okay. So sitting here today, these are the	09:24:34

1	terms that you remember, but there may have been	09:24:37
2	others; is that correct?	09:24:39
3	A There were surely others; I just can't	09:24:40
4	remember them.	09:24:43
5	Q Okay. Besides counsel, did you communicate	09:24:58
6	with anyone in order to prepare your declaration?	09:25:01
7	A No.	09:25:07
8	Q Your current rate is \$900 per hour,	09:25:11
9	correct?	09:25:13
10	A Yes.	09:25:15
11	Q How much have you billed so far in this	09:25:16
12	case?	09:25:22
13	A I can't tell you exactly because I don't	09:25:22
14	have my invoicing software in front of me, but in	09:25:24
15	light of the previous question you asked, that was	09:25:31
16	between 50 and a hundred hours and 50 a hundred	09:25:36
17	hours, presumably between 100 total times \$900 an	09:25:39
18	hour -- I'm not good at mental math -- and 200 times	09:25:45
19	\$900 an hour, so somewhere in there.	09:25:50
20	Q Okay. And are you owed any additional	09:25:55
21	money for this case?	09:25:58
22	A Meaning have every open invoice been paid?	09:26:04

1	Q	That is correct.	09:26:06
2	A	There are open invoices that have not yet	09:26:08
3		been paid.	09:26:10
4	Q	Have you or your laboratory ever received	09:26:13
5		any other compensation from GE or any GE-related	09:26:17
6		entity?	09:26:21
7	A	No, although GE is a massive company. I --	09:26:25
8		I can't -- at some point, a GE rep might have walked	09:26:30
9		through and given a pen to somebody for a PET	09:26:36
10		imaging machine, but, no, nothing -- nothing, to my	09:26:38
11		knowledge.	09:26:42
12	Q	Outside of your work on this PGR and	09:26:45
13		related cases, because I know you're also	09:26:48
14		involved -- you're also an expert in a related case,	09:26:55
15		so outside of your work with this Johns Hopkins'	09:26:58
16		patent family, have you ever communicated with	09:27:03
17		anyone at GE or affiliates?	09:27:05
18	A	I'm pausing because nothing substantive,	09:27:23
19		but the PET scanner at Sloan Kettering is made by	09:27:26
20		GE. So I may have called technical assistance a	09:27:32
21		decade ago when I was the one operating the PET	09:27:36
22		scanner to ask, and I think, maybe 15 years ago, I	09:27:39

1 gave a lecture outside London for GE for their
2 healthcare division, but I don't remember
3 specifically that it was GE. It might have been a
4 similarly blue-logoed medical tech company. I just
5 don't remember. I give so many lectures that it's
6 hard to remember.

7 But, no, nothing -- nothing recently.
8 Nothing within the last decade.

9 Q Okay. Do you remember if you were paid for
10 that lecture that you referred to?

11 A Oh, definitely not. No.

12 Q Do you have an ownership share in GE?

13 A A mutual fund that I own may have a small
14 ownership share in GE, but I own no securities on an
15 independent basis in GE.

16 Q And is your compensation here contingent on
17 the outcome of these proceedings?

18 A No. I am being compensated to give my
19 scientific opinion.

20 Q So let's talk about your scientific
21 opinion.

22 In your declaration, you provided opinions

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09:29:07

09:29:09

1 on patentability of the claims of the '233 patent,
2 and, specifically, you provided opinions regarding
3 obviousness of the patent claims, and my question
4 for you is: In assessing obviousness, what did you
5 analyze first?

6 A The exact temporal ordering of what I
7 analyzed first is hard to remember, given that it
8 was a long time ago, but the overarching conclusion
9 was that the claims were obvious. I mean, we can go
10 to --

11 Q We can go to your declaration in a minute.
12 I'm just curious about your methodology that you
13 applied here.

14 So you were approached by Sidley counsel,
15 given the patent, presumably. So my question for
16 you is: How did you start assessing obviousness of
17 the claims at issue here?

18 A I was not given the patent to start.

19 Q What --

20 A The first -- the first thing, independent
21 of the patent, never having seen the patent, was an
22 analysis of FAP-targeting pharmacophores, and based

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1 on the literature present that a skilled artisan 09:30:48
2 would have had access to in 2017, what -- which 09:30:51
3 FAP-targeted pharmacophores would that POSA or 09:30:59
4 person of ordinary skill in the art -- is it okay if 09:31:04
5 I use that abbreviation? 09:31:07

6 Q As long as you understand what that means. 09:31:09

7 A Yes, I do understand what that means. 09:31:11

8 A skilled artisan or POSA, given what they 09:31:13
9 would have known in 2017, would have referred to the 09:31:17
10 Jansen paper -- would have referred to a collection 09:31:25
11 of, really, three documents: A Jansen 2014 paper, a 09:31:28
12 Meletta paper, and the extension of the Meletta 09:31:36
13 paper, US-633, and would have -- it would have been 09:31:40
14 obvious to use -- to develop FAP-targeting 09:31:43
15 radiopharmaceuticals. And then, within the Jansen 09:31:51
16 paper, an analysis of the Jansen paper would have 09:31:53
17 delineated compound 60 in the Jansen paper as the 09:31:56
18 most promising choice. 09:31:59

19 Q Okay. Did counsel provide you with these 09:32:01
20 three papers: Jansen 2014, Meletta, and the US-633? 09:32:05

21 A I and a POSA would have found -- did find 09:32:12
22 Jansen 2014, the Meletta paper, and US-633. I don't 09:32:17

1 remember, especially vis-~~?~~-vis US-633 -- I would
2 have downloaded or I did download Jansen '14 and
3 Meletta.

4 I don't remember the exact file transfer
5 with regard to US-633, but they would have been
6 plainly obvious to look into for a skilled artisan
7 in 2017.

8 Q And how did you zero in on these three
9 papers?

10 A A -- how did I -- okay.

11 So I did this because -- thinking about --
12 thinking within the framework of a skilled artisan
13 in 2017 trying to develop a new FAP-targeted
14 radiopharmaceutical or thinking about FAP-targeted
15 radiopharmaceuticals in general, the Meletta paper
16 and other literature at the time, and a person -- a
17 skilled artisan at that time would have known that
18 FAP was a very enticing target for optical nuclear
19 imaging.

20 So a skilled artisan would have known that
21 FAP is an enticing target. The Meletta paper lays
22 out one potential FAP-targeting radiotracer -- I can

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1 tell you its exact name. I think MIP-1232 -- and

09:33:47

2 concludes that it was insufficiently selective.

09:33:55

3 So I or a skilled artisan would have

09:34:01

4 thought, okay. FAP is a great target. The Meletta

09:34:02

5 paper says that it's still a great target but not

09:34:08

6 selective enough and would have looked for more

09:34:13

7 selective pharmacophores, and that would have led a

09:34:16

8 search for more selective pharmacophores by a

09:34:21

9 skilled artisan in 2017, would have led, as the best

09:34:25

10 reference, to the 2014 paper from Jansen. And then

09:34:28

11 they'd go from there.

09:34:32

12 Q How did you know what -- what the level of

09:34:34

13 skill in this art is if you had not seen the patent,

09:34:35

14 Doctor?

09:34:39

15 A Can you please ask the question again? The

09:34:44

16 level of skill in the art?

09:34:46

17 Q Sure.

09:34:47

18 So you keep talking about what a POSA would

09:34:47

19 have done --

09:34:50

20 A Mm-hmm.

09:34:50

21 Q -- and what references a POSA would have

09:34:50

22 found and how a POSA would have gone about selecting

09:34:53

1 a FAP-imaging agent or preparing a FAP-imaging
2 agent, but you had also testified that you had not
3 seen the patent when you were doing this analysis
4 and when you were researching papers.

5 So my question for you is --

6 A Which patent do you mean? I'm sorry. I
7 interrupted.

8 Q I'm talking about the challenged patent
9 here, the '233 patent.

10 So my question for you here is: How did
11 you know what the level of skill in the art is here,
12 i.e., who is a POSA here, if you never saw the
13 patent before you started your analysis?

14 A Okay. A -- well, counsel explained to me
15 what a POSA is, and so that we're all on the same
16 page, I can read it.

17 So paragraph 21 of the declaration: "I
18 have been informed that one requirement for
19 patentability is that an invention must not have
20 been obvious to a person of ordinary skill in the
21 art in view" -- "in view of what was known in the
22 prior art before the filing date of the patent. I

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1 also have been informed that if a patent claim
2 encompasses a compound that would have been obvious
3 in light of the prior art, that claim is
4 unpatentable."

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09:36:43

5 Oh, that's not the one.

09:36:45

6 Oh, here we go. I'm sorry.

09:36:46

7 Q That's okay.

09:36:48

8 A Paragraph 12.

09:36:49

9 Ah, paragraph 15: "I have been informed by
10 counsel that a person of ordinary skill in the art
11 is a hypothetical person who is presumed to have the
12 typical skills and knowledge of someone working in
13 the field of the invention. Based on my review of
14 the patent and my experience, I believe a person of
15 ordinary skill in the art (who I may refer to as 'a
16 skilled artisan') would have had an undergraduate
17 degree and a Ph.D. in chemistry, biochemistry,
18 medicinal chemistry or a comparable field. The
19 person would have had experience with and/or
20 knowledge of chemical synthesis methods...assessment
21 of cellular targets for" --

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09:37:28

22 THE COURT REPORTER: I'm sorry. "Knowledge

09:37:30

1	of"? You're reading a little too fast.	09:37:31
2	THE WITNESS: -- "chemical synthesis	09:37:33
3	methods (e.g., organic synthesis, radiometal	09:37:37
4	chelation, and radiohalogen labeling of prosthetic	09:37:42
5	groups), assessment of cellular targets for	09:37:46
6	radiopharmaceuticals, and other techniques used in	09:37:50
7	the design, development, testing, and/or evaluation	09:37:53
8	of radiopharmaceuticals. The person" also -- "would	09:37:58
9	also be familiar with how radiopharmaceuticals are	09:38:02
10	distributed and used in patients to perform therapy	09:38:05
11	or nuclear imaging of diseases, including cancer."	09:38:08
12	So to get back to the question, kind of	09:38:12
13	midway through that is assessment of cellular	09:38:15
14	targets for radiopharmaceuticals. So a skilled	09:38:17
15	artisan in 2017 would have been well aware -- from	09:38:21
16	the literature and from conferences and just	09:38:26
17	generally being part of the field -- that FAP was a	09:38:32
18	very promising target in -- for optical imaging and	09:38:35
19	nuclear imaging.	09:38:42
20	BY DR. PARTINGTON:	09:38:43
21	Q Thank you, Doctor. However, that was not	09:38:43
22	my question.	09:38:45

1	A	Okay.	09:38:46
2	Q	My question was: How did you determine	09:38:46
3		what the skill of the art is here without reviewing	09:38:50
4		the patent?	09:38:55
5		You have testified a few minutes ago that	09:39:00
6		counsel informed you what a POSA here is --	09:39:01
7	A	Mm-hmm.	09:39:01
8	Q	-- and then you read in a paragraph from	09:39:04
9		your declaration where you clearly state: "Based on	09:39:05
10		my review of the patent and my experience..."	09:39:10
11		So which one is it, Doctor? Did you review	09:39:13
12		the patent and then you conducted your analysis	09:39:16
13		or -- and determined what a skilled POSA is, or did	09:39:20
14		counsel inform you what a POSA is, you did analysis	09:39:24
15		without looking at the patent, and then you provided	09:39:31
16		your declaration?	09:39:34
17	MR. KUSHAN:	Objection to form. Also	09:39:35
18		objection to foundation.	09:39:37
19	THE WITNESS:	There was a lot of questions	09:39:40
20		within that question. Could you please ask them	09:39:42
21		individually?	09:39:43
22	BY DR. PARTINGTON:		09:39:43

1	Q	You testified here today that counsel	09:39:55
2		informed you what a POSA is, correct?	09:40:00
3	A	Yes. That is in the declaration.	09:40:04
4	Q	What is in the declaration, however, is the	09:40:07
5		following quote: "Based on my review of the patent	09:40:12
6		and my experience, I believe a person of ordinary	09:40:16
7		skill in the art (who I may refer to as 'a skilled	09:40:20
8		artisan') would have had an undergraduate degree..."	09:40:25
9		and so forth. I'm not going to read the whole	09:40:29
10		thing.	09:40:32
11	A	Mm-hmm.	09:40:32
12	Q	Did you yourself analyze what a POSA is	09:40:33
13		here, or did counsel tell you what a POSA is?	09:40:40
14	A	My opinions are represented in this	09:40:51
15		paragraph. This paragraph -- this paragraph and	09:40:52
16		this declaration represent the lump sum of every --	09:40:59
17		all of the opinions I've formed up until -- sorry.	09:41:01
18		Let me check -- July 13th, 2025.	09:41:07
19		Your question before -- so, yes, between	09:41:13
20		the start of all of this and July 13th, 2025, I read	09:41:18
21		the '233 patent. And given that this declaration	09:41:25
22		represents the -- my opinions on the lump sum of	09:41:32

1 everything I learned, reading the patent happened 09:41:35
2 before finalizing this declaration. 09:41:38

3 But the question you asked before was: 09:41:42
4 "Did you read the patent before you conducted the 09:41:45
5 analysis of obviousness," and, no. My assessment of 09:41:48
6 the obviousness of the claims was started with 09:41:59
7 reading Jansen 2014, Meletta, et cetera, prior to 09:42:07
8 having read the '233 patent. 09:42:12

9 Q Okay. Doctor, we're going in circles here. 09:42:17
10 We've already gone through all of this, and I've 09:42:20
11 asked you -- you've already given this testimony, 09:42:22
12 and I've asked you, "How did you zero in on Jansen, 09:42:25
13 Meletta, and 633," and your answer was, "Well, this 09:42:30
14 what is a POSA would have done," and I said, "How 09:42:33
15 did you determine what a POSA is without looking at 09:42:36
16 the patent." Your testimony was, "Counsel told me 09:42:38
17 what a POSA is." 09:42:40

18 So you see how we've come to a circle here? 09:42:42

19 A Uh-huh. 09:42:45

20 Q So I'm just trying to understand. How did 09:42:46
21 you conduct your obviousness analysis? Please walk 09:42:48
22 me through it. 09:42:52

1	A	Okay. I'll walk you through it again.	09:42:54
2	Q	Great.	09:42:57
3	A	So without having seen the '233 patent, I	09:42:58
4		thought -- and I thought, if I'm in 2017 and I'm	09:43:05
5		interested in FAP-targeting imaging agents, what	09:43:10
6		would I do? Nuclear imaging agents, optical imaging	09:43:15
7		agents, in vivo imaging agents, in vitro imaging	09:43:20
8		agents. And me in 2017, but also a skilled artisan	09:43:25
9		in 2017 would have known that FAP was an enticing	09:43:28
10		target for nuclear imaging.	09:43:37
11	Q	And how did you know what a skilled artisan	09:43:39
12		is in this field without looking at the patent?	09:43:44
13	A	Because the definition of a skilled artisan	09:43:48
14		in radiopharmaceutical chemistry is -- does not	09:43:53
15		contain anything within the patent.	09:43:59
16		A skilled artisan in radiopharmaceutical	09:44:02
17		chemistry is someone with: "...an undergraduate	09:44:05
18		degree and a Ph.D. in chemistry, biochemistry,	09:44:10
19		medicinal chemistry or a comparable field. The	09:44:16
20		person would have had experience with and/or	09:44:18
21		knowledge of chemical synthesis methods...assessment	09:44:20
22		of cellular targets for radiopharmaceuticals, and	09:44:22

1 other techniques used in the design, development,
2 testing and/or evaluation of radiopharmaceuticals.
3 The person would" have always -- "also been familiar
4 with" radiopharmaceutical -- "how
5 radiopharmaceuticals are distributed and used in
6 patients to perform therapy or nuclear imaging
7 diseases, including cancer."

8 None of -- that understanding, what a
9 skilled artisan in molecular imaging would have been
10 in 2017, does not require any knowledge of the '233
11 patent.

12 Q Do you have an understanding of how a
13 person of ordinary skill in the art is determined?

14 A I understand, as represented here in
15 paragraph 15, what a person of ordinary skill in the
16 art is. I describe that in paragraph 15.

17 How that benchmark is created, I'm not sure
18 I understand what you mean by the process by which
19 definition of a skilled artisan. I understand the
20 definition of the term, as I lay out in -- in
21 paragraph 15.

22 Q And where -- how did you determine that

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09:45:04
09:45:04
09:45:09
09:45:14
09:45:17
09:45:24
09:45:31
09:45:42
09:45:44
09:45:46
09:45:50
09:45:50

1 definition as you laid out it in paragraph 15?

09:45:54

2 A By thinking about what my definition of a
3 skilled artisan in molecular imaging chemistry would
4 have been in 2017, what would a skilled artisan know
5 about? They would know about these things.

09:46:00

09:46:06

09:46:11

09:46:15

6 Q So fair to say you did not consider
7 educational level and specialty of the inventors,
8 correct?

09:46:19

09:46:22

09:46:26

9 MR. KUSHAN: Objection. Foundation.

09:46:27

10 THE WITNESS: My definition -- no. My
11 opinion on what a skilled artisan is, is here and
12 doesn't refer to any of what you just mentioned.
13 The definition of what a skilled artisan is, as I
14 understand it, is in paragraph 15.

09:46:35

09:46:39

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09:46:54

15 BY DR. PARTINGTON:

09:46:56

16 Q And you proffered this definition in
17 paragraph 15 without reviewing the patent, correct?

09:47:34

09:47:41

18 MR. KUSHAN: Objection. Foundation.

09:47:44

19 THE WITNESS: The paragraph 15 is included
20 in the declaration which was written -- which was
21 finalized on July 13th, 2025. Between when all this
22 started and when this declaration was finalized, I

09:47:50

09:47:52

09:47:57

09:48:10

1 had read the patent, as I explained to you when I

09:48:17

2 said I read all of the exhibits for this.

09:48:21

3 BY DR. PARTINGTON:

09:48:23

4 Q But not before you identified Jansen 2014,
5 Meletta, and US-633, correct?

09:48:23

09:48:27

6 A I identified those as part of my analysis
7 of obviousness prior to reading the patent in
8 question, '233.

09:48:29

09:48:32

09:48:37

9 Q What were you tasked with doing that --
10 what -- strike that.

09:49:06

09:49:09

11 What were you tasked with doing that led
12 you to identify these references?

09:49:11

09:49:15

13 A I don't remember the specific directive
14 because, again, it's quite a long time ago. But,
15 generally speaking, tasked with deciding how I, in
16 2017, would have approached making a FAP-targeted
17 molecular imaging agent in light of the literature
18 available to me in 2017.

09:49:25

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09:49:41

09:49:50

09:49:53

19 Q So in assessing obviousness, you believe
20 that the problem facing a person of ordinary skill
21 in the art was the design of FAP-targeting radio for
22 tumor imaging, correct?

09:50:03

09:50:05

09:50:08

09:50:15

1	MR. KUSHAN: Objection. Foundation.	09:50:17
2	THE WITNESS: No. All -- the question was	09:50:19
3	molecular imaging agents that could be -- molecular	09:50:25
4	imaging, in vivo imaging, in vitro imaging, optical	09:50:32
5	imaging, PET imaging. Also, potentially,	09:50:38
6	radiotherapy, SPECT imaging, all of these molecular	09:50:40
7	imaging and therapy areas.	09:50:45
8	BY DR. PARTINGTON:	09:50:45
9	Q Okay. And so you've mentioned, multiple	09:50:51
10	times now, Jansen 2014, Meletta, and US-633.	09:50:53
11	A Mm-hmm.	09:50:53
12	Q Were there additional references you	09:50:57
13	considered beyond these three references?	09:50:59
14	A Those are the primary references from which	09:51:03
15	the argument flows, but I did read other papers,	09:51:09
16	yes.	09:51:12
17	Q Which papers, Doctor?	09:51:18
18	A At the minimum, the exhibits cited during	09:51:22
19	the discussion in the declaration.	09:51:26
20	Q And at the maximum?	09:51:31
21	A Papers that I looked at and read as I was	09:51:35
22	searching for the papers that are in the	09:51:38

1 declaration.

09:51:41

2 Q And to the extent that you found any papers
3 but did not include them in your declaration, those
4 papers were not important for your opinion in this
5 declaration, correct?

09:51:44

09:51:47

09:51:50

09:51:56

6 A No, not not important, but created a point
7 that might have been redundant, given other papers
8 cited in the declaration.

09:51:57

09:52:03

09:52:08

9 Q At the time you offered your obviousness
10 opinion regarding the claims of the '233 patent, you
11 did not understand that evidence of copying by
12 others can be relevant in that obviousness, correct?

09:52:16

09:52:18

09:52:23

09:52:26

13 MR. KUSHAN: Objection. Foundation. Also
14 objection to form.

09:52:32

09:52:33

15 THE WITNESS: It seems like there might
16 have even been a double negative in that question.

09:52:34

09:52:37

17 Could you simplify it for me? It was a
18 little long, and I have trouble understanding what
19 to answer.

09:52:40

09:52:43

09:52:44

20 BY DR. PARTINGTON:

09:52:47

21 Q When you prepared -- strike that.

09:52:47

22 Before concluding obviousness, you did not

09:52:51

1 have an understanding that evidence of copying by
2 others is relevant to obviousness analysis, correct?

3 A I'm having trouble with your
4 phrase "evidence of copying." What do you mean by
5 that?

6 I mean, copying could mean, like, Xeroxing,
7 like -- like -- and, again, I don't think you mean
8 Xeroxing, but I'm having trouble understanding that
9 particular word in the context of the question.

10 Q Do you have an understanding of copying in
11 the context of obviousness?

12 A Again, the word "copying" is giving me
13 trouble in that question. Is there a different way
14 you could phrase it so that I understand it better?

15 Q In forming your obviousness opinion
16 regarding the '233 patent, did you inquire whether
17 there was any evidence that others copied the
18 invention claimed in the '233 patent?

19 A I still don't understand exactly what you
20 mean by "copied." It's -- it isn't a word that
21 we -- that I use in the declaration, and it has
22 several meanings. So if there's a synonym or

09:52:58

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09:54:03

09:54:09

09:54:12

09:54:22

09:54:28

1	something else you could use so that I make sure	09:54:34
2	that I can be precise in my language, I would	09:54:36
3	appreciate it.	09:54:39
4	Q So based on your answers, you do not,	09:54:39
5	sitting here today, have an understanding of what	09:54:55
6	evidence of copying by others is and how it can be	09:54:57
7	relevant to obviousness analysis, correct?	09:55:01
8	A My opinion is --	09:55:04
9	MR. KUSHAN: Objection to form and also	09:55:07
10	objection to foundation.	09:55:08
11	THE WITNESS: My opinion is not -- has	09:55:09
12	no -- what I'm answering here doesn't have anything	09:55:14
13	to do with my understanding of the concept. It's	09:55:16
14	having to do with the -- your use of the	09:55:19
15	word "copying," and I would prefer you to use a	09:55:23
16	different word that -- because, in the context of	09:55:26
17	what we're talking about, I'm unclear what you mean	09:55:30
18	by "copying."	09:55:32
19	BY DR. PARTINGTON:	09:55:34
20	Q Okay.	09:55:34
21	A Because there's many meanings of the	09:55:34
22	word "copying."	09:55:37

1 Q I understand that.

09:55:38

2 When somebody makes a duplicate of the
3 invention, somebody takes the invention disclosed
4 and makes a duplicate of it, that's what I mean by
5 copying.

09:55:39

09:55:41

09:55:45

09:55:54

6 So my question -- does that clarify it for
7 you?

09:55:55

09:55:57

8 A Not really. My opinion is that the claims
9 in '233 -- and the opinion is laid out here in a way
10 that does not use, to my remembering, the
11 word "copying," the claims in '233 would have been
12 obvious -- are obvious.

09:56:00

09:56:07

09:56:13

09:56:19

09:56:26

13 Q Okay. Did you make any investigation into
14 the following: Whether a third party looked at the
15 '233 patent, looked at the claims of the '233
16 patent, and made a duplicate of the invention
17 disclosed in the '233 patent? So let me repeat that
18 slowly.

09:56:27

09:56:31

09:56:34

09:56:37

09:56:41

09:56:48

19 Did you make any investigation into whether
20 a third party looked at the '233 patent, looked at
21 the claims of the '233 patent, and made a duplicate
22 of the invention disclosed in the '233 patent?

09:56:49

09:56:54

09:56:59

09:57:04

1	A	All of my investigations for this	09:57:11
2		declaration would have pertained to the pre-2017	09:57:15
3		period. What you're describing would have	09:57:22
4		necessarily had to take place after the 2017 period.	09:57:26
5		All my investigations/thought process happened in	09:57:30
6		the pre-2017 period.	09:57:36
7	Q	So that's a no to my question, correct?	09:57:38
8	A	I still don't quite understand your	09:57:42
9		question, but suffice to say, everything represented	09:57:43
10		in here pertains to the pre-2017 period.	09:57:48
11	Q	So then by the same token, you did not	09:57:53
12		conduct any investigation into whether the '233	09:57:57
13		patent was licensed to any third party --	09:58:00
14		correct? -- before concluding obviousness?	09:58:03
15	A	I do not know whether '233 was licensed to	09:58:09
16		anyone.	09:58:13
17	Q	Okay.	09:58:13
18		So I think we've been going for about an	09:58:14
19		hour. Is that a good time to take a break?	09:58:16
20	A	Sure.	09:58:21
21		(Recessed at 9:58 a.m.)	09:58:22
22		(Reconvened at 10:15 a.m.)	10:15:46

1	BY DR. PARTINGTON:	10:15:51
2	Q Welcome back.	10:15:51
3	Doctor, you provided an opinion that the	10:15:53
4	'233 patent does not adequately describe or enable	10:15:57
5	the claimed radiopharmaceuticals.	10:16:00
6	So my question for you is: In assessing	10:16:03
7	adequacy of written description and enablement, what	10:16:08
8	did you analyze first?	10:16:15
9	A Remembering the exact sequence -- sequence	10:16:18
10	of events is hard because, again, it was a while	10:16:20
11	ago, but in terms of enablement --	10:16:26
12	Q Mm-hmm.	10:16:26
13	A -- there -- the general premise is that the	10:16:33
14	sheer number of compounds -- so, for example, in	10:16:37
15	paragraph 251, the second -- well, starting at the	10:17:11
16	beginning: "The specification provides surveys of	10:17:31
17	possible choices for radiolabeled prosthetic groups,	10:17:33
18	chelators and optical imaging components as well as	10:17:38
19	a tremendous number of possible linker structures.	10:17:41
20	The number of possible B-L-A combinations from these	10:17:43
21	large sets of...'B' and 'L' components is enormous	10:17:48
22	(~greater than 10 to the 27th to 10 to the 36th	10:17:52

1 different possible combinations.)"

10:17:56

2 So with respect to enablement, an undue
3 amount of experimentation would be needed to figure
4 out -- to make all those compounds and to figure out
5 whether they -- and to use them for optical or
6 nuclear imaging.

10:17:58

10:18:00

10:18:02

10:18:08

10:18:14

7 Q Doctor, I'm not asking what your opinions
8 are.

10:18:14

10:18:16

9 A Okay.

10:18:16

10 Q I can -- I've read your declaration,
11 believe it or not.

10:18:17

10:18:19

12 A Okay.

10:18:19

13 Q I'm asking what methodology you used in
14 conducting your analysis.

10:18:21

10:18:23

15 MR. KUSHAN: Objection to form.

10:18:29

16 THE WITNESS: Was there a question there?

10:18:36

17 BY DR. PARTINGTON:

10:18:36

18 Q The question is: In assessing adequate
19 written description and enablement, what did you
20 analyze first?

10:18:38

10:18:41

10:18:46

21 A The temporal arrangement of the acts is too
22 far in the past for me to remember, but with respect

10:18:50

10:18:53

1 to enablement, the sheer number of compounds, I 10:18:55
2 analyzed the possibilities that would be covered by 10:19:01
3 the claims and the tremendous number, ten to the 10:19:04
4 27th and ten to the 36th, so that is what I 10:19:11
5 analyzed. 10:19:17

6 Q Anything else? 10:19:18

7 A And -- with regard to enablement? 10:19:18

8 Q Both enablement and written description. 10:19:23

9 A Okay. With respect to written description, 10:19:24
10 that centered on -- the analysis there centered on 10:19:30
11 important prosthetic groups, chelators that would 10:19:34
12 have been known to a skilled artisan at the time 10:19:38
13 that were not described in the '233 patent. 10:19:43

14 Q Okay. So with regard to enablement, did 10:19:50
15 you analyze anything else besides what you have just 10:19:53
16 testified to? 10:19:57

17 A Sure. I mean the -- I mean, for example, 10:19:58
18 what I just mentioned was the possible combinations 10:20:19
19 of B and L. 10:20:21

20 Apologize for the delay. I'm just trying 10:20:44
21 to find -- 10:20:48

22 Q Let me reask. 10:20:55

1	A	Okay.	10:20:56
2	Q	What methodology you used in conducting	10:20:57
3		your analysis on enablement?	10:20:59
4		MR. KUSHAN: Objection. Form.	10:21:08
5		THE WITNESS: There's not a specific name	10:21:19
6		of the methodology. In so doing, I looked at the	10:21:21
7		number of possible combinations. I considered	10:21:28
8		whether that was a -- making and testing all of	10:21:30
9		those compounds would have required undue	10:21:35
10		experimentation or not. There's not a name for that	10:21:40
11		process, other than having done it.	10:21:44
12		BY DR. PARTINGTON:	10:21:44
13	Q	Okay. Anything else?	10:21:51
14	A	I mean, I considered compounds that have --	10:21:52
15		I don't know if this counts as else, but I	10:22:14
16		considered compounds, for example, compounds C1 and	10:22:16
17		similar that would necessarily require testing to	10:22:22
18		see if they would function, and in order to get the	10:22:28
19		total number of -- or total putative number of	10:22:33
20		possible B-L-A compounds, I also analyzed all of the	10:22:38
21		possibilities of the pharmacophore as well.	10:22:42
22	Q	Anything else?	10:22:56

1 A I can't say that there wasn't some other 10:23:00
2 small contribution to that thought process unless I 10:23:04
3 read that entire section again right now, but that's 10:23:08
4 the general process. 10:23:11

5 Q And what methodology you used in conducting 10:23:16
6 your analysis on written description? And, again, 10:23:18
7 you don't have to give me the name. Just describe 10:23:21
8 the process, please. 10:23:24

9 A The process there was considering the -- 10:23:25
10 considering the, for example, prosthetic group and 10:23:35
11 chelator structures that are contained in the patent 10:23:43
12 and then considering the available -- well then 10:23:50
13 considering two things. Excuse me. 10:23:53

14 Considering how many are described, how 10:23:55
15 many full B-L-A sets are described in the patent and 10:24:00
16 then also considering common, well-known prosthetic 10:24:04
17 group classes and common, well-known chelator 10:24:11
18 classes that were not described in '233. 10:24:15

19 Q Anything else? 10:24:20

20 A I also discussed pairs of radionuclides and 10:24:46
21 chelators that weren't represented. 10:24:53

22 So it is -- I don't want to say nothing 10:24:59

1 else because I can't say that there's not a sentence
2 in the declaration that describes some other line of
3 thinking than the ones I've laid out, but, again,
4 what I've described is the general thought process
5 behind that analysis.

6 Q Doctor, is it your understanding that a
7 patent specification needs to redescribe things that
8 were already well-known in the art in order to
9 satisfy written description?

10 MR. KUSHAN: Objection to form.

11 THE WITNESS: I am not a lawyer, but I can
12 read to you my understanding of written description.

13 BY DR. PARTINGTON:

14 Q You don't need to read the -- I'm just
15 asking you if your understanding is that a patent
16 specification needs to describe things that were
17 already well-known in the art to satisfy written
18 description.

19 MR. KUSHAN: Objection. Form.

20 THE WITNESS: Again, I'm not a lawyer.
21 What I know is that many common prosthetic groups
22 and many common chelators were not described in the

1	'233 patent.	10:27:08
2	BY DR. PARTINGTON:	10:27:08
3	Q Okay. I'm going to hand you Exhibit 1001.	10:27:11
4	A Okay.	10:27:26
5	Q Do you recognize this document, Doctor?	10:27:32
6	A It is the challenged patent or '233.	10:27:39
7	Q When was the last time you reviewed this	10:27:47
8	patent?	10:27:49
9	A Within the last week.	10:27:54
10	Q Is this patent generally in the field of	10:28:00
11	development imaging and radiotherapeutic agents?	10:28:04
12	A The title of the patent is: "IMAGING AND	10:28:09
13	RADIOTHERAPEUTICS AGENTS TARGETING	10:28:14
14	FIBROBLAST-ACTIVATION PROTEIN..."	10:28:17
15	Q Is that a yes?	10:28:19
16	A Yes.	10:28:20
17	Q And specifically, is -- this patent is in	10:28:21
18	the field of FAP targeting imaging and	10:28:30
19	radiotherapeutic agents?	10:28:35
20	A Yes, citing the title of the patent, yes.	10:28:38
21	Q Doctor, your laboratory focuses on the	10:28:42
22	design and synthesis of radiopharmaceuticals,	10:28:44

1	correct?	10:28:47
2	A Not only that, but that's one of the things	10:28:49
3	we focus on.	10:28:51
4	Q What else do you focus on?	10:28:52
5	A We focus on developing optical imaging	10:28:54
6	agents, both for in vivo and in vitro uses.	10:28:59
7	Q Anything else?	10:29:09
8	A We've dabbled in antibody drug conjugates,	10:29:15
9	approaches to bioconjugation, radiosynthetic	10:29:19
10	chemistry, synthetic chemistry, inorganic chemistry.	10:29:24
11	The focus is molecular imaging and therapy.	10:29:31
12	Q I'm going to ask you this question, and	10:29:42
13	forgive me if this is an inane question, but are	10:29:48
14	radiopharmaceuticals the same -- is it the same term	10:29:52
15	as saying imaging and therapy agents?	10:29:54
16	A Not necessarily. Imaging agents can	10:30:04
17	encompass nuclear imaging, but also things like	10:30:07
18	optical imaging.	10:30:12
19	Q Mm-hmm.	10:30:12
20	A So radiopharmaceuticals, as a term,	10:30:14
21	generally encompasses nuclear imaging agents and	10:30:17
22	radiotherapeutics.	10:30:27

1	Q	I'm trying to figure out which term I	10:30:28
2		should use so that we all understand we're on the	10:30:32
3		same page.	10:30:36
4		If I use the term "radiopharmaceuticals"	10:30:36
5		generally, as I'm asking you questions, is that	10:30:38
6		sufficient for you to understand that I'm ask --	10:30:43
7		well, strike that.	10:30:47
8		So the patent is related to imaging and	10:30:48
9		radiotherapeutic agents, correct?	10:31:00
10	A	Mm-hmm.	10:31:01
11	Q	Is radiopharmaceutical a generic name for	10:31:06
12		this or no?	10:31:09
13	A	No.	10:31:10
14	Q	And you said that your laboratory focuses	10:31:27
15		on molecular imaging and therapy?	10:31:30
16	A	Mm-hmm.	10:31:33
17	Q	Does your laboratory focus on design and	10:31:33
18		synthesis of radiopharmaceuticals?	10:31:39
19	A	That's one of the things my lab does, but	10:31:40
20		we do other imaging agent work that is not	10:31:44
21		radioactivity based.	10:31:48
22	Q	Which is optical imaging that you	10:31:49

1	mentioned, correct?	10:31:51
2	A Which is the optical.	10:31:52
3	Q Okay.	10:31:53
4	A There are other ones also, but for us it's	10:31:54
5	optical.	10:31:56
6	Q Got it.	10:31:56
7	And the radiopharmaceuticals that you are	10:31:57
8	studying, they are primarily biological constructs,	10:32:01
9	not traditional small molecules, correct?	10:32:06
10	A Primarily biologics, but we also have done	10:32:28
11	a good deal of work in small molecules over the	10:32:33
12	years as well.	10:32:40
13	Q A good deal of work with small molecules in	10:32:44
14	the arena of radiopharmaceuticals?	10:32:47
15	A Yes.	10:32:53
16	Q Did you publish your work on	10:33:03
17	radiopharmaceuticals related to small molecules?	10:33:06
18	A Yeah.	10:33:09
19	Q Are those publications in your CV?	10:33:11
20	A Yes.	10:33:13
21	Q Can we look at of them, please?	10:33:14
22	A Sure.	10:33:19

1	Q	Can you just point me to some of them?	10:33:19
2	A	How would you like me to do this?	10:33:34
3	Q	Just give me a few examples. I just want	10:33:36
4		to see what they are.	10:33:39
5	A	Sure. I'll just work back -- start back in	10:33:40
6		time and move forward.	10:33:49
7		List No. 100 is a small molecule.	10:33:53
8	Q	Okay.	10:34:02
9	A	98 involved making a small molecule	10:34:06
10		chelator complex. Oh, sorry. 102 involved small	10:34:09
11		molecules. 94 involved small radiolabeled	10:34:14
12		molecules. 92 involved making a radiolabeled	10:34:22
13		chelator small molecule.	10:34:25
14	Q	I'm sorry. You said 92?	10:34:26
15	A	92. 91 covered some small molecules. 87	10:34:28
16		was a small molecule.	10:34:43
17	Q	I'm sorry. Quick question. 91 is a review	10:34:44
18		paper?	10:34:47
19	A	91's a review paper, but it discusses small	10:34:47
20		molecules.	10:34:51
21	Q	I know. I just want to confirm.	10:34:51
22	A	85 is a small molecule. 81 involved	10:34:54

1	radiolabeled small molecules and biologics. 79	10:35:04
2	involved radiolabeled small molecules and biologics.	10:35:13
3	76 involved radiolabeled small molecules and	10:35:20
4	biologics. 71 involved radiolabeled small molecules	10:35:28
5	and biologics.	10:35:37
6	Q Okay. I think I get the --	10:35:39
7	A 70 involved --	10:35:41
8	Q I get the idea. Thank you.	10:35:42
9	Have you ever personally developed or	10:35:44
10	tested a radioimmunoconjugate -- I'm sorry --	10:35:48
11	radiopharmaceutical --	10:35:58
12	A Mm-hmm.	10:35:58
13	Q -- that targets fibroblast activation	10:35:58
14	protein, FAP?	10:36:02
15	A No.	10:36:05
16	Q Has your lab developed or tested	10:36:23
17	radiopharmaceutical agents that target FAP?	10:36:27
18	A No.	10:36:41
19	Q You do a lot of research that involved	10:36:44
20	radioimmunoconjugates, correct?	10:36:49
21	A Yes.	10:36:52
22	Q And radioimmunoconjugate involves	10:36:56

1	conjugating an antibody to a radionuclide, correct?	10:37:00
2	A Strictly speaking, sort of. It involves	10:37:07
3	finding ways to attach either chelators, prosthetic	10:37:10
4	groups to antibodies and then radiolabeling those or	10:37:17
5	preinstalling them radiolabeled. But, yes, it	10:37:21
6	involves attaching radioactivity, prosthetic groups	10:37:24
7	and chelators, to antibodies --	10:37:28
8	Q Okay.	10:37:31
9	A -- or antibody fragments.	10:37:32
10	Q Okay.	10:37:35
11	Your lab uses antibodies because they	10:37:39
12	provide high affinity and high specificity for their	10:37:42
13	targets, correct?	10:37:45
14	A That is one of the reasons my lab uses	10:37:46
15	antibodies.	10:37:50
16	Q What are some other reasons why your lab	10:37:54
17	uses antibodies?	10:37:56
18	A There are epitopes of biomarkers that are	10:37:57
19	typically only bound via antibodies.	10:38:04
20	Q I see. Anything else -- any other reasons	10:38:13
21	were there?	10:38:19
22	A That's the primary one. There are probably	10:38:28

1 others, but that's probably the -- that's the
2 primary one.

3 Q Affinity and specificity are particularly
4 valuable in cancer imaging and therapy, correct?
5 Strike that. Let me rephrase. That was a bad
6 question.

7 Affinity and specificity of imaging agents
8 are particularly valuable in cancer imaging and
9 therapy, correct?

10 A Well, affinity and specificity of an
11 imaging agent is invaluable for therapy, which was
12 what -- if I said, "correct," to your question, I
13 would have said, "correct," to that sentence, which
14 is not correct.

15 Q Let me clarify the record.

16 A I'm sorry.

17 Q It was not a good question.

18 Is affinity and specificity particularly
19 valuable in cancer imaging?

20 MR. KUSHAN: Objection. Form.

21 THE WITNESS: In vitro or in vivo imaging?

22 BY DR. PARTINGTON:

1	Q	In vivo imaging.	10:39:32
2	A	For in vivo imaging and for in vitro	10:39:35
3		imaging really, specificity is very important and	10:39:38
4		affinity is very important, but those are not the	10:39:43
5		only two things that are important.	10:39:46
6	Q	And is affinity and specificity important	10:39:55
7		in cancer therapy?	10:39:59
8		MR. KUSHAN: Objection to form.	10:40:06
9		THE WITNESS: Those two things are	10:40:07
10		important. Specificity is important, and I presume	10:40:09
11		you mean targeted radiotherapy or --	10:40:14
12		BY DR. PARTINGTON:	10:40:16
13	Q	Yes.	10:40:16
14	A	In targeted radiotherapy, specificity or	10:40:18
15		selectivity is very important, and affinity is very	10:40:22
16		important. But, again, those are not the only two	10:40:27
17		important things.	10:40:30
18	Q	For cancer imaging, besides affinity and	10:40:41
19		specificity, what else is important?	10:40:45
20	A	Important in what -- for a probe? Can you	10:40:51
21		make the question a little more specific so I can be	10:40:54
22		precise?	10:40:56

1 Q Well, you said: "In targeted radiotherapy,
2 specificity or selectivity is very important, and
3 affinity is very important. But, again, those are
4 not the only two important things."

5 A Yeah.

6 Q So what do you mean by "important"?

7 A I cover that here. So on page 30 -- or
8 sorry -- paragraph 54 of my declaration -- that's
9 under subsection E -- I talk about considerations
10 influencing the development of radiopharmaceuticals
11 and optical imaging agents.

12 And so I say: "There are [sic] a number of
13 functional and practical considerations influence
14 the design of a radiopharmaceutical, particularly
15 for one intended for use in nuclear imaging. I
16 summarize these considerations below, many of which
17 also apply to optical imaging" -- and many of which
18 also apply to in vitro imaging agents.

19 So first is selectivity and affinity, as we
20 talked about. I can read that but --

21 Q You don't have to read that.

22 A Second is the stability of the probe, the

10:40:57

10:41:05

10:41:08

10:41:11

10:41:13

10:41:13

10:41:15

10:41:42

10:41:49

10:41:53

10:41:55

10:41:57

10:42:00

10:42:02

10:42:05

10:42:07

10:42:10

10:42:13

10:42:17

10:42:19

10:42:21

10:42:23

1 bioavailability of the probe is important, the 10:42:26
2 pharmacokinetic profile of the probe is important, 10:42:33
3 and the amenability to radiolabeling or the 10:42:39
4 attachment of a fluorophore is important. That's 10:42:40
5 covered in paragraphs 58 and 59, subsections A, B, 10:42:45
6 C, and D. 10:42:55

7 And then some other more logistical 10:43:02
8 concerns about the development of nuclear imaging 10:43:05
9 agents are covered starting in paragraph 60, 10:43:07
10 specifically requirements for distributing 10:43:09
11 radiopharmaceuticals, but that applies primarily to 10:43:12
12 radiopharmaceuticals and not optical imaging. 10:43:17

13 Does that answer your question? 10:43:23

14 Q Yeah, and I might come back to it later. 10:43:24
15 Thank you for that. 10:43:26

16 In general, antibodies are more specific 10:43:39
17 for their targets than small molecules, correct? 10:43:41

18 A Without a huge number of numbers in front 10:43:47
19 of me -- I also don't know what you mean by 10:43:49
20 specific. Do you mean selective for their targets? 10:43:52

21 Q Is specificity and selectivity two 10:43:55
22 different concepts? 10:43:57

1	A	They have fluxional meanings that are hard	10:44:00
2		to track down, but in this case, I think selectivity	10:44:09
3		is probably the term that I use in the declaration.	10:44:11
4		So, like, paragraph 55, selectivity and affinity.	10:44:21
5	Q	55. Okay. So selectivity then. Sorry	10:44:23
6		about that. So then let me reask the question.	10:44:29
7		In general, are antibodies more selective	10:44:38
8		for their targets than small molecules?	10:44:42
9		MR. KUSHAN: Sorry. Objection.	10:44:45
10		THE WITNESS: I can't comment --	10:44:47
11		MR. KUSHAN: Sorry. Objection.	10:44:48
12		Foundation.	10:44:50
13		Go ahead.	10:44:50
14		THE WITNESS: I can't comment upon that	10:44:52
15		without a tremendous number of selectivity indexes	10:44:54
16		in front of me. Antibodies can be very selective	10:44:58
17		and small molecules can be very selective.	10:45:01
18		BY DR. PARTINGTON:	10:45:04
19	Q	But, generally speaking, antibodies	10:45:04
20		recognize large, three-dimensional epitopes,	10:45:06
21		correct?	10:45:10
22	A	No, I -- large, three-dimensional epitopes,	10:45:10

1 I don't know what you mean by "large" there. I 10:45:16
2 mean, so without kind of an area or volume of 10:45:19
3 interaction, I can't say that that's true of large. 10:45:23
4 Antibodies recognize antigens. 10:45:27
5 Q Okay. Let me ask it this way. 10:45:30
6 A Okay. 10:45:32
7 Q Are you aware of any examples where a small 10:45:33
8 molecule provided more specificity for FAP than an 10:45:37
9 antibody did? And let me rephrase. I'm sorry. 10:45:42
10 Are you aware of any examples where a small 10:45:47
11 molecule provided more selectivity for FAP than an 10:45:49
12 antibody did? 10:45:53
13 A Selectivity for FAP over what? Selectivity 10:45:54
14 is a relative indices -- index. Excuse me. So for 10:46:01
15 something to be selective for FAP, it must be 10:46:07
16 compared to its binding to something else. 10:46:10
17 Q Over PREP, P-R-E-P. 10:46:12
18 A So the question again? Could you rephrase 10:46:33
19 the question with that information so I can be 10:46:36
20 precise? 10:46:38
21 Q Are you aware of any examples where a small 10:46:39
22 molecule provided more selectivity for FAP over PREP 10:46:41

1 than an antibody did?

10:46:45

2 A Well, I'm not aware of any examples of
3 that, but, again, selectivity, though very, very
4 important, is not the only concern in this context.

10:46:58

10:47:01

10:47:04

5 Q I understand that.

10:47:15

6 The field of radiopharmaceuticals is not
7 limited to antibodies, correct?

10:47:21

10:47:23

8 A No. There are other vectors that are used
9 in radiopharmaceuticals that are not immunoglobulins
10 or full-length antibodies.

10:47:31

10:47:33

10:47:38

11 Q One of those are peptides, correct?

10:47:40

12 A Yes.

10:47:45

13 Q Another one is oligonucleotides, correct?

10:47:46

14 A Yes.

10:47:53

15 Q And, of course, small molecules is another
16 choice, correct?

10:47:54

10:47:57

17 A Yes.

10:47:58

18 Q And even within the antibodies, we can talk
19 about full-length antibodies or antibody fragments
20 or engineered proteins, correct?

10:48:02

10:48:04

10:48:09

21 A I'm not sure I know what you mean by
22 engineered proteins, but, yes, antibody fragments

10:48:10

10:48:13

1	are used.	10:48:16
2	Q Okay.	10:48:16
3	Your lab does not work with	10:48:28
4	radiopharmaceuticals made using peptides as a	10:48:32
5	targeting moiety, correct?	10:48:37
6	A I mean, all antibodies are peptides.	10:48:46
7	Q They're not proteins?	10:48:52
8	A Well, antibodies are proteins are peptides.	10:48:53
9	They're all made of the same thing. But do you mean	10:48:59
10	short peptides?	10:49:03
11	Q I mean short peptides.	10:49:04
12	A We've worked on those, yeah. We have	10:49:09
13	worked with short peptides for radiopharmaceutical	10:49:12
14	chemistry.	10:49:19
15	Q But your focus is on antibodies over short	10:49:19
16	peptides, correct?	10:49:23
17	A We have done more antibody work than we	10:49:25
18	have done short peptide work, but we have short	10:49:30
19	peptide work in the laboratory going on right now.	10:49:34
20	Q Okay. And in terms of oligonucleotides,	10:49:37
21	your focus is over -- is on antibodies as opposed to	10:49:42
22	oligonucleotides, correct?	10:49:46

1	A	We have never done any oligonucleotide	10:49:49
2		work.	10:49:52
3	Q	Got it.	10:49:52
4		Same question for small molecules: Your	10:49:53
5		focus is on antibodies over small molecules.	10:49:57
6		Would you agree with that?	10:50:01
7		MR. KUSHAN: Objection. Form. Objection.	10:50:03
8		Foundation.	10:50:04
9		THE WITNESS: The work that we've done in	10:50:10
10		pretargeting involves radiolabeled small molecules	10:50:12
11		and biomolecules. Given the volume of work that	10:50:14
12		we've done in that, using the radiolabeled small	10:50:18
13		molecules, I can't say right now what the ratio of	10:50:21
14		papers is, but we've done significant work in both.	10:50:24
15		Also very, very, very many of the	10:50:31
16		principles that apply to the design and synthesis of	10:50:34
17		small molecule oligonucleotide, peptide,	10:50:41
18		immunoglobulin based radiopharmaceuticals apply to	10:50:45
19		the others.	10:50:49
20		BY DR. PARTINGTON:	10:50:50
21	Q	What is pretargeting work?	10:50:50
22		You said the work that is done in	10:50:59

1	pretargeting involves radiolabeled small molecules	10:51:01
2	and biomolecules.	10:51:03
3	What is pretargeting?	10:51:05
4	A Pretargeting is a way to improve the	10:51:06
5	pharmacokinetics of antibody-based	10:51:17
6	radiopharmaceuticals by using a small -- a	10:51:21
7	radiolabeled small molecule to label them when they	10:51:28
8	are already at the tumor site.	10:51:30
9	Q Is that the click chemistry that you're	10:51:34
10	talking about?	10:51:39
11	A That is not the click chemistry. That is	10:51:39
12	one application of click chemistry.	10:51:41
13	Q I understand now. Okay. But you're still	10:51:43
14	labeling an antibody with a -- with their radio	10:51:46
15	agent, correct?	10:51:52
16	A I mean, that's --	10:51:54
17	MR. KUSHAN: Objection to form.	10:51:57
18	THE WITNESS: That turns into a semantic	10:51:59
19	issue. The molecule that we, as radiopharmaceutical	10:52:02
20	chemists, are labeling is a small molecule in those	10:52:06
21	cases. That goes on to react in the body with an	10:52:09
22	immunoglobulin.	10:52:15

1	BY DR. PARTINGTON:	10:52:16
2	Q I understand.	10:52:16
3	The ultimate goal, however, is to make a	10:52:18
4	radiopharmaceutical that is antibody based, correct?	10:52:22
5	A The product of the reaction in the tumor or	10:52:29
6	in the blood or wherever that reaction occurs is a	10:52:33
7	radiolabeled antibody.	10:52:36
8	Q I understand. Thank you for explaining	10:52:38
9	that.	10:52:40
10	Okay. So we already kind of started	10:52:52
11	talking about the terminology, but I want to	10:52:54
12	understand the terminology better. So if we could	10:52:56
13	go to page 11 of your declaration, please.	10:52:59
14	And, again, forgive me if I'm going to be	10:53:14
15	asking you questions that will make you chuckle, but	10:53:16
16	I just -- I'm obviously not an expert in this.	10:53:19
17	So let's start with (e).	10:53:22
18	A Hold on. Got to make sure I'm oriented to	10:53:25
19	where we are.	10:53:28
20	Q Sorry.	10:53:28
21	A That's okay.	10:53:29
22	Okay.	10:53:38

1	Q	Okay. Hang on one second.	10:53:47
2		Okay. So radiopharmaceutical, we already	10:54:01
3		talked about radiopharmaceutical, but see where you	10:54:06
4		say: "'Radiopharmaceutical' is a chemical compound	10:54:09
5		that contains a radionuclide that is used for	10:54:12
6		therapeutic or diagnostic purposes."	10:54:16
7		Is there difference between the term	10:54:20
8		radionuclide and nuclide?	10:54:22
9	A	Radionuclide is a subset of the	10:54:29
10		word "nuclide."	10:54:35
11	Q	So then what is a -- what's the -- what is	10:54:37
12		a nuclide?	10:54:38
13	A	A nuclide is a word used to denote a	10:54:40
14		given -- an element with a given atomic composition.	10:54:57
15	Q	So when you look at the periodic table, all	10:55:01
16		of those are nuclides?	10:55:03
17	A	Yes, in a way.	10:55:15
18		A better way to explain it is that	10:55:16
19		hydrogen, 1H; deuterium; and tritium are all	10:55:22
20		nuclides.	10:55:28
21	Q	Gotcha. And -- but deuterium and tritium	10:55:29
22		are radionuclides, correct?	10:55:35

1	A	No.	10:55:39
2	Q	No? So to be a radionuclide you have to be	10:55:40
3		able to emit radiation?	10:55:43
4	A	Yes.	10:55:44
5	Q	Okay. Gotcha.	10:55:44
6		Radiotracer is a pharmaceutical that is	10:55:46
7		used for nuclear imaging purposes.	10:55:53
8		Again, could you please explain to me the	10:55:57
9		difference between radiotracer and	10:55:59
10		radiopharmaceutical?	10:56:03
11	A	Radiotracer -- I mean, it's in there. I'll	10:56:04
12		just read it.	10:56:08
13	Q	I can read it. I just don't understand	10:56:09
14		what -- so what is the difference between a	10:56:11
15		radiotracer and radiopharmaceutical?	10:56:14
16	A	Radiotracer is a radiopharmaceutical that	10:56:17
17		is used for nuclear imaging purposes.	10:56:19
18	Q	I --	10:56:19
19	A	In the sentence, it defines it as a subset	10:56:23
20		of radiopharmaceutical.	10:56:25
21	Q	And so another purpose for	10:56:26
22		radiopharmaceutical would be therapy?	10:56:31

1 A A radiotherapeutic would be another --
2 would be a different subset of radiopharmaceutical.

3 Q Okay. Okay. So then, on the next page,
4 you're talking about: "'Reporter moiety' refers to
5 the portion of the radiopharmaceutical" --

6 A Hold on, please, so I can --

7 Q Oh, sorry.

8 A Thank you.

9 Q Under (i), you see that?

10 A Yes.

11 Q So: "'Reporter moiety' refers to the
12 portion of the radiopharmaceutical or optical
13 imaging agent that sends a signal that can be
14 detected by a device to generate an image," and
15 then, right under that, you have: "'Radiolabeling
16 moiety' refers to the portion of a
17 radiopharmaceutical that is covalently linked to or
18 non-covalently complexed with a radionuclide."

19 Again, this might be a silly question for
20 you, but I'm trying to understand what is the
21 difference between a reporter moiety and
22 radiolabeling moiety.

1 A It's hard for me to explain this better
2 because I've laid it out right here, but one way to
3 understand that is that one subset of reporter
4 moieties is an optical -- is an optical dye, and
5 obvious in that would not be included within
6 radiolabeling moiety.

7 Q That's a perfect explanation. Thank you.

8 And imaging agent -- let me see if I get
9 this correctly. An imaging agent is a subset of
10 radiopharmaceutical?

11 A No. In (1): "'Imaging agent' is" -- I'm
12 quoting now -- "'Imaging agent' is a general term
13 that includes both optical imaging agents and
14 radiotracers, and may be used interchangeably with
15 'molecular imaging agent.'"

16 Q So is it kind of like a Venn diagram then,
17 between radiopharmaceutical and imaging agent?

18 A They are related words that are defined
19 here. Whether -- I don't have a -- I'm not equipped
20 to draw a Venn diagram right now, but it's defined
21 right in (1).

22 Q Can you give me an example of a

10:57:54

10:57:58

10:58:04

10:58:09

10:58:16

10:58:19

10:58:21

10:58:38

10:58:40

10:58:44

10:58:48

10:58:52

10:58:55

10:58:58

10:59:02

10:59:04

10:59:07

10:59:13

10:59:15

10:59:19

10:59:24

10:59:24

1	radiopharmaceutical that is not an imaging agent?	10:59:26
2	A A small molecule labeled with astatine-211.	10:59:44
3	Q Astatine?	10:59:52
4	A Mm-hmm.	10:59:53
5	Q What is that?	10:59:54
6	A It's an alpha-emitting radioisotope or	10:59:55
7	radionuclide.	11:00:00
8	Q And why isn't that a molecular imaging	11:00:00
9	agent?	11:00:08
10	A Because the alpha particles emitted by	11:00:08
11	astatine are therapeutic in nature, and there is no	11:00:12
12	current clinical technology or preclinical	11:00:22
13	technology that could be used to turn alpha particle	11:00:27
14	emissions into an image that can be interpreted by a	11:00:32
15	physician.	11:00:38
16	Q Got it.	11:00:51
17	A May I ask a question?	11:01:07
18	If I see a problem there, should I say it,	11:01:09
19	or no? There's a -- there's a transcript issue.	11:01:11
20	Q So in general, you'll have an opportunity	11:01:14
21	to review transcript, but if it's -- if something	11:01:17
22	just jumps at you?	11:01:20

1	A	Above, instead of astatine, it says: "As a	11:01:22
2		teen."	11:01:27
3	Q	She'll fix it.	11:01:27
4		THE COURT REPORTER: It's not defined yet.	11:01:29
5		MR. KUSHAN: At the break, she can also go	11:01:31
6		over some of the terms with you.	11:01:33
7		THE WITNESS: Sure. Perfect. That would	11:01:35
8		be great.	11:01:37
9		BY DR. PARTINGTON:	11:01:38
10	Q	Okay. And just for completion, can you	11:01:41
11		give me an example of an imaging agent that is not a	11:01:44
12		radiopharmaceutical?	11:01:47
13	A	An imaging agent that is not a	11:01:47
14		radiopharmaceutical.	11:01:50
15		A targeting moiety antibody,	11:01:50
16		oligonucleotide, peptide, small molecule labeled	
17		with a fluorophore --	
18		THE COURT REPORTER: I'm sorry. You lost	
19		me.	
20		THE WITNESS: I apologize.	
21		A targeting moiety such as an antibody,	11:02:06
22		antibody fragment, peptide, oligonucleotide, or	11:02:11

1	small molecule labeled with a fluorophore, such as	11:02:18
2	one called IR800 that is useful for fluorescence	11:02:26
3	imaging but not -- is not radioactive.	11:02:33
4	BY DR. PARTINGTON:	11:02:36
5	Q And that would be an optical imaging agent,	11:02:36
6	correct?	11:02:38
7	A That is an example of an optical imaging	11:02:39
8	agent.	11:02:41
9	Q Understood.	11:02:41
10	Doctor, in your declaration, you used the	11:02:53
11	term "viable diagnostic" or "imaging candidate," and	11:02:55
12	my question for you is the following: When we talk	11:03:02
13	about whether a compound is a viable diagnostic or	11:03:05
14	imaging candidate, the ultimate question is how it	11:03:09
15	performs in vivo, correct?	11:03:11
16	A Can you -- before I answer that question,	11:03:13
17	could you please orient me to where I say that?	11:03:19
18	Q Can you not answer this question without --	11:03:21
19	A I would just like to look at the	11:03:24
20	declaration and see the context in which I say the	11:03:26
21	sentence.	11:03:30
22	Q It's paragraph 276.	11:03:30

1	A	Okay. And where in paragraph 276 are you	11:03:53
2		referring to?	11:03:56
3	Q	Well, why don't you just orient yourself.	11:03:59
4		You asked to see where it is in the paragraph.	11:04:01
5	A	Okay.	11:04:04
6		Okay. Now I'm -- thank you very much.	11:04:36
7	Q	Sure.	11:04:38
8	A	Would you mind asking the question again?	11:04:39
9	Q	So when you talk about whether a compound	11:04:41
10		is a viable diagnostic or imaging candidate, the	11:04:43
11		ultimate question is how it performs in vivo,	11:04:48
12		correct?	11:04:50
13	A	No. Radiopharmaceuticals are typically	11:04:50
14		used in vivo. Optical imaging agents can be useful	11:04:58
15		in vivo or in vitro.	11:05:03
16	Q	Dr. Zeglis, prior to 2017, the field had	11:05:34
17		developed antibodies targeting FAP, correct?	11:05:38
18	A	Yes, I think so. I'd have to look at the	11:05:52
19		papers right in front of me to make sure, but, yes,	11:05:54
20		I think that is true.	11:05:56
21	Q	Do you know how many antibodies targeting	11:05:57
22		FAP were developed, i.e., published on, prior to	11:06:00

1	2017?	11:06:11
2	A I do not know an exact number.	11:06:12
3	Q And prior to 2017, the field developed	11:06:14
4	imaging agents targeting FAP using anti-FAP	11:06:18
5	antibodies, correct?	11:06:22
6	A Could you refer me to the paper that you're	11:06:27
7	speaking about?	11:06:30
8	Q I'm asking you if you're aware whether,	11:06:31
9	prior to 2017, the field developed imaging agents	11:06:34
10	targeting FAP using anti-FAP antibodies?	11:06:38
11	A Do you mind if I look through Appendix C	11:06:42
12	just to make sure?	11:06:53
13	Q Please.	11:07:00
14	A Almost done.	11:08:40
15	So we don't -- or I don't -- here's one	11:08:53
16	important note. As an academic, I am taught from a	11:08:56
17	very young age to refer to everything I do as "we"	11:09:02
18	so as to not inadvertently, in a lecture or paper,	11:09:07
19	take credit for somebody else's work. So if I say	11:09:10
20	"we," it is a mistake. I mean "I" in this.	11:09:14
21	I don't cite any specific examples, I don't	11:09:18
22	think, off the top of my head -- again, it's been a	11:09:22

1 while since I've read most of these -- of antibodies
2 that were developed as imaging agents, but that is
3 possible prior to 2017.

4 Q And before signing your declaration, did
5 you, Dr. Zeglis --

6 A Mm-hmm.

7 Q -- consider whether the field developed
8 imaging agents targeting FAP using anti-FAP
9 antibodies before 2017?

10 A The declaration represents all of my
11 opinions on this matter. What I considered or did
12 not consider prior to signing it is -- is -- I
13 cannot possibly tell you everything I did or did not
14 consider prior to signing it, but it represents all
15 of my opinions on the matter.

16 I don't know if I cited an anti-FAP
17 antibody reported before 2017. If there's one you'd
18 like me to speak about, you can -- I'm happy to look
19 at a paper.

20 Q Dr. Zeglis, in the field of
21 radiopharmaceuticals, there were both metallic
22 radionuclides and nonmetallic radionuclides known in

1	the art before 2017, correct?	11:10:44
2	A Metallic and nonmetallic radionuclides were	11:10:49
3	known before 2017, yes.	11:10:52
4	Q What are some of the common examples of	11:10:55
5	metallic radionuclides known before 2017?	11:10:59
6	A For imaging, or therapy?	11:11:04
7	Q Is there a difference?	11:11:08
8	A Yes. We went over that difference before.	11:11:09
9	Q I meant is there a difference between the	11:11:12
10	radionuclide that you would use for imaging versus	11:11:15
11	therapy?	11:11:18
12	A Yes. I discuss that in the declaration.	11:11:19
13	Q Okay.	11:11:21
14	A Let me find it.	11:11:22
15	Q So let's start with imaging then, please.	11:11:23
16	Give me --	11:11:25
17	A Let me find where I describe that in the	11:11:26
18	declaration.	11:11:29
19	So in paragraph 49, for example, I refer	11:12:00
20	to --	11:12:06
21	Q Hang on just one second.	11:12:07
22	A Oh, I apologize.	11:12:08

1	Q	Okay. I'm there.	11:12:10
2	A	Okay.	11:12:20
3		In paragraph 49, for example, I mention	11:12:20
4		four nonmetallic radionuclides: "... (11)C, (13)N,	11:12:22
5		(15)O, and (18)F..." Later in the same paragraph, I	11:12:29
6		mention four metallic radionuclides that could be	11:12:36
7		used for imaging: "... (64)Cu, (68)Ga, (86)Y and	11:12:38
8		(89)Zr..."	11:12:48
9	Q	Besides the examples of nonmetallic	11:12:52
10		radionuclides that you list in paragraph 49 of your	11:12:58
11		declaration, were there any other nonmetallic	11:13:01
12		radionuclides known before 2017?	11:13:06
13	A	Were there other nonmetallic radionuclides	11:13:10
14		known before 2017? Yes.	11:13:13
15	Q	How many?	11:13:16
16	A	You mean with medical applications, or	11:13:21
17		across all of science?	11:13:25
18	Q	Let's start with medical applications.	11:13:34
19	A	Okay. One example of one that I did not	11:13:37
20		list there that is listed on the next page -- so if	11:13:39
21		we turn to paragraph 50, above paragraph 50 there is	11:13:46
22		a chart --	11:13:53

1	Q	Mm-hmm.	11:13:53
2	A	-- that lists (124)I, for example, as a	11:13:56
3		halogen that can be used for PET imaging.	11:14:07
4	Q	Okay. And so thank you for that. My	11:14:11
5		original question, of course, was --	11:14:13
6	A	Okay. I'm sorry.	11:14:15
7	Q	-- how many. How many nonmetallic	11:14:15
8		radionuclides were known in 2017 besides the ones	11:14:24
9		that you have listed here, roughly.	11:14:29
10	A	I can't give you a number of how many were	11:14:32
11		known because I cannot speak to the entire history	11:14:34
12		of nuclear and radiochemistry. These, in 2017,	11:14:39
13		would have been the most common ones known.	11:14:47
14	Q	Were there maybe ten more?	11:14:50
15	A	Again, I can't give you a number.	11:14:54
16	Q	A hundred?	11:14:56
17	A	It all depends. The reason I can't give a	11:14:59
18		number is, as a scientist, I like to speak with	11:15:03
19		exactitude and precision. And so without specific	11:15:07
20		parameters with respect to your question, medical	11:15:11
21		applications -- realistic medical applications could	11:15:17
22		be used, I can't give you a number. These are the	11:15:20

1 common ones. 11:15:21

2 Q What about just orders of magnitude? I'm 11:15:22

3 just asking in general. Not limited to medical 11:15:24

4 applications, just known nonmetallic radionuclides 11:15:27

5 before 2017. 11:15:30

6 A I don't think it's reasonable to give a 11:15:32

7 number because I don't have exact parameters for the 11:15:33

8 question, and I don't have the time to go through 11:15:36

9 the chart of the nuclides to tell you all the 11:15:39

10 answers. 11:15:43

11 The chart in -- above paragraph 50 11:15:44

12 represents what would have been -- what are today, 11:15:48

13 and what would have been in 2017, a list of common 11:15:52

14 useful radionuclides for nuclear imaging, 11:15:58

15 specifically SPECT and PET. 11:16:03

16 Q Besides the common useful nuclides listed 11:16:06

17 in your declaration in paragraph 49, approximately 11:16:13

18 how many radionuclides were known prior to 2017? 11:16:21

19 Are you able to answer that question? 11:16:31

20 A Not without -- not without more specific 11:16:32

21 and useful parameters. 11:16:35

22 Q And is that because there are just so many 11:16:37

1	of them?	11:16:39
2	A No. It's because I don't have specific and	11:16:40
3	useful parameters to give a numerical quantitative	11:16:42
4	answer to the question.	11:16:45
5	Q What parameters would you want me to give	11:16:48
6	you?	11:16:51
7	A To ask what question?	11:16:56
8	Q Prior to 2017, how many, approximately,	11:17:00
9	nonmetallic radionuclides were known in the art?	11:17:07
10	A You'd have to give me all types of	11:17:19
11	parameters for me to give a quantitative. So you	11:17:21
12	ended that sentence, "in the art." Which art?	11:17:24
13	Nuclear chemistry? Radiochemistry? Would they need	11:17:27
14	to be used molecular imaging, medicinal purposes?	11:17:30
15	Would they be useful? Could they be made?	11:17:36
16	I cannot give a substantive, precise,	11:17:39
17	quantitative answer to that question.	11:17:54
18	Q Okay. How about the art relevant to the	11:17:55
19	'233 patent?	11:17:58
20	A Again, without quantitative -- the one --	11:18:00
21	without quantitative parameters, I don't feel	11:18:05
22	comfortable giving a quantitative answer. The chart	11:18:07

1 on -- above paragraph 50 is -- represents what -- 11:18:14
2 what were, in 2017, commonly used radionuclides for 11:18:18
3 PET and SPECT. Going back a page earlier, there's a 11:18:23
4 few more: (13)N, (15)O also listed. 11:18:27

5 Giving a quantitative numerical based 11:18:34
6 answer is something I'm not comfortable with, not 11:18:37
7 because I don't understand what we're talking about, 11:18:40
8 but rather because short of exact parameters, as a 11:18:41
9 scientist, I'm not comfortable giving really finite 11:18:44
10 numerical answers when I haven't had -- sorry. This 11:18:48
11 thing -- 11:18:55

12 THE COURT REPORTER: The internet went out 11:18:58
13 for a minute. 11:19:01

14 THE WITNESS: Would you like me to hit 11:19:02
15 "Okay" to "Anyone with access"? It also says I'm 11:19:03
16 muted. Would you like me to unmute? 11:19:06

17 THE COURT REPORTER: Don't turn that on. 11:19:13

18 THE WITNESS: Okay. Back to the question. 11:19:19
19 I apologize. 11:19:20

20 I cannot give you, with precision or 11:19:21
21 comfort, given the amount of time and data I have at 11:19:25
22 hand here -- this pooped out again -- a numerical 11:19:29

1	answer to that question.	11:19:37
2	BY DR. PARTINGTON:	11:19:38
3	Q Okay. So sitting here today, you cannot	11:19:38
4	give me an approximation of the number of	11:19:41
5	radionuclides, nonmetallic ones, that were known in	11:19:46
6	the art that relates to the '233 patent prior to	11:19:51
7	2017, correct?	11:19:57
8	A I can give you the ones listed here, and	11:19:59
9	beyond that I would need more quantification,	11:20:02
10	specification to give you a finite number. So here	11:20:11
11	we can go over it again.	11:20:13
12	Q We don't have to do that Doctor. I can	11:20:15
13	read.	11:20:19
14	So the answer to my question, though, is	11:20:19
15	no, you cannot -- sitting here today --	11:20:21
16	A Mm-hmm.	11:20:21
17	Q -- you cannot give me an approximate --	11:20:25
18	strike that.	11:20:30
19	Sitting here today, you cannot give me an	11:20:30
20	approximation of the number of non-metallic nuclear	11:20:34
21	nuclei -- radionuclides that were known in the art	11:20:41
22	that relates to the '233 patent prior to 2017,	11:20:45

1	correct?	11:20:50
2	MR. KUSHAN: Objection. Foundation.	11:20:52
3	THE WITNESS: I can't give an answer to	11:20:58
4	that question because I cannot give you a	11:20:59
5	quantitative number, even an approximation, because	11:21:02
6	that would be quantitative also without parameters.	11:21:05
7	You say relevant to the '233 patent. That's -- that	11:21:09
8	what exactly you mean by that, I don't have the	11:21:16
9	specifications for half-lives, productions. I can	11:21:18
10	give you, again above 50, a chart showing the	11:21:21
11	metallic and nonmetallic radionuclides and then a	11:21:24
12	couple more in paragraph 49 that are -- would have	11:21:28
13	been relevant in 2017 to the development of nuclear	11:21:32
14	imaging agents.	11:21:38
15	BY DR. PARTINGTON:	11:21:38
16	Q Okay. Is your answer the same for metallic	11:21:39
17	radionuclides?	11:21:42
18	A I also could not give you a finite number	11:21:42
19	of those without much more specification, data, and	11:21:45
20	time.	11:21:49
21	Q Okay. Radionuclides can be incorporated	11:21:58
22	into imaging agents in a variety of different ways,	11:22:01

1	correct?	11:22:04
2	A Well, depending on what you mean by variety	11:22:13
3	of different ways, but, yes, imaging agents --	11:22:16
4	radionuclides can be incorporated in a variety of	11:22:19
5	ways into radioconjugates, true.	11:22:22
6	Q One way is by substituting a radioactive	11:22:26
7	isotope for an identical nonradioactive atom in the	11:22:30
8	molecular structure, correct?	11:22:36
9	A Say that again.	11:22:37
10	Q One way would have been substituting a	11:22:38
11	radioactive isotope for an identical nonradioactive	11:22:45
12	atom in the molecular structure, correct?	11:22:52
13	A That is one way to do it.	11:22:55
14	Q And that way would have been known prior to	11:22:59
15	2017, correct?	11:23:02
16	A That way would have been known prior to	11:23:06
17	2017. I don't know exactly what you mean by	11:23:08
18	substituting. Are you talking about a literal	11:23:11
19	substitution reaction or replacing?	11:23:14
20	Q I'm talking about a replacement. If you	11:23:20
21	have -- I'm not talking about substitution reaction.	11:23:22
22	A So not a substitution reaction?	11:23:24

1	Q	No.	11:23:26
2		I'm talking about if you have a molecule,	11:23:27
3		let's say you have a halogen bromine or fluorine --	11:23:29
4		let's do fluorine -- as a -- as a substitute in the	11:23:34
5		molecule, replacing that fluorine with a radioactive	11:23:39
6		fluorine. That's what I'm talking about.	11:23:43
7	A	That is one method, and it was known before	11:23:45
8		2017.	11:23:48
9		One note, it's been about an hour. At your	11:23:49
10		convenience, if we can take a break, that'd be	11:23:52
11		great.	11:23:54
12	Q	Just last question on this, and then we can	11:23:54
13		go. Okay?	11:23:57
14	A	Of course.	11:23:58
15	Q	This approach that we're discussing, this	11:23:58
16		direct substitution or replacement, this approach	11:24:01
17		does not change the underlying molecular structure,	11:24:03
18		correct?	11:24:06
19	A	It generates a new molecule that, in a very	11:24:10
20		small way, has a different molecular structure. It	11:24:15
21		is an isotopologue of the starting structure.	11:24:18
22		Identical in all ways except for the number of	11:24:23

1	neutrons in the atom that you replaced.	11:24:26
2	Q The effect on the molecular structure is	11:24:29
3	minimal, correct?	11:24:32
4	MR. KUSHAN: Objection. Form.	11:24:34
5	THE WITNESS: Whether an added neutron is a	11:24:35
6	minimal structure and whether that's an effect on	11:24:37
7	the structure is -- is kind of a squishy question to	11:24:41
8	ask. Is there a different way that you could ask	11:24:48
9	that?	11:24:50
10	BY DR. PARTINGTON:	11:24:50
11	Q Sure.	11:24:51
12	It's -- it's a lot less disturbing to the	11:24:53
13	molecular structure than adding, let's say, a phenyl	11:25:01
14	group?	11:25:07
15	A Not necessarily. That depends on what you	11:25:08
16	mean by disturbing to the molecular structure.	11:25:11
17	Sorry. I just don't know what you mean by	11:25:20
18	disturbing to the molecular structure.	11:25:22
19	DR. PARTINGTON: Let's take a break. Let's	11:25:25
20	go off the record.	11:25:27
21	(Recessed at 11:25 a.m.)	11:25:28
22	(Reconvened at 11:41 a.m.)	11:41:38

1	BY DR. PARTINGTON:	11:41:41
2	Q Before the break, we were discussing about	11:41:41
3	different strategies for incorporating radionuclides	11:41:44
4	into imaging agents, correct? Remember that?	11:41:48
5	A Correct.	11:41:54
6	Q Yeah.	11:41:54
7	And so we talked about directly	11:41:55
8	substituting or directly replacing the radioisotope	11:41:59
9	for an identical nonradioactive atom is one of the	11:42:04
10	ways. Another way is direct labeling, such as	11:42:09
11	radiohalogenation, correct?	11:42:13
12	A What do you mean by "direct labeling"?	11:42:16
13	Q What I mean is that including or, like,	11:42:21
14	incorporating radionuclides, like radioiodine or	11:42:24
15	radiofluorine, directly into the molecule.	11:42:27
16	A In a place other than occupied by	11:42:32
17	isotopologous atom?	11:42:37
18	Q Correct.	11:42:41
19	A Yes, that is another way to do it.	11:42:42
20	Q And that method was also known prior to	11:42:44
21	2017, correct?	11:42:46
22	A Correct.	11:42:47

1 Q Another approach involves attaching a 11:42:48
2 prosthetic group that contains the radionuclide, 11:42:53
3 correct? 11:42:55

4 A Excuse me. 11:42:57

5 Another way is attaching a prosthetic group 11:42:58
6 that is either labeled prior to attachment or after 11:43:01
7 attachment with a radionuclide, yes. 11:43:04

8 Q And you attach that prosthetic group either 11:43:07
9 labeled or labeled after to the targeting moiety, 11:43:14
10 correct? 11:43:17

11 A It is attached to a linker that attaches to 11:43:17
12 the targeting moiety. 11:43:22

13 Q And do you use this approach when direct 11:43:25
14 labeling is not feasible? 11:43:28

15 A No. That's not when you use this approach. 11:43:29
16 You use this approach as an added -- not when direct 11:43:32
17 labeling is not feasible. You use this approach as 11:43:36
18 an alternative approach that provides its own family 11:43:39
19 of benefits. 11:43:43

20 Q And this technique was also well 11:43:44
21 established before 2017, correct? 11:43:46

22 A This approach was established before 2017. 11:43:48

1	Q	Another approach uses metallic	11:43:51
2		radionuclides, correct? We've already discussed	11:43:54
3		that.	11:43:57
4	A	Yes, but those aren't directly attached.	11:43:57
5		Yes, but metallic radionuclides can be used to	11:44:02
6		radiolabel vectors, correct.	11:44:07
7	Q	And when you're using metallic	11:44:09
8		radionuclides, the molecule is first modified with a	11:44:13
9		chelating group, correct?	11:44:17
10	A	The molecule in question is modified with a	11:44:19
11		linker and then a chelating group that holds onto	11:44:24
12		the radiometal.	11:44:29
13	Q	And this approach was routine in the field	11:44:31
14		prior to 2017, correct?	11:44:33
15	A	This approach was known in the field prior	11:44:36
16		to 2017.	11:44:39
17	Q	So as of 2017, a person of ordinary skill	11:44:44
18		in the art would have been well aware of each of	11:44:48
19		these labeling approaches that we just discussed,	11:44:50
20		correct?	11:44:52
21	A	A person of ordinary skill in the -- a	11:44:58
22		skilled artisan or POSA would have known of all	11:45:03

1 these approaches, but a POSA would not have weighed
2 them equally when creating a new
3 radiopharmaceutical.

4 Q Understand.

5 All right. So putting it all together, an
6 imaging agent or making an imaging agent can involve
7 using metallic or nonmetallic radionuclides
8 incorporated either directly or via chelator or
9 prosthetic group, correct?

10 A A metallic radionuclide could not be
11 incorporated directly. So the full scope of the
12 question you just asked is not the case.

13 Q I understand.

14 So nonmetallic radionuclides can be
15 incorporated either directly or via prosthetic
16 group, correct?

17 A Yes.

18 Q And metallic nuclides can be incorporated
19 via a chelator, correct?

20 A Yes, but both those prosthetic groups and
21 the chelators require a linker to the targeting
22 vector.

1	Q	Understand.	11:46:16
2		So chelation and prosthetic group	11:46:29
3		attachment, these approaches generally introduce	11:46:31
4		additional structural elements to the targeting	11:46:35
5		molecule, correct?	11:46:38
6	A	The addition of a chelator necessitates	11:46:41
7		adding a chelator to a targeting vector and a	11:46:46
8		linker, yes.	11:46:51
9	Q	And so that introduces additional	11:46:53
10		structural element to the molecule, correct?	11:46:57
11	A	Correct, but that isn't necessarily a bad	11:46:58
12		thing.	11:47:01
13	Q	And the same with the prosthetic group,	11:47:02
14		correct? It introduces additional structural	11:47:04
15		element to the molecule?	11:47:07
16	A	Prosthetic groups also require the	11:47:08
17		prosthetic group and the linker and then the	11:47:10
18		targeting moiety, so they require additional	11:47:12
19		structural components, but, again, that isn't	11:47:15
20		necessarily a bad thing within the context of making	11:47:18
21		imaging agents.	11:47:21
22	Q	By contrast, with direct radiohalogenation,	11:47:22

1 the radionuclide is incorporated directly into the 11:47:27
2 molecular structure, correct? 11:47:31

3 A That is correct, but it is not necessarily 11:47:35
4 preferable because it comes with its own set of 11:47:38
5 problems. 11:47:40

6 Q And this approach of direct 11:47:41
7 radiohalogenation does not require a chelator or 11:47:45
8 prosthetic group, correct? 11:47:48

9 MR. KUSHAN: Objection. Foundation. 11:47:55

10 THE WITNESS: Say the question again, 11:47:58
11 please. 11:47:59

12 BY DR. PARTINGTON: 11:47:59

13 Q Direct radiohalogenation does not require a 11:48:00
14 chelator or prosthetic group, correct? 11:48:03

15 A Well, the prosthetic groups, when they were 11:48:05
16 created, are radiohalogenated. 11:48:07

17 Q But direct radiohalogenation does not 11:48:11
18 require a prosthetic group, correct? 11:48:15

19 A If you're -- 11:48:18

20 MR. KUSHAN: Objection. Foundation. 11:48:19

21 THE WITNESS: I'm not sure I understand the 11:48:23
22 question. Because if you're attaching a prosthetic 11:48:24

1 group to something, that prosthetic group must be 11:48:26
2 radiolabeled or radiohalogenated. 11:48:29
3 BY DR. PARTINGTON: 11:48:32
4 Q I'm asking you a question -- earlier, 11:48:32
5 before the break, we talked about directly 11:48:36
6 substituting radioisotopes for an identical 11:48:39
7 nonradioactive atom. 11:48:44
8 Remember that? 11:48:46
9 A Yes. 11:48:47
10 Q In that case, you don't need a prosthetic 11:48:47
11 group, correct? 11:48:50
12 A In that case where you are replacing one 11:48:50
13 atom with a radioactive isotopologue, that does not 11:48:53
14 require a prosthetic group. 11:48:56
15 Q And also, for another example, if you have 11:48:58
16 a molecule and all you're doing is substituting or 11:49:01
17 attaching, rather, a radiohalogen to that molecule 11:49:04
18 on the structure of the molecule -- 11:49:10
19 A Sure. 11:49:10
20 Q -- you don't need a prosthetic group, 11:49:11
21 right? 11:49:13
22 A Well, all you're doing is a hard phrase in 11:49:13

1 that sentence because that's a very hard thing to 11:49:17
2 do. 11:49:19

3 So, yes, if you're just incorporating a 11:49:20
4 single atom into -- 11:49:22

5 Q Mm-hmm. 11:49:22

6 A -- you do not need a prosthetic group, but 11:49:24
7 calling that all you're doing, I'm not comfortable 11:49:28
8 with that terminology because that, attaching a 11:49:31
9 radiohalogen directly to a pharmacophore structure, 11:49:37
10 can be very difficult and problematic in its own set 11:49:40
11 of ways. 11:49:44

12 Q Okay. But -- I understand that. 11:49:45

13 But it does not -- you don't necessarily 11:49:47
14 need a prosthetic group? 11:49:49

15 A If you are attaching a radiohalogen 11:49:50
16 directly to the structure of a pharmacophore, you do 11:49:54
17 not necessarily need a prosthetic group. But, 11:49:59
18 again, my point before was to characterize that as, 11:50:01
19 quote, all you're doing is incorrect because that's 11:50:07
20 a very challenging thing to do. 11:50:09

21 Q I understand. 11:50:11

22 Now, when you're talking about direct 11:50:12

1	halogenation, you do not introduce an additional	11:50:15
2	linker, correct?	11:50:19
3	MR. KUSHAN: Objection. Foundation.	11:50:21
4	THE WITNESS: First of all, I don't really	11:50:25
5	know what you mean by "you." Second of all, again,	11:50:27
6	in prosthetic group chemistry, the prosthetic groups	11:50:30
7	are radiohalogenated and they require a linker to	11:50:33
8	the vector in question.	11:50:38
9	BY DR. PARTINGTON:	11:50:40
10	Q I'm not talking about the prosthetic group	11:50:40
11	chemistry. I'm talking about direct halogenation of	11:50:43
12	a molecule such as, for example, either replacement	11:50:48
13	of nonradioactive halogen with radioactive halogen	11:50:52
14	or attaching a radioactive halogen -- nothing	11:50:58
15	else --	11:51:02
16	A Okay.	11:51:02
17	Q -- just radioactive halogen -- to a	11:51:02
18	molecule.	11:51:07
19	This does not require a linker, correct?	11:51:08
20	A Okay. I understand: So if you are doing	11:51:10
21	an isotopologous substitution or attaching a	11:51:15
22	radionuclide radiohalogen directly to the core	11:51:20

1 structure of a pharmacophore, that does not require 11:51:23
2 a linker, but the inclusion of a linker has its own 11:51:28
3 values and -- and advantages. 11:51:33

4 Q The design of an imaging agent depends on 11:51:35
5 the type of targeting moiety, correct? 11:51:38

6 A Design's a really squishy word in that 11:51:45
7 question. But insomuch as a targeting -- I'm sorry. 11:51:50
8 Say the question again. I don't think I understand. 11:51:58

9 Q A design of an imaging agent depends on the 11:52:00
10 type of targeting moiety, correct? 11:52:03

11 A The general principles involved in creating 11:52:08
12 an imaging agent persist regardless of the targeting 11:52:10
13 moiety. Those are common principles across imaging 11:52:19
14 agents. 11:52:25

15 Q When you incorporate a radionuclide into a 11:52:56
16 small molecule, there's a risk that you may alter 11:52:58
17 how that molecule interacts with its receptor, 11:53:02
18 correct? 11:53:05

19 A Yes. Altering -- introducing -- I mean 11:53:14
20 making any structural change to a small molecule or 11:53:19
21 any targeting vector can alter its binding to its 11:53:23
22 intended target. 11:53:27

1 Q And that's because small molecules rely on 11:53:30
2 precise molecular interactions with their targets, 11:53:33
3 correct? 11:53:36

4 A Can you state the question again? Precise 11:53:45
5 molecular inter- -- I mean precision, I'm not sure 11:53:47
6 applies here. 11:53:52

7 Q Small molecules rely on specific molecular 11:53:54
8 interactions with their targets? 11:53:57

9 MR. KUSHAN: Objection. Foundation. 11:54:03

10 THE WITNESS: All targeting moieties 11:54:04
11 interact with their targets. So structural 11:54:06
12 alterations to all targeting moieties can, but not 11:54:10
13 necessarily would, change/impact that binding. 11:54:14

14 BY DR. PARTINGTON: 11:54:28

15 Q And even with relatively small structural 11:54:28
16 changes, you can affect binding affinity or 11:54:31
17 specificity of a small molecule to its target, 11:54:37
18 correct? 11:54:40

19 A Can we speak in terms of -- I mean, 11:54:40
20 specificity, selectivity, what are you -- again, 11:54:42
21 it'd be great if we can use the same terminology. 11:54:47

22 Q Well, I did say specificity. 11:54:49

1	Do you have an understanding what binding	11:54:53
2	specificity means?	11:54:55
3	A I do have an understanding of that.	11:54:57
4	Q What is that?	11:54:59
5	A Specificity generally denotes -- I mean,	11:55:01
6	specificity and selectivity are generally used in	11:55:08
7	the clinical context -- but in the context of small	11:55:10
8	molecules, they are generally used for target over	11:55:13
9	the lump sum of all other interactions, whereas	11:55:15
10	selectivity is typically a comparison of one target	11:55:18
11	to another.	11:55:21
12	Q Okay. So then my question is: Keeping	11:55:22
13	that definition of specificity in mind, relatively	11:55:25
14	small structural changes can affect binding affinity	11:55:32
15	or specificity of a small molecule to its target,	11:55:36
16	correct?	11:55:39
17	A It depends on the small molecule. It	11:55:47
18	depends on the target. It depends on what you mean	11:55:51
19	by relatively small, the answer to that question.	11:55:54
20	But changes, again, however you define relatively	11:55:59
21	small, can impact binding interactions.	11:56:05
22	Q So radiolabeling a small molecule can	11:56:12

1 change its behavior, correct? 11:56:16

2 A What do you mean by "behavior"? 11:56:18

3 Q Its ability to recognize its target. 11:56:22

4 A What do you mean by "recognize"? I'm 11:56:25

5 sorry. I'm not being obtuse -- 11:56:31

6 Q It's okay. 11:56:31

7 A -- but recognizing this is not a word I 11:56:33

8 understand in this context. 11:56:35

9 Q Its ability -- in the milieu of other 11:56:36

10 molecular structures around it, a small molecule 11:56:42

11 must be able to recognize its target before it binds 11:56:47

12 to it? 11:56:52

13 A I'm sorry. You used the word "recognize" 11:56:54

14 again. What do you mean by "recognize"? 11:56:57

15 Q Let me ask it this way. 11:57:12

16 What principles govern how small molecule 11:57:13

17 is going to bind to -- strike that. 11:57:15

18 What principles govern whether a small 11:57:17

19 molecule is going to bind to its target? 11:57:19

20 A There are many different molecular 11:57:31

21 interaction principles that govern the binding of 11:57:35

22 small molecules to targets, and so I wouldn't 11:57:39

1 necessarily feel comfortable listing a comprehensive 11:57:42
2 list because that's not -- I don't have data in 11:57:48
3 front of me or appropriate references. 11:57:57

4 Q Okay. And radiolabeling a small molecule 11:58:02
5 can change its molecular interactions with its 11:58:04
6 target, correct? 11:58:10

7 A Attaching a radionuclide to a targeting 11:58:13
8 vector can impact its binding to a target, correct. 11:58:17

9 Q In developing radiopharmaceuticals, it is 11:58:33
10 desirable to ensure that the radiolabel does not 11:58:36
11 disturb how a small molecule interacts with its 11:58:39
12 receptor, correct? 11:58:43

13 A When designing a radiopharmaceutical, the 11:58:49
14 manner in which you attach the linker and 11:58:56
15 radionuclide or any modifications you make to the 11:58:59
16 central vector, you -- one does not want to 11:59:03
17 significantly adversely affect the ability of that 11:59:14
18 vector to bind its target. 11:59:20

19 Q In fact, this is often a central design 11:59:23
20 goal for small molecule imaging agents, correct? 11:59:29

21 A One does not want to impact the binding of 11:59:39
22 the vector to the target, so significantly adversely 11:59:44

1 affecting its binding is something that one wants to 11:59:50
2 avoid. 11:59:53

3 Q And that's because if labeling 11:59:58
4 significantly adversely affects its binding to its 12:00:00
5 target, the imaging agent may no longer faithfully 12:00:04
6 report on that target, correct? 12:00:10

7 MR. KUSHAN: Objection. Form. 12:00:12

8 THE WITNESS: What do you mean by "report 12:00:12
9 on that target"? You mean without a data and 12:00:14
10 information with regard to the magnitude of that 12:00:24
11 adverse -- adverse effect, I couldn't say, in 12:00:27
12 abstract, whether that would be problematic or not. 12:00:33

13 BY DR. PARTINGTON: 12:00:38

14 Q But you can imagine the situation where you 12:00:38
15 have a specific and selective small molecule that 12:00:40
16 specifically and selectivity binds to its receptor 12:00:47
17 with high affinity, but then you change something in 12:00:51
18 that molecule and you no longer have the same 12:00:55
19 specificity selectivity binding affinity. 12:00:58

20 A Mm-hmm. 12:00:58

21 Q In that case -- in that case, that molecule 12:01:01
22 is no longer going to be able to be a viable -- 12:01:12

1	strike that.	12:01:12
2	For a small molecule to work as a	12:01:29
3	radiolabeling agent or radiopharmaceutical -- for a	12:01:38
4	small molecule to work as a radiopharmaceutical, it	12:01:42
5	has to be able to bind to its target, correct?	12:01:44
6	A I mean, the small molecule is not the only	12:01:50
7	component of the radiopharmaceutical.	12:01:53
8	Q I'm asking you: On the level of the	12:01:56
9	interactions between a small -- or between a	12:02:00
10	radiopharmaceutical and its target, there needs to	12:02:05
11	be a recognition between this radiopharmaceutical	12:02:09
12	and its target, correct?	12:02:11
13	A Yes. On page 31, paragraph 55, I say:	12:02:14
14	"When choosing the pharmacophore that will act as	12:02:22
15	the targeting moiety...two issues are	12:02:25
16	paramount...the selectivity of the pharmacophore for	12:02:28
17	the molecular target...and...the affinity of the	12:02:30
18	pharmacophore for the molecular target..."	12:02:34
19	Q Right. So labeling --	12:02:38
20	A And then -- oh, sorry.	12:02:41
21	Q I was going to say that labeling a small	12:02:44
22	molecule with the radionuclide can disturb the	12:02:46

1	selectivity and/or affinity for the molecular	12:02:50
2	target, correct?	12:02:55
3	A Let's go to paragraph 59, subsection B:	12:02:57
4	"Amenable to Radiolabeling," where I write: "To	12:03:01
5	become a viable radiopharmaceutical, the targeting	12:03:05
6	moiety must be modified to append a chelator or	12:03:09
7	prosthetic group for radiolabeling. This can often	12:03:14
8	be a tricky endeavor, as slight modifications to the	12:03:17
9	structure of a targeting moiety can alter its	12:03:19
10	selectivity and affinity for its target. Thus, it	12:03:20
11	is desirable to have several possible sites on the	12:03:24
12	targeting moiety that can serve as a point of	12:03:27
13	attachment for the linker and radiolabeling moiety	12:03:29
14	that are far enough away from the structural motif	12:03:31
15	of the targeting moiety that interacts with the	12:03:33
16	target on the targeted cells."	12:03:36
17	Q This presumes, though, using a linker and a	12:03:37
18	chelator prosthetic group, correct?	12:03:42
19	A Modified to append a chelator or prosthetic	12:03:44
20	group for radiolabeling, but the same principles	12:03:47
21	apply to attaching a radionuclide.	12:03:50
22	Q Do the same --	12:03:57

1	A	The same concerns would apply.	12:03:58
2	Q	Sure.	12:04:03
3		This far enough concept: "...far enough	12:04:10
4		away from the structural motif of the targeting	12:04:13
5		moiety that interacts with the target on the	12:04:16
6		targeted cells," how does this apply to direct	12:04:21
7		halogenation?	12:04:23
8	A	Because if the direct halogenation occurs	12:04:24
9		in a spot that impacts the binding --	12:04:27
10	Q	I see.	12:04:29
11	A	-- of the targeting vector, it can also	12:04:30
12		alter its selectivity and affinity for its target.	12:04:34
13	Q	Okay.	12:04:38
14		But there are strategies used to ensure	12:04:42
15		that radiolabeling minimally disturbs the small	12:04:45
16		molecule -- strike that.	12:04:50
17		There are strategies that can be used to	12:04:50
18		ensure that radiolabeling minimally disturbs	12:04:52
19		selectivity and affinity of the molecule for its	12:04:59
20		target, correct?	12:05:03
21	MR. KUSHAN:	Objection. Form.	12:05:12
22	THE WITNESS:	Directly radiolabeling, as	12:05:18

1	we've been talking about, makes small changes	12:05:20
2	structurally, but it is still very difficult to do	12:05:29
3	and doesn't come with the attendant benefits of	12:05:35
4	using things like linkers and chelators and	12:05:39
5	prosthetic groups that enable much more modularity	12:05:44
6	and functionality and variability.	12:05:50
7	BY DR. PARTINGTON:	12:06:05
8	Q So my question, Doctor, was the following:	12:06:05
9	There are strategies that can be used to ensure that	12:06:07
10	radiolabeling minimally disturbs selectivity and	12:06:10
11	affinity of the molecule for its target, correct?	12:06:13
12	MR. KUSHAN: Objection. Form.	12:06:22
13	THE WITNESS: I mean minimally disturbed	12:06:23
14	is -- I don't -- it's hard to really visualize what	12:06:35
15	you mean by "minimally disturbed," but I can say it	12:06:38
16	again.	12:06:41
17	The attachment, either isotopologue	12:06:44
18	substitution or direct radiohalogenation, cause	12:06:48
19	minor, on the atom level, less structural change,	12:06:54
20	but those can also significantly impact the binding	12:07:00
21	of a -- of a prosthetic group -- or of a targeting	12:07:05
22	vector to its target, and on top of that, they tend	12:07:11

1	to be very difficult and don't come with the	12:07:15
2	advantages that using a targeting vector, linker,	12:07:17
3	prosthetic group, or chelator architecture come	12:07:23
4	with.	12:07:26
5	BY DR. PARTINGTON:	12:07:37
6	Q But direct halogenation -- strike that.	12:07:37
7	Direct halogenation preserves the chemical	12:07:42
8	structure of the starting molecule as close as	12:07:45
9	possible, correct?	12:07:48
10	MR. KUSHAN: Objection. Form.	12:07:48
11	THE WITNESS: Excuse me.	12:07:57
12	Isotopologous substitution would -- like a	12:08:03
13	literal substitution reaction, would cause the	12:08:10
14	smallest amount of structural perturbation to the	12:08:16
15	molecule, but it can also cause -- but direct	12:08:23
16	halogenation can cause its own set of -- can also	12:08:26
17	impair, impede, affect -- adversely affect the	12:08:30
18	affinity and selectivity of the compound, and,	12:08:34
19	again, those come with their own challenges.	12:08:39
20	BY DR. PARTINGTON:	12:08:42
21	Q And isotopologous substitution minimally --	12:08:42
22	strike that.	12:08:49

1	Isotopologous substitution minimizes changes	12:08:49
2	to the receptor binding of the small molecule,	12:08:54
3	correct?	12:08:57
4	A I can't speak to that without seeing	12:08:57
5	literal data on that, but it changes -- swapping out	12:09:05
6	a cold nonradioactive radiohalogen for a radioactive	12:09:08
7	radiohalogen changes the overarching molecular	12:09:14
8	structure of the vector by only a single neutron.	12:09:18
9	Q Mm-hmm.	12:09:21
10	A But, again, it's very difficult to do and	12:09:21
11	difficult to do in a way that is useful for	12:09:23
12	molecular imaging and therapy.	12:09:27
13	Q Okay. So I'm going to hand you	12:10:31
14	Exhibit 1010.	12:10:34
15	You're familiar with this exhibit, Doctor?	12:11:39
16	A It's been a long time, but, yes, I am.	12:11:41
17	Q This is a publication authored by you, and,	12:11:43
18	I'm assuming, Dr. Jason Lewis, correct?	12:11:46
19	A Mm-hmm. Yes.	12:11:50
20	Q When was the last time you reviewed this	12:11:51
21	publication?	12:11:56
22	A I've read this within the last couple	12:11:56

1	months.	12:11:58
2	Q Let's go to page 3. So on -- you see	12:11:59
3	there's two columns, left and right?	12:12:11
4	A Mm-hmm.	12:12:13
5	Q So let's go to the right column --	12:12:13
6	A Mm-hmm.	12:12:16
7	Q -- and, I guess, the full -- the first full	12:12:20
8	paragraph starting with: "Importantly..." you see	12:12:22
9	that?	12:12:24
10	A Sure. Would you give me a moment to orient	12:12:24
11	myself?	12:12:26
12	Q Absolutely.	12:12:28
13	A Okay.	12:13:02
14	Q Do you see where it says: "In small	12:13:03
15	molecule tracers..."?	12:13:05
16	You see that?	12:13:06
17	A Yes.	12:13:07
18	Q It says: "In small molecule tracers, the	12:13:07
19	radionuclide most often replaces an isotopologue	12:13:11
20	(e.g. [(11)C]-acetate or [(15)O]-H(2)O) or is	12:13:15
21	incorporated into the basic structure of a molecule	12:13:22
22	with either the intent of strategically altering the	12:13:25

1 behavior of the parent molecule (e.g., [(18)F]-FDG) 12:13:29

2 or, more likely, disturbing the activity of the 12:13:34

3 parent molecule as little as possible (e.g. 12:13:37

4 [(18)F]-FDHT or [(18)F]-FES)." 12:13:42

5 Did I read that correctly? 12:13:47

6 A You read that correctly. 12:13:49

7 Q And that is your statement, correct? 12:13:50

8 A That is my statement as of 2011. 12:13:51

9 Q And when you wrote that, you were 12:13:54

10 explaining that the preferred goal in small molecule 12:13:56

11 labeling is to disturb the activity of the parent 12:14:01

12 molecule as little as possible, correct? 12:14:04

13 A No. Because in the sentence above, I say: 12:14:06

14 "One of the strategies is strategically altering the 12:14:08

15 behavior of the parent molecule." 12:14:11

16 Q But then, right after that, you say: 12:14:13

17 "...or, more likely, disturbing the activity of the 12:14:15

18 parent molecule as little as possible..." 12:14:18

19 Didn't you say that? 12:14:20

20 A One possible goal in synthesizing a small 12:14:22

21 molecule radiotracer is radiolabeling it in a way 12:14:26

22 that disturbs the behavior as little as possible, 12:14:30

1	correct.	12:14:33
2	Q And as we discussed, this is because you're	12:14:40
3	risking disturbing the interactions between the	12:14:42
4	small molecule and the receptor, correct?	12:14:47
5	A Modifying the molecule with a radionuclide	12:14:53
6	can pose a risk -- excuse me -- can pose a risk of	12:14:57
7	interfering or adversely affecting the binding of	12:15:01
8	the molecule itself to its target.	12:15:06
9	Q And this concern is particularly acute for	12:15:10
10	small molecules compared to antibodies because small	12:15:14
11	molecules are much smaller and less tolerant to	12:15:16
12	modification than antibodies, correct?	12:15:19
13	A One has to be careful about this concern in	12:15:24
14	both contexts, and the context -- the degree of	12:15:26
15	sensitivity of the molecule being radiolabeled can	12:15:33
16	change dramatically even within the context of small	12:15:39
17	molecules and large molecules. Generally, that is	12:15:45
18	less of a concern in the context of full-length	12:15:50
19	immunoglobulins than it is in the context of small	12:15:53
20	molecules.	12:15:59
21	Q So strategies that may be acceptable for	12:15:59
22	antibodies are not necessarily acceptable for small	12:16:05

1 molecules, correct? 12:16:11

2 A No. The guiding principles are the same. 12:16:18

3 The guiding principles are to modify the targeting 12:16:21

4 vector in a way that does not impede or adversely 12:16:25

5 affect its binding to its target. 12:16:33

6 Q But are the strategies in doing so the 12:16:39

7 same? 12:16:46

8 A Now we're running into a definitional 12:16:46

9 problem with regard to the word "strategies." 12:16:48

10 I would argue that an overarching 12:16:51

11 philosophy of how to do this is a strategy, and for 12:16:53

12 both small molecules and big molecules, the guiding 12:16:56

13 principles, strategy, philosophy is to modify the 12:16:59

14 targeting vector while perturbing the -- its ability 12:17:09

15 to bind its target as much as possible. 12:17:14

16 But, again, that's not the only 12:17:18

17 consideration across all time and space. There's 12:17:20

18 also the importance of the ease of radiolabeling, 12:17:24

19 the amenability, the modularity, how readily one can 12:17:27

20 alter pharmacokinetic profiles, and those ultimately 12:17:33

21 all favor using something like a linker and a 12:17:40

22 prosthetic group or chelator because those provide 12:17:43

1	the most flexibility and modularity and	12:17:46
2	adaptability.	12:17:50
3	Q Okay. But ways of labeling antibodies	12:17:51
4	versus small molecules might be different, correct?	12:17:54
5	MR. KUSHAN: Objection. Foundation.	12:18:02
6	THE WITNESS: I can't possibly know every	12:18:05
7	single way that's ever been used to label a small	12:18:08
8	molecule and every single way that's ever been used	12:18:11
9	to label an antibody and tell you, on the spot,	12:18:14
10	whether every single one way could or could not be	12:18:19
11	used in the other context. Again, the guiding	12:18:23
12	principle is the same.	12:18:26
13	BY DR. PARTINGTON:	12:18:36
14	Q Are you aware of the differences between	12:18:36
15	labeling a small molecule versus an antibody?	12:18:39
16	MR. KUSHAN: Objection. Foundation.	12:18:46
17	DR. PARTINGTON: Strike that.	12:18:49
18	BY DR. PARTINGTON:	12:18:50
19	Q Are you aware of differences in techniques	12:18:51
20	between labeling small molecules versus antibodies?	12:18:52
21	A Many of the same techniques are used in	12:19:01
22	both contexts insomuch as going to the second	12:19:05

1 sentence of this paragraph, where it says: "In
2 small molecule tracers, the radionuclide most often
3 replaces an isotopologue..." These are talking
4 about very, very, very small molecules, acetate and
5 water, also ammonia.

6 In those cases, literally on the
7 cyclotron -- the cyclotron replaces the atom in the
8 middle of the ammonia -- that is not used to label
9 antibodies. But the guiding principles of how to
10 radiolabel a molecule are the same for small
11 molecules, especially small molecules that target
12 specific proteins and antigens and immunoglobulins.
13 And many of the same ways that are used to label
14 large molecules can be used and have been used to
15 great effect to label small molecules.

16 DR. PARTINGTON: I would like to mark as
17 Exhibit, I believe, 2019.

18 - - -

19 (Deposition Exhibit 2019 was marked
20 for identification.)

21 - - -

22 BY DR. PARTINGTON:

12:19:12
12:19:15
12:19:19
12:19:21
12:19:25
12:19:28
12:19:31
12:19:35
12:19:38
12:19:42
12:19:47
12:19:49
12:19:55
12:19:58
12:20:02
12:20:37
12:20:39
12:20:39
12:20:39
12:20:39
12:21:02
12:21:02

Transcript of Brian Zeglis, Ph.D.
Conducted on March 11, 2026

121

1	Q	Do you recognize this reference, Doctor?	12:21:02
2	A	Yes, I recognize this reference.	12:21:05
3	Q	You are also co-author of this reference,	12:21:08
4		credibility?	12:21:11
5	A	I am a co-author of this reference, but it	12:21:11
6		was written by five people.	12:21:13
7	Q	Sure.	12:21:14
8		When was the last time you reviewed this	12:21:19
9		reference?	12:21:21
10	A	This -- I don't recall it being an exhibit,	12:21:23
11		but I've reviewed this within the last year,	12:21:28
12		probably.	12:21:32
13	Q	And why would you -- why did you review	12:21:33
14		this reference in the last year?	12:21:35
15	A	Probably because somebody contacted me and	12:21:37
16		said, "Hey, it would cost a bunch of money to buy	12:21:42
17		this paper. Can you send me a copy, please?"	12:21:46
18	Q	Got it.	12:21:51
19	A	And I will send them a copy. And in so	12:21:52
20		doing, I would say, "Oh, that was a long time ago.	12:21:56
21		Let me look through it."	12:21:58
22	Q	In this paper, you discuss using -- or	12:22:00

1	strike that.	12:22:23
2	In this paper, you discuss labeling small	12:22:23
3	molecules with radionuclides, correct?	12:22:26
4	A One of the things in this paper is a	12:22:50
5	discussion of labeling small molecules with	12:22:54
6	radionuclides.	12:22:58
7	Q Okay. Let me direct your attention to page	12:22:58
8	40, please.	12:23:03
9	Are you there?	12:23:18
10	A Mm-hmm.	12:23:18
11	Q Second full paragraph starting with:	12:23:19
12	"Given these considerations..." you see that?	12:23:22
13	A "Given these considerations, it is not	12:23:27
14	surprising that the incorporation of the	12:23:30
15	radionuclide is the single most important step in	12:23:32
16	the synthesis of a radiotracer. Synthetic	12:23:35
17	methodologies for the radiolabeling of small	12:23:39
18	molecules are often either nucleophilic or	12:23:42
19	electrophilic in nature, and reaction schemes can	12:23:45
20	vary widely from one tracer to the next. These	12:23:49
21	methods will be addressed on a case-by-case basis	12:23:52
22	throughout the chapter. Strategies for	12:23:54

1	radiolabeling larger molecules are more easily	12:23:56
2	generalized and are presented here as a precursor to	12:24:00
3	the discussion of the agents themselves."	12:24:03
4	Q Okay. So it lists here, you do make a	12:24:06
5	distinction between small molecules and antibodies	12:24:09
6	and strategies for labeling those, correct?	12:24:11
7	A No, I don't. I don't think I do that.	12:24:14
8	Synthetic methodologies for small molecules	12:24:17
9	are often, not always, and they can vary widely, and	12:24:19
10	the methods will be addressed in a case-by-case	12:24:24
11	basis. All I say is that strategies for	12:24:28
12	generalizing larger molecules are more easily	12:24:30
13	generalizable.	12:24:34
14	Q Okay.	12:24:34
15	A So there isn't a distinct line drawn	12:24:35
16	between them. And mostly what is meant there --	12:24:38
17	again, this paper had five authors -- is that those	12:24:41
18	techniques that I was telling you about before,	12:24:46
19	incorporating a radioactive atom in the center of	12:24:48
20	the molecule, is -- that's not typically used in the	12:24:53
21	context of large molecules.	12:24:59
22	Q Okay. You do, however, comment on the	12:25:10

1	variability between tracers in the context of	12:25:13
2	labeling small molecules, correct?	12:25:21
3	A "...can vary widely from one tracer to the	12:25:27
4	next."	12:25:29
5	An important thing also to say is that this	12:25:30
6	was a textbook chapter designed to capture what was	12:25:33
7	going on in the moment, but, also, all time going	12:25:36
8	backwards. And so one of the ways to reduce the	12:25:40
9	variability of labeling small molecules would be to	12:25:43
10	use linkers and prosthetic groups or chelators	12:25:47
11	because that makes the radiolabeling of small	12:25:53
12	molecules more modular, more adaptable.	12:25:59
13	Q Okay. But this variability that you're	12:26:01
14	discussing here, it exists because different small	12:26:04
15	molecule tracers have different chemical structures,	12:26:07
16	correct?	12:26:09
17	A That's not the only reason it exists. It	12:26:11
18	also exists because directly radiolabeling small	12:26:14
19	molecules is very hard.	12:26:18
20	Q Okay. But differences between --	12:26:22
21	difference in structure between small molecules is	12:26:23
22	one of the reasons why the variability exists,	12:26:26

1	correct?	12:26:29
2	A One of the reasons the variability -- that	12:26:30
3	reaction schemes can vary widely from one tracer to	12:26:35
4	the next -- one of the reasons, not the only reason,	12:26:40
5	is that different tracers -- different	12:26:42
6	pharmacophores have different structures.	12:26:45
7	Q Right.	12:26:47
8	And those structural differences affect	12:26:47
9	where and how a radionuclide can be incorporated,	12:26:50
10	correct?	12:26:53
11	A Not necessarily. Those structural	12:26:55
12	differences, that's only if you want to incorporate	12:26:57
13	a radionuclide directly. Again, if one uses a	12:27:00
14	system that provides more modularity and	12:27:03
15	variability, the entire process becomes easier.	12:27:06
16	Q Okay. But if one wanted to use direct	12:27:08
17	halogenation, structural differences would affect	12:27:12
18	where and how a radionuclide -- radionuclide can be	12:27:15
19	incorporated, correct?	12:27:20
20	A If one wanted to directly radiohalogenate a	12:27:22
21	molecule, the structure of that molecule would	12:27:26
22	affect whether that was possible or not.	12:27:32

1	Q	Okay. And some molecules might not be	12:27:34
2		amenable to direct halogenation, correct?	12:27:39
3	A	I mean, I can't comment on all molecules,	12:27:43
4		but water is not -- you can't directly	12:27:48
5		radiohalogenate water.	12:27:50
6	Q	Would you ever make an imaging agent out of	12:27:53
7		water, Doctor?	12:27:56
8	A	Yeah. Absolutely. It's right here	12:27:56
9		(indicating.)	12:27:58
10	Q	For --	12:27:58
11	A	O(15), water. It's used every day.	12:28:00
12	Q	For targeting cancer?	12:28:02
13	A	Yeah.	12:28:04
14	Q	Okay. Interesting. I learned something.	12:28:04
15		Okay. So some molecules can or cannot be	12:28:31
16		directly halogenated. Some molecules will require	12:28:34
17		prosthetic group, correct?	12:28:39
18		MR. KUSHAN: Objection. Foundation.	12:28:46
19		THE WITNESS: Again, I mean, you're --	12:28:47
20		that's encompassing the entirety of chemical space.	12:28:48
21		A small molecule -- it is my opinion that a	12:28:53
22		small molecule, if possible, should be labeled using	12:28:58

1 a linker and a chelator or a prosthetic group 12:29:05
2 because that provides both spatial separation and 12:29:09
3 the maximum amount of adaptability modularity, the 12:29:13
4 maximum amount of radionuclides. 12:29:18

5 That is a much easier and derisked and 12:29:20
6 higher likelihood of success way of doing it than 12:29:22
7 isotopologous substitution or direct 12:29:26
8 radiohalogenation. 12:29:32

9 DR. PARTINGTON: All right. Let's take 12:29:34
10 lunch, please. Let's go off the record. 12:29:35

11 (Whereupon, at 12:29 p.m., the 12:29:38
12 proceedings in the above-entitled matter were 12:29:38
13 recessed, to reconvene at 1:06 p.m., this same day.) 12:29:38

14 AFTERNOON SESSION 12:29:38

15 (1:06 p.m.) 12:39:04

16 CONTINUED EXAMINATION BY COUNSEL FOR PATENT OWNER 13:06:25

17 BY DR. PARTINGTON: 13:06:25

18 Q Welcome back, Doctor. 13:06:26

19 A Thank you. 13:06:28

20 Q Before 2017 there were small molecules 13:06:28
21 known to bind to fibroblast activation protein, 13:06:32
22 correct? 13:06:35

1	A	Yes. Correct.	13:06:37
2	Q	In fact, there were many small molecules	13:06:39
3		that are known to bind to FAP, correct?	13:06:41
4		MR. KUSHAN: Objection. Foundation.	13:06:45
5		THE WITNESS: Depends on what you mean by	13:06:46
6		"many," but there were several.	13:06:48
7		BY DR. PARTINGTON:	13:06:50
8	Q	More than ten?	13:06:50
9	A	I mean, the Jansen 2014 paper covers	13:06:51
10		several but, I mean, also it depends on what you	13:06:55
11		mean by, "bind to," and the threshold for affinity,	13:06:58
12		but, yeah, generally speaking, correct.	13:07:02
13	Q	Those molecules were typically referred to	13:07:05
14		as FAP inhibitors or FAPIs, correct?	13:07:08
15		THE COURT REPORTER: "FAP inhibitors or"?	13:07:08
16		BY DR. PARTINGTON:	13:07:08
17	Q	F-A-P-I-S, FAPI -- FAPIs, plural, correct?	13:07:14
18	A	Those molecules are often called FAP	13:07:23
19		inhibitors, correct.	13:07:26
20	Q	Okay. So I'm going to direct your	13:07:33
21		attention to Exhibit 2003.	13:07:34
22	A	Would you mind giving me a couple minutes	13:07:55

1	to orient myself to this?	13:07:58
2	Q Go for it.	13:08:01
3	A Thank you.	13:08:02
4	Okay.	13:08:48
5	Q Okay. Do you recognize this exhibit,	13:08:48
6	Doctor?	13:08:50
7	A I have seen this exhibit before, yes.	13:08:51
8	Q When was the last time you reviewed that	13:08:52
9	exhibit?	13:08:55
10	A A few days ago.	13:08:55
11	Q So this document discloses small-molecule	13:09:02
12	FAPIs, correct?	13:09:05
13	A Selective inhibitors of fibroblast	13:09:09
14	activation protein. They don't call them FAPIs, at	13:09:12
15	least in the title, but, yes they are, by the title	13:09:15
16	of the paper, inhibitors of fibroblast activation	13:09:19
17	protein.	13:09:22
18	Q Let's turn to page -- I'm sorry -- to Table	13:09:22
19	3, please.	13:09:25
20	A Sure.	13:09:26
21	Q It's page 1703. This table -- are you	13:09:26
22	there?	13:09:40

1	A	I am at Table 3. Would you mind giving me	13:09:40
2		a minute --	13:09:42
3	Q	Sure.	13:09:43
4	A	-- to kind of internalize what's being	13:09:44
5		disclosed here?	13:09:49
6		Okay.	13:10:09
7	Q	This table lists a number of different	13:10:10
8		FAPIs, correct?	13:10:12
9	A	Yes. One, two, three, four, five, six,	13:10:13
10		seven, eight, nine, ten, 11. The table lists 11	13:10:17
11		different inhibitors.	13:10:22
12	Q	Okay. Could you please turn to Table 4?	13:10:26
13	A	May I have a minute to orient to this one?	13:10:35
14	Q	Yes, you may.	13:10:41
15	A	Okay.	13:11:22
16	Q	Table 4 also lists a number of different	13:11:22
17		FAPIs, correct?	13:11:25
18	A	Hmm, I mean, I suppose. Strictly speaking,	13:11:28
19		most of these are better DPPIV inhibitors.	13:11:33
20		THE COURT REPORTER: Say that again. "Most	13:11:33
21		of these are"?	13:11:33
22		THE WITNESS: Most of these compounds are	13:11:38

1	what the data tells us. Most of these compounds are	13:11:40
2	better DPPIV inhibitors than they are FAP	13:11:44
3	inhibitors --	13:11:49
4	BY DR. PARTINGTON:	13:11:56
5	Q Okay.	13:11:56
6	A -- have higher -- lower IC(50) values.	13:11:50
7	Q But they're also FAPIs, correct?	13:11:57
8	A I can't speak to 13o, 13p, 13q, 13r, 13s,	13:11:58
9	13t, 13u, 13w, 13v, 13x or 13y because all of their	13:12:05
10	FAP IC(50) values are not listed, and therefore I	13:12:16
11	cannot tell, as a new reader of this article,	13:12:21
12	whether they inhibit FAP at all. I guess I could	13:12:25
13	tell you that 13k, 13l, 13m, and 13n do inhibit FAP	13:12:32
14	at some concentration.	13:12:38
15	Q Okay.	13:12:39
16	Why did you say that you were a new reader	13:12:40
17	of this article? I thought you said that you just	13:12:43
18	reviewed it in the last couple of days?	13:12:45
19	A I mean, it's new to me right now. I've	13:12:47
20	looked at the paper, but I wouldn't want to comment	13:12:50
21	on this table without carefully examining the table.	13:12:53
22	Q Okay. But you did review this paper in the	13:12:58

1	last --	13:13:00
2	A I did review this paper, but --	13:13:01
3	Q So you're not a new reader to this paper,	13:13:02
4	correct?	13:13:05
5	A I'm a new, careful examiner to this	13:13:05
6	particular table.	13:13:07
7	Q Okay.	13:13:08
8	A So I wanted to do it carefully so that I	13:13:08
9	could answer the questions.	13:13:11
10	Q Fair enough.	13:13:12
11	You can put that aside.	13:13:19
12	The next exhibit I'm handing you is	13:13:31
13	Exhibit 1044.	13:13:33
14	Have you seen this exhibit before, Doctor?	13:13:43
15	A I have seen this exhibit before.	13:13:45
16	Q And when was the last time you reviewed	13:13:47
17	this exhibit?	13:13:49
18	A Within the last couple months.	13:13:49
19	Q And this is a Jansen --	13:13:55
20	A Just -- yeah.	13:13:56
21	Q Good?	13:13:58
22	A Yeah.	13:14:20

1	Q	So this is Jansen patent application,	13:14:21
2		correct?	13:14:24
3	A	Mm-hmm.	13:14:24
4	Q	And this exhibit, Exhibit 1044, also	13:14:24
5		discloses small-molecule FAPIs, correct?	13:14:31
6	A	It doesn't use the words "small molecule"	13:14:42
7		in the abstract, but it says: "NOVEL FAP	13:14:46
8		INHIBITORS," as the title.	13:14:49
9	Q	Okay. Let's go to Table 3, page 42.	13:14:51
10	A	Mm-hmm.	13:15:24
11	Q	Table 4 lists multiple different FAPIs,	13:15:24
12		correct?	13:15:27
13	A	Oh, you said page 42 and then you said	13:15:27
14		Table 4.	13:15:32
15	Q	Oh, I'm sorry. Table 3. My bad. Table 3,	13:15:32
16		page 42. Let me reask the question.	13:15:35
17		Table 3 lists multiple different FAPIs,	13:15:38
18		correct?	13:15:41
19	A	If I could take a moment to familiarize	13:15:46
20		myself with this table again.	13:15:48
21	Q	Of course.	13:15:49
22	A	Yes, this table lists, across several	13:16:20

1 pages, four -- like, 11 or so inhibitors of FAP.

13:16:26

2 Q Okay. And these FAP inhibitors are
3 different from the ones that we had just looked at
4 in the previous exhibit, correct?

13:16:34

13:16:37

13:16:39

5 A The previous exhibit used a xanthine
6 scaffold. Since it's been a little while, I'm not
7 entirely comfortable reconstructing the scaffold
8 here, but presumably these are the scaffolds. So,
9 yes, these are different -- these are different FAP
10 inhibitors.

13:16:43

13:16:48

13:16:57

13:17:05

13:17:08

13:17:11

11 Q Okay. Let's look at Table 4 of the same
12 exhibit, please. This table also lists more FAPIs,
13 correct?

13:17:11

13:17:15

13:17:23

14 A Yes. Correct.

13:17:49

15 Q Okay. And these are also different from
16 the xanthine FAPIs, correct?

13:17:50

13:17:52

17 A Again, I'm not entirely comfortable having
18 this in front of me and knowing the R(5), R(6) -- I
19 presume the R(5), R(6) is denoted in that structure,
20 and the star is denoting -- let me just take a
21 moment to make sure -- I'm having trouble finding
22 the identity of the asterisk structure, but based on

13:18:00

13:18:02

13:18:06

13:18:11

13:18:19

13:19:06

1	my memory, I do not -- I believe these to be	13:19:09
2	distinct inhibitors --	13:19:12
3	Q Mm-hmm.	13:19:12
4	A -- compared to the xanthine-based --	13:19:15
5	xanthine-based compounds in the --	13:19:19
6	Q Does the -- if you'd go to page 43 in the	13:19:21
7	bottom, does that help you?	13:19:24
8	A That does help me. Thank you.	13:19:28
9	Q So different than xanthine?	13:19:30
10	A So these are different than -- well, let me	13:19:32
11	just look through each of them and make sure there's	13:19:35
12	no xanthines. Let me make sure no xanthine.	13:19:38
13	Yes, none of these have xanthine core	13:19:56
14	structures.	13:19:59
15	Q Okay. And the compounds in Table 4 are not	13:20:00
16	the same as the compounds in Table 3, correct?	13:20:05
17	A I can go through each one. I remember,	13:20:11
18	from reviewing this patent, that the nomenclature	13:20:15
19	with compound and examples list -- numbers listed	13:20:18
20	separately gets a little confusing. So I do not	13:20:22
21	think that any of the same compounds are listed in	13:20:28
22	both tables.	13:20:31

1	Q	Okay. You can put that aside.	13:20:34
2		I'm handing you Exhibit 1007.	13:20:44
3		Do you recognize this exhibit, Doctor?	13:20:59
4	A	I do.	13:21:01
5	Q	When was the last time you saw this, or	13:21:06
6		rather -- strike that.	13:21:09
7		When was the last time you reviewed this	13:21:10
8		paper?	13:21:12
9	A	Within the last couple weeks.	13:21:12
10	Q	Exhibit 1007 discloses small-molecule	13:21:20
11		FAPIs, correct?	13:21:25
12	A	I'm sorry. Which -- which -- which is	13:21:25
13		Exhibit 1007?	13:21:28
14	Q	The one that I just handed you.	13:21:29
15	A	Oh, okay. You used the word "disclosed,"	13:21:31
16		so I -- this -- yeah, I guess it --	13:21:34
17	Q	Describes?	13:21:36
18	A	Yeah, I got in -- I was thinking about	13:21:37
19		making sure I got the lawyer terms correct.	13:21:40
20	Q	Let me just reask then --	13:21:42
21	A	Yes.	13:21:43
22	Q	-- to make the record clear.	13:21:44

1	Exhibit 1007 describes small-molecule	13:21:45
2	FAPIs, correct?	13:21:51
3	A Yes.	13:21:52
4	Q Let's go to Table 2, please.	13:21:55
5	A Okay. Give me a second, please.	13:22:03
6	Okay.	13:22:21
7	Q Table 2 discloses a number of different	13:22:21
8	FAPIs, correct?	13:22:23
9	A Yes. That number is -- there are 13	13:22:26
10	different FAP inhibitors described in Table 2.	13:22:34
11	Q And Table 3 also discloses a number of	13:22:40
12	different FAP inhibitors, correct?	13:22:43
13	A Yes. It's unclear whether Compound 22 is a	13:22:56
14	FAP inhibitor because an exact IC(50) value is not	13:22:59
15	reported, but excluding that one, Table 3 describes	13:23:05
16	15.	13:23:15
17	Q And FAPIs disclosed in Table 2 and 3 of	13:23:18
18	Exhibit 1007 are different from the FAPIs disclosed	13:23:24
19	in the xanthine paper, correct?	13:23:27
20	A Different from the xanthine paper?	13:23:30
21	Q Right.	13:23:32
22	A Yes.	13:23:32

1	Q	Okay. You can put that aside.	13:23:33
2		DR. PARTINGTON: All right. Let's mark	13:23:45
3		this exhibit as Exhibit 2020, please.	13:23:46
4		- - -	13:23:46
5		(Deposition Exhibit 2020 was marked	13:23:46
6		for identification.)	13:23:46
7		- - -	13:23:57
8		BY DR. PARTINGTON:	13:23:57
9	Q	Are you familiar with this reference,	13:23:57
10		Doctor?	13:23:58
11	A	I think I've seen this reference in the	13:23:58
12		past.	13:24:00
13	Q	When was the last time you reviewed this	13:24:02
14		reference?	13:24:05
15	A	I can't remember specifically reviewing	13:24:05
16		this reference, but I can't out -- rule out that I	13:24:07
17		haven't looked at it in the past.	13:24:11
18	Q	Okay. This paper also discloses	13:24:15
19		small-molecule FAPIs, correct?	13:24:16
20	A	It identifies small -- small-molecule	13:24:19
21		inhibitors of FAP and prolyl oligopeptidase.	13:24:24
22	Q	Okay.	13:24:34

1	Let's look at Table 1, and to make it	13:24:34
2	easier for you, it is page 23 -- actually, I'm	13:24:40
3	sorry. Table 2, so page 24.	13:24:48
4	A I need a minute.	13:24:57
5	Q Okay.	13:24:58
6	A Okay. I'm prepared to talk about table --	13:25:23
7	oh, you said table which?	13:25:27
8	Q Two.	13:25:29
9	A I'm sorry. I was looking at Table 1.	13:25:29
10	Okay.	13:25:53
11	Q Table 2 lists multiple FAPIs, correct?	13:25:53
12	A Yeah, depending whether you would qualify	13:25:58
13	Compound 8 as a FAP inhibitor with a 500 nanomolar	13:26:01
14	IC(50) is debatable, but excluding Compound 8, one,	13:26:07
15	two, three, four, five different molecules	13:26:11
16	investigated for inhibiting FAP.	13:26:14
17	Q Let's look at Table 3, and let me know when	13:26:17
18	you're ready for me to ask you a question.	13:26:30
19	A Okay. Thank you.	13:26:32
20	Okay.	13:26:58
21	Q Table 3 also lists several FAPIs, correct?	13:26:59
22	A Yes. Most of these would be better	13:27:04

1 described as -- in the case of 17 and 15, those are 13:27:08
2 primarily PREP inhibitors; 14 and 16 would be 13:27:15
3 described as poorly selective FAP inhibitors; and 13:27:21
4 Compound 13 would be accurately described as a FAP 13:27:26
5 inhibitor. 13:27:29

6 Q Okay. And Table 4, please. 13:27:32

7 A I can't really assess Table 4 because the 13:27:53
8 IC -- IC(50) values at the top of figure 4 are in 13:27:57
9 units of HM, and I don't understand what that unit 13:28:02
10 is. 13:28:10

11 Q Okay. 13:28:10

12 These FAPIs that we've looked at in this 13:28:13
13 exhibit that you have in front of you marked 13:28:17
14 Exhibit 2020, are different from the xanthine FAPIs 13:28:24
15 that we looked at, correct? 13:28:27

16 A Correct. 13:28:28

17 Q They're also different from the 13:28:29
18 quinolinoyl -- quinolinoyl-based FAPIs that we 13:28:32
19 looked at from Jansen, correct? 13:28:36

20 A Well, many of these are also -- hold on. 13:28:38
21 Make sure I can speak plainly. 13:28:41

22 Yes, none of these -- no. So Table 3 has 13:28:49

1	quinoline-based structures.	13:28:54
2	Q Do you know if these quinoline-based	13:28:57
3	structures are the same as the structures we just	13:28:59
4	looked at in --	13:29:03
5	A They are different from the Jansen	13:29:03
6	quinoline structures.	13:29:05
7	Q Great. You can put that aside.	13:29:06
8	A Okay.	13:29:09
9	Q Doctor, you testified that binding	13:29:18
10	selectivity is ultimately the most important factor	13:29:20
11	when choosing the pharmacophore that will act as the	13:29:25
12	targeting moiety of a radiopharmaceutical, and my	13:29:30
13	question is: When you used the term "selectivity,"	13:29:32
14	you mean the ability of a ligand to bind its	13:29:36
15	intended target preferentially over other biological	13:29:40
16	targets, correct?	13:29:46
17	A That was a very long question. Can you	13:29:47
18	shorten the question just so I can be precise.	13:29:48
19	Q When you use the term "selectivity" --	13:29:51
20	A Yes.	13:29:55
21	Q -- you mean the ability of a ligand to bind	13:29:56
22	its intended target preferentially over other	13:30:00

1 biological targets, correct?

13:30:04

2 A No. Relative to a specific different
3 target. Selectivity in the context of most of the
4 FAP inhibitors we've discussed here is relative to a
5 different enzyme, the prolyl oligopeptidase PREP.

13:30:07

13:30:09

13:30:13

13:30:18

6 Q Okay. So just to make the record clear,
7 when you use the term "selectivity," you mean the
8 ability of a ligand to bind FAP preferentially over
9 PREP, correct?

13:30:26

13:30:29

13:30:33

13:30:38

10 MR. KUSHAN: Objection. Foundation.

13:30:39

11 THE WITNESS: That's not what I mean every
12 time you use the word "selectivity."

13:30:40

13:30:42

13 In the context of the declaration, when we
14 specifically speak about FAP over PREP selectivity,
15 that's what I mean by the word "selectivity."

13:30:46

13:30:48

13:30:52

16 BY DR. PARTINGTON:

13:30:55

17 Q Thank you.

13:30:55

18 In other words, you want strong binding to
19 the desired target and minimal binding to off
20 target, correct?

13:31:01

13:31:05

13:31:11

21 A You -- selectivity is simply a ratio of the
22 binding to the intended target protein over the

13:31:12

13:31:20

1 binding to the other protein over which you'd like 13:31:23
2 selectivity. Whether that numerator in that 13:31:29
3 equation is strong binding or not, that's a question 13:31:33
4 of affinity. That's a different question. But 13:31:36
5 affinity is simply a ratio. 13:31:38

6 Q You mean selectivity is simply a ratio? 13:31:53

7 A I apologize. Let me correct that. 13:31:56

8 Q Yeah. 13:31:58

9 A Selectivity is a ratio. 13:31:58

10 Q Mm-hmm. Got it. 13:32:00

11 You described selectivity as the most 13:32:09
12 important factor because a radiopharmaceutical is 13:32:11
13 intended to report on the specific biological 13:32:13
14 target, correct? 13:32:16

15 A Can you tell me exactly where I say that in 13:32:17
16 the declaration just so I can get the context? 13:32:19

17 Q Paragraph 55. 13:32:24

18 A Allow me to read it, please. 13:32:55

19 Okay. 13:33:20

20 Q So let me ask you again. 13:33:20

21 You describe selectivity as the most 13:33:23
22 important factor because a radiopharmaceutical is 13:33:25

1 intended to report on a specific biological target, 13:33:29
2 correct? 13:33:32

3 A I say, in the declaration: "... two issues 13:33:39
4 are paramount...the selectivity of the pharmacophore 13:33:44
5 for the molecular target (i.e. how much better it 13:33:46
6 binds the desired target compared to related 13:33:50
7 biomolecules) and (ii) the affinity of the 13:33:53
8 pharmacophore for the molecular target (i.e. how 13:33:56
9 tightly it binds the molecular target.) While both 13:34:00
10 are necessary, binding selectivity is ultimately the 13:34:03
11 most important factor." 13:34:06

12 Q Right. 13:34:07

13 And my question for you is: The reason you 13:34:08
14 describe selectivity as the most important factor is 13:34:10
15 because a radiopharmaceutical is intended to report 13:34:16
16 on the specific biological target, correct? 13:34:19

17 A Yes. Do I say -- do I say the intend -- 13:34:22
18 that intended sentence somewhere that I'm missing? 13:34:25

19 Q I'm just asking you a question. 13:34:28

20 Is that why you -- you stated that 13:34:29
21 selectivity is ultimately the most important factor? 13:34:33

22 A I explain -- 13:34:37

1	MR. KUSHAN: Sorry. Objection.	13:34:39
2	Foundation.	13:34:41
3	THE WITNESS: I explain why selectivity is	13:34:41
4	more important in the bottom. I'll just read that	13:34:43
5	and, hopefully, that will answer your question.	13:34:46
6	"While both are necessary, binding	13:34:49
7	selectivity is ultimately the most important factor.	13:34:52
8	For example, a radiotracer that has high affinity	13:34:55
9	but low selectivity for a desired molecular target	13:34:58
10	may bind to both the desired target and other	13:35:01
11	targets in vivo, thereby potentially visualizing	13:35:04
12	non-target tissues in the body and producing 'false	13:35:08
13	positive' imaging results. Conversely, a	13:35:11
14	radiotracer that has high selectivity but low	13:35:15
15	affinity for a desired molecular target may not bind	13:35:18
16	the desired molecular target well but will at least	13:35:22
17	not bind other targets in vivo. Such a radiotracer	13:35:24
18	could be effective if the desired target was highly	13:35:29
19	abundant but could produce 'false negative' imaging	13:35:32
20	results if the desired target was scarce."	13:35:35
21	BY DR. PARTINGTON:	13:35:38
22	Q So the answer to my question then is, yes,	13:35:39

1 you describe selectivity as the most important
2 factor because the radiopharmaceutical is intended
3 to report on the specific biological target,
4 correct?

13:35:41

13:35:44

13:35:45

13:35:48

5 A I'm much more comfortable explaining why I
6 think selectivity is important by reading exactly
7 how -- why I say it's important in the declaration.

13:35:48

13:35:51

13:35:54

8 Q I realize, Doctor, that you're much more
9 comfortable referring to your declaration, but if
10 you recall, at the beginning of the deposition you
11 agreed that you're going to answer my questions the
12 way I ask them. So could you please answer the
13 question the way I ask it, without --

13:35:58

13:36:03

13:36:05

13:36:07

13:36:10

13:36:14

14 MR. KUSHAN: Objection.

13:36:18

15 BY DR. PARTINGTON:

13:36:19

16 Q -- pointing me to multiple sentences in
17 your declaration? Let me rephrase the question
18 again.

13:36:19

13:36:22

13:36:25

19 A Okay.

13:36:26

20 Q You describe selectivity as the most
21 important factor because a radiopharmaceutical is
22 intended to report on the specific biological

13:36:26

13:36:29

13:36:33

1	target, correct?	13:36:37
2	A The relation --	13:36:38
3	MR. KUSHAN: Objection. Foundation.	13:36:40
4	Objection as to form.	13:36:41
5	THE WITNESS: The relationship between a	13:36:42
6	radiopharmaceutical, its intended target, and other	13:36:44
7	possible targets are -- that question I answered	13:36:48
8	already when I read that passage. I feel like I've	13:36:53
9	answered that question already.	13:36:56
10	BY DR. PARTINGTON:	13:36:57
11	Q Is selectivity most important because a	13:36:58
12	radiopharmaceutical is intended to report on the	13:37:01
13	specific biological target, yes or no, Doctor?	13:37:03
14	MR. KUSHAN: Objection to form.	13:37:09
15	THE WITNESS: Again, I mean, a	13:37:16
16	radiopharmaceutical and reporting on, I think even	13:37:21
17	the premise of that question is confusing because a	13:37:24
18	radiopharmaceutical can be therapeutic, but -- and	13:37:28
19	that doesn't report on anything.	13:37:33
20	But, again, the importance of selectivity	13:37:36
21	and why I think selectivity is important, I answered	13:37:38
22	specifically in the relationship between a single	13:37:43

1	biological target -- as you asked, I answer	13:37:47
2	specifically and clearly in that passage of the	13:37:50
3	declaration.	13:37:53
4	BY DR. PARTINGTON:	13:38:07
5	Q Is selectivity concerns specially acute for	13:38:08
6	small-molecule radiopharmaceuticals?	13:38:21
7	THE COURT REPORTER: I'm sorry. I missed a	13:38:21
8	word. "Is selectivity"?	13:38:21
9	BY DR. PARTINGTON:	13:38:21
10	Q -- concerns specifically acute for	13:38:21
11	small-molecule radiopharmaceuticals as compared to,	13:38:22
12	let's say, antibody?	13:38:23
13	A Selectivity is always a concern in the	13:38:24
14	context of radiopharmaceuticals.	13:38:27
15	Q Is it more acute for small molecules versus	13:38:34
16	antibody because small molecules are more likely to	13:38:38
17	interact with multiple biological targets?	13:38:40
18	A I will not say that is true. Selectivity	13:38:45
19	is always important for all radiopharmaceuticals and	13:38:48
20	imaging agents.	13:38:51
21	Q Is a small molecule more likely to interact	13:38:52
22	with multiple biological targets than an antibody?	13:38:55

1 A It's impossible for me to answer that
2 without knowing the entire lump sum of all small
3 molecule interactions and all antibody interactions.
4 Myself would not worry about selectivity more with a
5 small molecule than an antibody, per se, because
6 selectivity is always important within the context
7 of radiopharmaceuticals, optical imaging agents, in
8 vitro imaging agents across the board.

9 Q And does your answer regarding the
10 importance of selectivity depend on whether it's
11 imaging agent versus therapeutic agent?

12 A Selectivity is important for
13 radiopharmaceuticals, the entire group, and optical
14 imaging agents, all of them. Selectivity is always
15 important.

16 Q And this means that starting with a small
17 molecule that already has a high selectivity is
18 critical for developing a successful
19 radiopharmaceutical, correct?

20 MR. KUSHAN: Objection. Foundation.

21 THE WITNESS: Having a molecule, as I say
22 here -- I mean, I'll just read it here. "When

1	choosing the pharmacophore that will act as the	13:40:21
2	targeting moiety of a radiopharmaceutical, two	13:40:24
3	issues are paramount...the selectivity of the	13:40:25
4	pharmacophore...and...the affinity of the	13:40:28
5	pharmacophore..."	13:40:30
6	BY DR. PARTINGTON:	13:40:34
7	Q And starting with the pharmacophore that	13:40:34
8	has high selectivity is important because you cannot	13:40:37
9	create selectivity if it doesn't already exist,	13:40:41
10	correct?	13:40:44
11	A I don't really understand what you mean	13:40:48
12	by "creating selectivity where it doesn't exist."	13:40:50
13	Q Okay.	13:40:54
14	A I've never thought about that concept. I	13:40:54
15	can tell you that when developing a	13:40:58
16	radiopharmaceutical imaging agent, selectivity is	13:41:00
17	very important, but I don't know what you mean	13:41:02
18	by "creating selectivity."	13:41:05
19	Q So let's say you're starting with a	13:41:07
20	compound that is not selective for FAP. Attaching a	13:41:09
21	radionuclide to that compound is not going to create	13:41:17
22	selectivity for that compound, correct?	13:41:21

1 A I cannot speak -- without data I can't 13:41:24
2 really speak to what would happen in that particular 13:41:30
3 instance. I don't really even understand the 13:41:32
4 question. 13:41:34

5 Q Okay. Let me ask it differently. 13:41:35

6 A Okay. 13:41:35

7 Q You're starting with a compound that has 13:41:38
8 poor selectivity for FAP, and you are attaching a 13:41:42
9 prosthetic group to it with a radionuclide. Is it 13:41:51
10 true that attaching a prosthetic group to a molecule 13:41:58
11 that has poor selectivity to begin with is not going 13:42:02
12 to increase its selectivity for its intended target? 13:42:06

13 A I think it's really hard for me to comment 13:42:10
14 about a -- I mean, I would need to know about the 13:42:12
15 FAP inhibitor that you have in mind. I would need 13:42:17
16 to know why it's not selective in the first place. 13:42:20
17 So I don't really think I could accurately or -- or 13:42:24
18 reasonably answer that question. 13:42:29

19 Q Are you aware of any examples in which 13:42:31
20 adding a radionuclide to a small molecule increased 13:42:34
21 its selectivity for its intended target? 13:42:36

22 A Not that I can think of off the top of my 13:42:54

1	head.	13:42:56
2	Q Okay.	13:42:56
3	Given the importance of selectivity that	13:43:17
4	we've been discussing, you would want to start with	13:43:19
5	a compound that has the highest selectivity for its	13:43:25
6	target, all other things being equal, correct?	13:43:28
7	A Oh, I'm really not comfortable with "all	13:43:32
8	other things being equal," because all other things	13:43:36
9	are often not equal.	13:43:39
10	Like I explain: "A number" -- in paragraph	13:43:40
11	54: "A number of functional and practical	13:43:44
12	considerations influence the design of a	13:43:47
13	radiopharmaceutical..." and then, in paragraph 55, I	13:43:50
14	say that selectivity is important, but it's very	13:43:53
15	difficult, if not impossible, to envision a scenario	13:43:56
16	in which all other structural things are equal,	13:43:59
17	because that is hard to imagine.	13:44:02
18	Q Okay.	13:44:07
19	A So I'm having trouble understanding that	13:44:08
20	question.	13:44:10
21	Q That's fine.	13:44:10
22	I'm handing you Exhibit 1006.	13:44:14

1	Are you familiar with this exhibit, Doctor?	13:44:28
2	A Yeah. Yes.	13:44:29
3	Q When was the last time you saw this	13:44:30
4	exhibit?	13:44:32
5	A In the last couple days.	13:44:33
6	Q And let me ask it more correctly.	13:44:34
7	When was the last time you reviewed this	13:44:37
8	exhibit?	13:44:39
9	A In the last couple days.	13:44:39
10	Q Okay. Let's go to page 3062, please.	13:44:42
11	A Okay.	13:45:10
12	Q Table 5, you see Table 5 discloses Compound	13:45:10
13	60, correct?	13:45:16
14	A Yes.	13:45:18
15	Q That's the compound that you are -- that	13:45:18
16	you have testified that a person of ordinary skill	13:45:24
17	in the art would have picked for substituting in	13:45:26
18	Meletta's compound, correct?	13:45:29
19	A For substituting into Meletta's compound is	13:45:36
20	a phrase that I'm not comfortable with, but to build	13:45:38
21	a vector-linker-reporter-type, linker-based,	13:45:45
22	radiopharmaceutical, a skilled artisan would have	13:45:57

1	chosen Compound 60.	13:46:00
2	Q Okay. Fair enough.	13:46:01
3	What is the selectivity of Compound 60?	13:46:02
4	A The selectivity index, as reported by -- in	13:46:08
5	the right-hand column, is 562.5.	13:46:12
6	Q Okay. So please keep that open.	13:46:17
7	A Okay.	13:46:20
8	Q And I'm going to hand you the next exhibit.	13:46:20
9	Oh, you already have it. Exhibit 1044.	13:46:26
10	A I'm sorry. I don't know which one that is.	13:46:31
11	Q So it should say on the bottom left -- on	13:46:36
12	the bottom right -- I'm sorry -- 1044.	13:46:40
13	A Okay.	13:46:43
14	Q Let's turn to page 47 there, please.	13:46:44
15	What -- are you there?	13:47:10
16	A I am there.	13:47:11
17	Q What is the selectivity of Compound 21?	13:47:12
18	A Compound 21 is -- the selectivity is 1,700	13:47:21
19	and Compound twenty -- Compound -- yes, Compound 21	13:47:29
20	is 1,700.	13:47:37
21	Q Okay. Is that -- does this mean that	13:47:37
22	Compound 21 is more selective than Compound 60 from	13:47:40

1	Jansen, Exhibit 1006?	13:47:46
2	A Compound 21 from Exhibit 1044 has a higher	13:47:50
3	selectivity index than Compound 60 from	13:47:56
4	Exhibit 1006, but, of course, selectivity isn't the	13:48:01
5	only criterion that a skilled artisan would use to	13:48:03
6	select this compound.	13:48:08
7	Q Okay. And when you say it has high	13:48:11
8	selectivity index, that means that it's more	13:48:13
9	selective, correct?	13:48:15
10	A For FAP over PREP?	13:48:17
11	Q Correct.	13:48:20
12	A Yes.	13:48:21
13	Q Okay. Let's look at Compound 22, same	13:48:21
14	page.	13:48:28
15	What is the selectivity index for Compound	13:48:28
16	22?	13:48:31
17	A Greater than 4,500.	13:48:32
18	Q Does that make Compound 22 more selective	13:48:35
19	for FAP over PREP versus Compound 60?	13:48:37
20	A Yes, it does. But, again, that's not the	13:48:41
21	only criterion that one would use.	13:48:44
22	Q Let's look at page 48, please, Compound 24.	13:48:46

1	What is the selectivity of this Compound	13:48:59
2	24?	13:49:02
3	A Compound 24, Example 28, which I think is	13:49:06
4	also the same as Compound 61 in Exhibit 1006. 970.	13:49:14
5	Q That makes it more selective for FAP over	13:49:24
6	PREP versus Compound 60, correct?	13:49:27
7	A That is true.	13:49:29
8	Q Okay. Let's go to page 45, Compound 11,	13:49:35
9	please.	13:49:45
10	A Okay.	13:49:57
11	Q What's the number -- what's the selectivity	13:49:59
12	index for Compound 11?	13:50:02
13	A 677.	13:50:06
14	Q And that makes it more selective than	13:50:09
15	Compound 60, correct?	13:50:11
16	A Yes, but, again, that isn't the only	13:50:12
17	criterion.	13:50:14
18	Q Right.	13:50:16
19	If you'd go back to Exhibit 1006, please.	13:50:17
20	A Yes.	13:50:21
21	Q Page 3061, Compound 53. Compound --	13:50:21
22	A Two one --	13:50:44

1	Q	Go ahead.	13:50:46
2	A	I'm sorry?	13:50:48
3	Q	Go ahead.	13:50:49
4	A	Go ahead with what?	13:50:50
5	Q	Well, you started saying something. You	13:50:52
6		started saying something.	13:50:53
7		Let me ask you a question then.	13:50:55
8	A	Sure.	13:50:56
9	Q	What is the selectivity index for Compound	13:50:57
10		53?	13:51:02
11	A	2,116.3.	13:51:02
12	Q	That makes it more selective than Compound	13:51:05
13		60 in Jansen, correct?	13:51:08
14	A	Yes.	13:51:09
15	Q	Okay. You can put that aside.	13:51:12
16		I'm handing you Exhibit 1005.	13:51:25
17		Are you familiar with this exhibit, Doctor?	13:51:47
18	A	Yes.	13:51:50
19	Q	When was the last time you reviewed this	13:51:51
20		exhibit?	13:51:53
21	A	Let me make sure it's the exact same	13:51:56
22		version.	13:51:58

1	I'm not sure what the A1 means in the	13:52:22
2	corner, but, yes. So I reviewed this in the last	13:52:24
3	couple months.	13:52:27
4	Q A1 just means that it's application -- it's	13:52:27
5	just the way the Patent Office --	13:52:30
6	A Okay. So, yes, I've reviewed this in the	13:52:32
7	last couple months.	13:52:34
8	Q And, in fact, you -- your obviousness	13:52:35
9	analysis involves this exhibit, correct?	13:52:39
10	A Yes.	13:52:42
11	Q Does Exhibit 1005 relate to small molecule	13:52:44
12	radiopharmaceuticals targeting FAP?	13:52:49
13	A Does this exhibit relate to FAP?	13:52:51
14	Q (Nodding.)	13:52:54
15	A No. This exhibit relates to PSMA-targeting	13:52:54
16	compounds and the uses thereof.	13:52:59
17	Q Okay. All right. Let's go back to	13:53:01
18	Exhibit 1006. Sorry for jumping around. But --	13:53:03
19	A That's okay.	13:53:07
20	Q You also used this exhibit in your	13:53:15
21	obviousness analysis, correct?	13:53:18
22	A Yes.	13:53:19

1	Q	Does Exhibit 1006 relate to small-molecule	13:53:20
2		radiopharmaceuticals targeting FAP?	13:53:26
3	A	Does Exhibit 1006 relate to	13:53:29
4		radiopharmaceuticals? No. It relates to	13:53:32
5		pharmacophores that inhibit FAP.	13:53:36
6	Q	Okay. I'm handing you Exhibit 1004, and	13:53:45
7		Exhibit 1008.	13:53:55
8		Let's start with Exhibit 1004.	13:54:00
9	A	Okay.	13:54:04
10	Q	Do you recognize this exhibit?	13:54:04
11	A	Sorry. Yes.	13:54:09
12	Q	You relied on this exhibit for your	13:54:11
13		obviousness analysis, correct?	13:54:16
14	A	Yes.	13:54:18
15	Q	When was the last time you reviewed this	13:54:22
16		exhibit?	13:54:24
17	A	Within the last couple months.	13:54:24
18	Q	And then back to Exhibit 1008, do you	13:54:25
19		recognize that exhibit?	13:54:29
20	A	Sorry. I'm getting dizzy.	13:54:30
21	Q	You and me both.	13:54:31
22	A	Yes.	13:54:33

1	Q	When was the last time you reviewed that	13:54:36
2		exhibit?	13:54:38
3	A	Within the last couple weeks.	13:54:38
4	Q	Okay. And Exhibit 1008 is also cited by	13:54:41
5		you for your obviousness analysis, correct?	13:54:46
6	A	Yes.	13:54:49
7	Q	Both Exhibit 1005 -- strike that.	13:54:53
8		Both Exhibit 1004 and Exhibit 1008 relate	13:54:56
9		to small-molecule radiopharmaceuticals targeting	13:55:03
10		FAP, correct?	13:55:07
11	A	Yes. Exhibit 1008, it's in the title:	13:55:10
12		"...Boronic Acid-Based FAP Inhibitor" --	13:55:14
13		"Radiolabeled Boronic Acid-Based FAP Inhibitor..."	13:55:18
14		In Exhibit 1004 or the '633 patent, they	13:55:22
15		use a synonym for FAP, "SEPRASE," but it also	13:55:26
16		focuses on radiolabeled seprase or FAP inhibitors.	13:55:31
17	Q	Are you aware of any other references that	13:55:36
18		disclose small molecule FAP imaging agents before	13:55:42
19		2017?	13:55:48
20	A	I don't think so, but let me look through	13:56:01
21		these.	13:56:02
22		I mean, presumably, the authors Schibli,	13:56:04

1 Meletta probably had an abstract at a conference
2 that might be in the literature, but allow me to
3 look through the exhibit list just to make sure.

4 There are several papers that identify FAP
5 as a potential target in cancer.

6 Q That wasn't quite my question.

7 A I know. I'm -- I feel like that's
8 important context.

9 I mean, Exhibit No. 1035, Marquis, et al.,
10 targeting tumor micro- --

11 THE COURT REPORTER: I'm sorry. Say that
12 slower. "Targeting tumor"?

13 THE WITNESS: I apologize.

14 Exhibit 1035, Marquis, et al., Abstract No.
15 4467: Targeting Tumor Microenvironment With
16 Radiolabeled Inhibitors of Seprase.

17 BY DR. PARTINGTON:

18 Q Do you know if this is the same -- strike
19 that.

20 Do you know if this is the abstract that
21 you previously referred to from the Meletta group?

22 A Off the top of my head, I don't know.

1	Q	Okay.	13:58:21
2	A	So there's that. There may be an abstract	13:58:21
3		related to the Meletta paper, to answer your	13:58:23
4		question.	13:58:26
5	Q	Okay. But you're not aware of one, sitting	13:58:26
6		here today, correct?	13:58:29
7	A	Well, 1035.	13:58:29
8	Q	But you don't know what 1035 is. You don't	13:58:30
9		know if it's Meletta. You don't know if it's	13:58:34
10		something else?	13:58:37
11	A	I know that in the title it says	13:58:37
12		radiolabeled FAP inhibitors. I do not know	13:58:40
13		specifically if that is Meletta, if that's that	13:58:43
14		group, off the top of my head.	13:58:46
15	Q	Okay. And besides this Exhibit 1035	13:58:49
16		Marquis and Exhibit 1004 and Exhibit 1005, you're	13:58:52
17		not aware of any other references that disclose	13:58:58
18		small molecule FAP imaging agents before 2017,	13:59:00
19		correct?	13:59:04
20	A	None that talk about small molecule FAP	13:59:06
21		imaging agents, but plenty that talk about FAP as a	13:59:10
22		target, so correct. What you've said is correct.	13:59:15

1	Q	So, please, let's go to Exhibit 1008,	13:59:19
2		Meletta.	13:59:22
3		You ready?	13:59:40
4	A	Yes.	13:59:40
5	Q	Meletta studied a radiotracer called	13:59:41
6		MIP-1232, correct?	13:59:46
7	A	A published boronic acid-based FAP	13:59:51
8		inhibitor MIP-1232. So the radiotracer wasn't	13:59:55
9		MIP-1232. The radiotracer was an I(125) labeled	14:00:01
10		variant of that inhibitor.	14:00:07
11	Q	I understand.	14:00:09
12		And it is a boronic acid-based FAP	14:00:10
13		inhibitor, correct?	14:00:15
14	A	Yes.	14:00:16
15	Q	One of the features that attracted Meletta	14:00:26
16		to this particular FAPI is the possibility to	14:00:28
17		radioiodinate MIP-1232 without altering its	14:00:33
18		structure, correct?	14:00:37
19	A	I do not see the native structure of	14:00:48
20		unlabeled MIP-1232 in Exhibit 1004. I can't speak	14:00:51
21		to what attracted Meletta, et al., to this compound	14:01:14
22		because I can't be in their minds, but they did make	14:01:17

1 an I(125)-labeled variant of MIP-1232. 14:01:23

2 Q All right. Well, luckily, we don't have to 14:01:29

3 be in their minds. 14:01:32

4 A Oh, good. 14:01:33

5 Q If you turn to page 2083, Meletta explains 14:01:33

6 some of the considerations for choosing MIP-1232. 14:01:37

7 At the bottom, see last paragraph, it 14:01:44

8 starts with: "Marquis et al..."? 14:01:46

9 A Mm-hmm. 14:01:48

10 Q And about halfway through it, it says: 14:01:48

11 "The high binding affinity to FAP..." 14:01:50

12 You see that? 14:01:54

13 A Yeah. Do you mind if I read the whole 14:01:55

14 paragraph? 14:01:57

15 Q Please do. 14:01:58

16 A Okay. 14:02:52

17 Q Do you see where he says: "The high 14:02:52

18 binding affinity to FAP..."? 14:02:54

19 You see that sentence? 14:02:55

20 A Yes. 14:02:57

21 Q So you would agree, then, that one of the 14:02:57

22 features that attracted Meletta to this FAPI is a 14:03:01

1	possibility to radioiodinate MIP-1232 without	14:03:05
2	altering its structure, correct?	14:03:15
3	A They did not fundamentally alter the	14:03:16
4	structure of MIP-1232.	14:03:19
5	Q And, in fact, this was one of the features	14:03:21
6	that attracted Meletta to this particular FAPI --	14:03:23
7	correct? -- is the possibility to radioiodinate it	14:03:26
8	without altering its structure?	14:03:32
9	A So they say that. I think my concern	14:03:35
10	there, in answering that question, is I would think	14:03:38
11	my chemical instincts tell me that the	14:03:49
12	pharmacologically active core of this molecule is	14:03:52
13	the pyrrolidone boronic acid with the glycine right	14:03:55
14	next to it.	14:04:00
15	So calling and my experience tell me that	14:04:01
16	Meletta and Marquis attached the para-iodo	14:04:07
17	substituent to that to make a model compound. So	14:04:13
18	calling MIP cold -- unlabeled MIP-1232 as the	14:04:16
19	inhibitor in itself, I'm not sure that's a fair	14:04:23
20	characterization of the molecule.	14:04:26
21	I think that the MIP -- that the	14:04:29
22	radiolabeling there is really, as I look at the	14:04:35

1 structure, an example of having the pharmacophore
2 core, the pyrrolidone boronic acid, a short linker,
3 and then the prosthetic group of the phenyl group
4 and iodine.

5 Q Okay. Thank you for your -- for providing
6 your chemical instincts. That's not what Meletta
7 says, though -- correct? -- what you just explained?

8 MR. KUSHAN: Objection. Foundation.

9 THE WITNESS: I think we would need to look
10 in Marquis and look and read the Marquis that they
11 cite at the beginning of that paragraph to glean
12 their intent with making MIP-1232.

13 BY DR. PARTINGTON:

14 Q Have you read Marquis?

15 A I've looked at Marquis, but it's been a
16 while since I looked at Marquis.

17 Q Did you look at Marquis before signing your
18 declaration?

19 A I don't know which Marquis paper they're
20 talking about there. Is that a Marquis paper? Is
21 that the exhibit? I don't know.

22 Q Well, let's look. It's reference 29.

1	Am I reading this correctly?	14:06:01
2	A So that is the abstract that was -- that	14:06:11
3	was an exhibit. So at some point during the	14:06:13
4	preparation of the declaration, I did read through	14:06:15
5	that.	14:06:18
6	Q Okay.	14:06:18
7	So Meletta tested its MIP-1232-labeled	14:06:19
8	compound for binding to endarterectomized tissue,	14:06:28
9	correct?	14:06:40
10	A I can't say it either, but	14:06:41
11	endarterectomized -- oh, my goodness gracious. A	14:06:44
12	type of carotid plaque. We can say that.	14:06:49
13	Q Okay. Ultimately Meletta concluded that	14:06:54
14	this radiotracer did not selectively accumulate in	14:06:57
15	the atherosclerotic tissue, correct?	14:07:01
16	A The overarching conclusion of this paper	14:07:05
17	was that FAP is an interesting target for nuclear	14:07:08
18	imaging, but the conclusion in the last sentence of	14:07:12
19	the abstract is: "Binding of the tracer to" -- the	14:07:15
20	tissue whose name is hard to say -- "was similar in	14:07:18
21	plaques and normal arteries, hampering its use for	14:07:23
22	atherosclerosis imaging."	14:07:32

1 Q And on page 2090, first full sentence, 14:07:40
2 Meletta concluded that: "For future studies more 14:07:46
3 selective inhibitors are needed to reduce 14:07:49
4 non-specific tissue accumulation. To overcome 14:07:52
5 limitations in specificity, novel lead structures 14:07:56
6 and the use of antibodies and fusion proteins was 14:07:59
7 proposed to minimize off-target effects..." correct? 14:08:03

8 A Let me make sure I see that because you 14:08:06
9 started reading before I got there. 14:08:09

10 Yeah, it's very strange wording, "was 14:08:20
11 proposed," but, yes, that is what the paragraph 14:08:22
12 says. 14:08:25

13 Q And they're citing to three references 14:08:25
14 here, correct? 14:08:30

15 A 24, 34, and 44. 14:08:30

16 Q All right. So let's look at each of them. 14:08:32
17 Let's look at reference 24. Reference 24 was Jansen 14:08:39
18 2013, which is Exhibit 1007, correct? 14:08:52

19 A Mm-hmm. 14:08:55

20 THE COURT REPORTER: Is that a yes? 14:08:56

21 THE WITNESS: Yes. 14:08:58

22 BY DR. PARTINGTON: 14:08:58

1	Q	Let's look at reference 34. It's a Fischer	14:09:00
2		reference, correct?	14:09:09
3	A	Yes, radioimmunotherapy of fibroblast	14:09:11
4		activation protein positive tumors by rapidly	14:09:15
5		internalizing antibodies.	14:09:19
6	Q	Have you ever read this reference?	14:09:20
7	A	I've seen the reference. I can't say that	14:09:21
8		I've literally read the reference cover to cover,	14:09:23
9		but I've seen the reference.	14:09:26
10	Q	Did you see -- have you seen this reference	14:09:33
11		prior to signing the declaration?	14:09:34
12	A	Yes.	14:09:39
13	Q	But you haven't read it cover to cover,	14:09:40
14		correct?	14:09:44
15	A	I have reviewed the reference.	14:09:44
16	Q	Not cover to cover though, correct?	14:09:46
17	A	Whether I read through all of the	14:09:48
18		references, I can't say.	14:09:51
19	Q	44.	14:09:52
20	A	That's the Jansen 2014 paper, Exhibit 1006.	14:09:56
21	Q	Okay. Great.	14:10:03
22		We've been going for an hour, actually a	14:10:05

1	little bit longer. You want to take a break? Is	14:10:08
2	five minutes okay?	14:10:10
3	A I think ten minutes will be great.	14:10:11
4	Q Ten minutes. Okay.	14:10:16
5	(Recessed at 2:10 p.m.)	14:10:19
6	(Reconvened at 2:32 p.m.)	14:32:06
7	BY DR. PARTINGTON:	14:32:11
8	Q Before the break, Doctor, we were talking	14:32:12
9	about Meletta.	14:32:14
10	A Mm-hmm.	14:32:15
11	Q Are you aware of any other studies	14:32:16
12	conducted after Meletta's publication but before	14:32:19
13	2017 that made or tested small molecule radiotracers	14:32:25
14	for FAP imaging?	14:32:28
15	A Well, there's the Marquis reference that we	14:32:31
16	mentioned before, the abstract, the AACR meeting.	14:32:34
17	THE COURT REPORTER: The what? I didn't	14:32:34
18	hear you.	14:32:34
19	THE WITNESS: Abstract for the American	14:32:43
20	Association of Cancer Research. It is Reference 29	14:32:45
21	in the Meletta paper, and then Exhibit 1035 in my	14:32:51
22	declaration.	14:33:03

1	BY DR. PARTINGTON:	14:33:04
2	Q Marquis was published in 2009, correct?	14:33:04
3	A Let me make sure.	14:33:09
4	Yes.	14:33:14
5	Q So before Meletta published, correct?	14:33:15
6	A Yes.	14:33:17
7	Q Okay.	14:33:17
8	So my question was: Are you aware of any	14:33:18
9	references or any studies conducted after Meletta's	14:33:20
10	publication but before 2017 that made or tested	14:33:26
11	small molecule radiotracers for FAP imaging?	14:33:29
12	A Oh, I apologize. I misunderstood the	14:33:32
13	question.	14:33:34
14	Q That's okay.	14:33:34
15	A Not off the top of my head, no.	14:33:35
16	Q Okay.	14:33:35
17	Let's go back to Exhibit 1001, please, in	14:33:48
18	the documents.	14:33:54
19	A Which one is that again?	14:33:55
20	Q It's the patent, the '233 patent.	14:33:57
21	A Sorry.	14:34:14
22	Q That's okay.	14:34:14

1	A	Yes.	14:34:20
2	Q	Let's go to column 64, please.	14:34:21
3	A	Yes.	14:34:34
4	Q	You see where it starts: "That which is	14:34:34
5		claimed"?	14:34:38
6	A	Yes.	14:34:39
7	Q	And it says one?	14:34:39
8	A	Yes.	14:34:42
9	Q	So independent claim 1 claims a:	14:34:43
10		"...compound of Formula (I): B-L-A," correct?	14:34:46
11	A	Beginning of --	14:34:51
12		MR. KUSHAN: Objection. Foundation.	14:34:53
13		THE WITNESS: -- that which is claimed, the	14:34:54
14		first thing is: "A low molecular weight compound of	14:34:56
15		Formula (I): B-L-A," in the first line there.	14:35:00
16		BY DR. PARTINGTON:	14:35:04
17	Q	Okay.	14:35:04
18		Does claim 1 include any functional	14:35:05
19		language describing how the compound behaves in the	14:35:07
20		body?	14:35:10
21	A	It has -- claim 1 has two functional	14:35:12
22		components to it. So B has to be: "...an [sic]	14:35:19

1	optical or radiolabeled functional group" -- it's	14:35:23
2	right there, the word "functional" -- "suitable for	14:35:25
3	optical imaging, positron-emission	14:35:29
4	tomography...single-photon emission computed	14:35:29
5	tomography" --	14:35:34
6	THE COURT REPORTER: You're going too fast.	14:35:34
7	"Positron"?	14:35:34
8	THE WITNESS: I apologize. These are --	14:35:35
9	yeah, of course. These are words I think about	14:35:37
10	every day, so I don't -- the functional language	14:35:38
11	there is: "B is any optical or radiolabeled	14:35:40
12	functional group suitable for optical imaging,	14:35:44
13	positron-emission tomography (PET) imaging,	14:35:51
14	single-photon computed tomography (SPECT) imaging,	14:35:56
15	or radiotherapy."	14:36:01
16	The other functional language is: "...L is	14:36:03
17	a linker having bi-functionalization adapted to form	14:36:06
18	a chemical bond with B and A."	14:36:09
19	So L's job -- the function of L is to	14:36:12
20	combine to B and A and the function of B is to be	14:36:14
21	suitable for optical imaging, PET, SPECT, or	14:36:18
22	radiotherapy.	14:36:24

1 BY DR. PARTINGTON:

14:36:25

2 Q Okay. But claim 1 does not include any
3 functional language describing how compound B-L-A
4 behaves in the body, correct?

14:36:25

14:36:28

14:36:32

5 MR. KUSHAN: Objection. Foundation.

14:36:35

6 THE WITNESS: All of that language, the
7 functional language that would apply to B applies to
8 the combination of those elements in B-L-A. The
9 definition -- the functional language that covers B
10 states its function as part of the B-L-A construct.

14:36:37

14:36:40

14:36:43

14:36:48

14:36:51

11 BY DR. PARTINGTON:

14:36:58

12 Q Why do you say that?

14:36:58

13 A Because, well, I mean -- I mean, both the
14 functional language in the claims is B is any
15 optical or radiolabeled functional group suitable
16 for all those types of imaging, and then B, that's
17 the functional language describing what B must be,
18 and then B is part of B-L-A; therefore, B must still
19 have that function within the context of B-L-A.

14:37:03

14:37:17

14:37:21

14:37:24

14:37:29

14:37:32

14:37:38

20 Beyond that, I understand the claims in the
21 context of the specifications of the patent, which
22 lay out, right at the beginning, imaging and

14:37:41

14:37:45

14:37:50

1 radiotherapeutics agents targeting fibroblast

14:37:52

2 activation protein.

14:37:56

3 Q Are there any words in the claims --

14:37:58

4 looking at claim 1, are there any words in claim 1

14:38:02

5 that say that this functional language applies to

14:38:05

6 the whole claim?

14:38:10

7 A I feel like I already answered that

14:38:18

8 question. It describes the functional -- function

14:38:20

9 of B, and it describes the function of L, and B and

14:38:22

10 L are components of B-L-A, and right below B-L-A is

14:38:28

11 "wherein." So B and L are in B-L-A.

14:38:36

12 Q That is a different question, Doctor.

14:38:44

13 My question was: Are there words in the --

14:38:46

14 in claim 1 that say that this functional language

14:38:50

15 applies to the whole claim?

14:38:56

16 MR. KUSHAN: Objection. Form.

14:38:59

17 THE WITNESS: I feel like I've answered

14:39:02

18 that question already.

14:39:04

19 There are words in column 64 in the claim

14:39:06

20 that say what the function of B is.

14:39:10

21 BY DR. PARTINGTON:

14:39:10

22 Q Okay. Where -- which words? Could you

14:39:13

1	point me to any words that say that the same	14:39:15
2	function that applies to B must apply to B-L-A?	14:39:18
3	A Two things. B is a part of B-L-A, and I	14:39:24
4	interpret the claims within the context of the	14:39:32
5	specifications, and the title of the patent is:	14:39:34
6	"IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING	14:39:37
7	FIBROBLAST-ACTIVATION PROTEIN-ALPHA..."	14:39:41
8	Q Claim 1 does not require that compound	14:39:45
9	B-L-A have any in vivo stability, correct?	14:40:35
10	MR. KUSHAN: Objection. Foundation.	14:40:41
11	THE WITNESS: It does not explicitly say in	14:40:50
12	vivo stability, but for B to be a function --	14:40:53
13	radiolabeled functional group suitable for positron	14:40:57
14	emission tomography, single-photon emission computed	14:41:00
15	tomography or radiotherapy, B must necessarily have	14:41:09
16	stability in vivo. So the requirement for stability	14:41:12
17	is within the functional language of "suitable for."	14:41:16
18	BY DR. PARTINGTON:	14:41:23
19	Q The requirement -- the requirement for	14:41:23
20	stability for B, not B-L-A, correct?	14:41:24
21	A But B is part of B-L-A.	14:41:26
22	Q So L is part of B-L-A also, correct?	14:41:32

1	A	Yes.	14:41:39
2	Q	Does this mean that B-L-A must be suitable	14:41:39
3		-- or I'm sorry -- that B-L-A must have	14:41:44
4		bi-functionalization adapted to form a chemical bond	14:41:48
5		with B and A?	14:41:52
6	A	No. It means that L's role in B-L-A is to	14:41:53
7		form a chemical bond with B and A. Each of the	14:41:59
8		components have a role. B and L's role are	14:42:03
9		functionally defined, and they have that role within	14:42:09
10		the context of B-L-A, both because it is said that	14:42:12
11		here and because I can -- I understand the claims in	14:42:17
12		the context of the specifications.	14:42:21
13	Q	Okay. I'm asking about the claims for now.	14:42:23
14	A	Okay.	14:42:25
15	Q	So my question is the following: Why are	14:42:25
16		you imposing B's function onto the entire B-L-A	14:42:28
17		compound and L's function only to the L insofar as	14:42:31
18		its part of B-L-A compound?	14:42:36
19	A	Because L's function is defined in relation	14:42:40
20		to B and A. L is a linker having	14:42:45
21		bi-functionalization adapted to form a chemical bond	14:42:49
22		with B and A. So L's function is linking B and A.	14:42:53

1	That's L's job in the B-L-A.	14:42:59
2	B has a job, and it has a job within the	14:43:04
3	context of B-L-A also.	14:43:09
4	Q But the claim doesn't require for B-L-A to	14:43:12
5	be an imaging or radiotherapeutic agent, correct?	14:43:16
6	MR. KUSHAN: Objection. Foundation.	14:43:23
7	THE WITNESS: The claim requires that B, as	14:43:25
8	part of B-L-A, is any optical or radiolabeled	14:43:28
9	function group suitable for optical imaging;	14:43:33
10	positron emission tomography, PET imaging;	14:43:37
11	single-photon emission computed tomography imaging;	14:43:41
12	or radiotherapy. That is the functional language	14:43:46
13	describing B's job within B-L-A.	14:43:49
14	BY DR. PARTINGTON:	14:43:54
15	Q Claim 1 does not require any particular	14:43:54
16	pharmacokinetic profile for B-L-A, correct?	14:43:57
17	MR. KUSHAN: Objection. Foundation.	14:44:03
18	THE WITNESS: It requires that B is a	14:44:07
19	functional group suitable for PET imaging, and part	14:44:10
20	of being suitable for PET imaging is -- is that	14:44:17
21	component of things. And, again, I construct the	14:44:23
22	claims within the context of the specifications	14:44:28

1 which say that they're imaging and radiotherapeutics 14:44:30
2 agents targeting fibroblast activation protein 14:44:36
3 alpha. 14:44:39

4 BY DR. PARTINGTON: 14:44:39

5 Q Is it your position that the properties of 14:44:40
6 B determine the properties of B-L-A? 14:44:42

7 A B has a functionally defined job, so the 14:44:49
8 properties of B are part of the properties of B-L-A 14:44:53
9 because B is part of B-L-A. 14:44:58

10 Q All right. Let's look at Exhibit 1004. 14:46:10
11 That is the US-633. 14:46:14

12 Are you looking at Exhibit 1004? 14:46:43

13 A I'm looking at Exhibit 1004 here, but I 14:46:45
14 also talk about Exhibit 1004 a lot in the 14:46:49
15 declaration, so I figured I'd queue up the sections 14:46:52
16 in the declaration. 14:46:55

17 Q I'll queue you up. Why don't you go to 14:46:58
18 paragraph 105 of your declaration. 14:47:01

19 A Okay. 14:47:01

20 Do you mind if I take a minute to make sure 14:47:16
21 I have the context of that paragraph? 14:47:18

22 Q Okay. 14:47:18

1	Okay so you testified in this paragraph	14:48:03
2	that: "The radiopharmaceuticals being described in	14:48:06
3	US-633 employ a modular three-component design, in	14:48:09
4	which the FAP targeting moiety is connected via a	14:48:13
5	'tether' (a linker) to a radiolabeling moiety..."	14:48:16
6	You see that?	14:48:23
7	A Second sentence of paragraph 105: "The	14:48:23
8	radiopharmaceuticals being described in US-633	14:48:26
9	employ a modular three-component design, in which	14:48:28
10	the FAP targeting moiety is connected via a	14:48:31
11	'tether' (a linker) to a radiolabeling moiety shown	14:48:37
12	[sic] (below)."	14:48:41
13	Okay.	14:48:41
14	Q Okay. So it is your position that the	14:48:42
15	term "tether" in US-633 the same as "linker" in the	14:48:44
16	challenged claim?	14:48:48
17	A That's -- yeah, that's what we mean --	14:48:49
18	that's what I mean. Excuse me. That's an old	14:48:51
19	academic habit.	14:48:54
20	That's what I mean when I put a linker in	14:48:56
21	parentheses.	14:48:59
22	Q Okay.	14:49:00

1	And you also testified that a linker should	14:49:00
2	spatially separate the reporter moiety from the	14:49:03
3	targeting moiety, correct?	14:49:07
4	A That is one application and use of a	14:49:10
5	linker.	14:49:12
6	Q But it is an application and use of a	14:49:12
7	linker?	14:49:16
8	A That is one -- yes, that is a -- a	14:49:16
9	component of being a linker is spatially separating	14:49:17
10	two things.	14:49:20
11	Q And that separation is intended to prevent	14:49:21
12	the reporter moiety from interfering with the	14:49:24
13	targeting moiety's ability to bind its target,	14:49:28
14	correct?	14:49:30
15	A That is one value of that separation.	14:49:30
16	Q Okay. And you also testified that a POSA	14:49:36
17	would have wanted to separate the reporter moiety	14:49:38
18	from the targeting moiety by about ten to 20 bond	14:49:41
19	length to avoid interactions between the two parts	14:49:47
20	of the radiotracer, correct?	14:49:49
21	A That is what I -- where do I testify that?	14:49:53
22	Just so I can make sure about that context.	14:50:00

1	Q	187.	14:50:02
2	A	Paragraph 187?	14:50:04
3	Q	Yes.	14:50:05
4	A	Okay. Great. Just let me make sure.	14:50:06
5		Yes, in the first sentence of paragraph 187	14:50:14
6		is: "Generally, a skilled artisan would have wanted	14:50:16
7		to separate the reporter moiety from the targeting	14:50:19
8		moiety by about 10 to 20 bond lengths to avoid	14:50:22
9		interactions between the two parts of the	14:50:27
10		radiotracer."	14:50:29
11	Q	And it is because a linker shorter than 10	14:50:30
12		bond length would place the reporter moiety too	14:50:33
13		close to the targeting moiety and interfere with	14:50:36
14		binding of the targeting moiety to its target,	14:50:40
15		correct?	14:50:43
16	A	That is not necessarily true of shorter	14:50:43
17		than ten bonds. The reason you would start or a	14:50:45
18		skilled artisan would start with ten to 20 bonds is	14:50:48
19		because that is derisked, but you can't predict it	14:50:51
20		based on a bond-to-bond kind of situation.	14:50:54
21	Q	Okay. So let's -- what I'm going to do is	14:50:57
22		we're going to look at the usage of the	14:51:03

1 term "tether" in the '633 patent, but because 14:51:05
2 it's -- they're chemical structures, what I've done 14:51:10
3 is I've printed out pages from the '633 patent. I'm 14:51:13
4 going to hand them to you. 14:51:18

5 A Okay. 14:51:20

6 Q I represent that this is -- these are the 14:51:20
7 correct pages from the '633 patent, but I would like 14:51:22
8 to introduce them as new -- as exhibits in this 14:51:27
9 case. So I think it's Exhibit 2021. 14:51:30

10 - - - 14:51:30

11 (Deposition Exhibit 2021 was marked 14:51:30
12 for identification.) 14:51:30

13 - - - 14:51:36

14 BY DR. PARTINGTON: 14:51:36

15 Q And feel free to confirm that this is the 14:51:36
16 right one. 14:51:38

17 And so the reason I'm handing you the 14:51:53
18 separate exhibit is because I think I'm going to ask 14:51:56
19 you to mark it, which I'll explain in a minute. 14:51:58

20 A I mean I've marked structures here -- 14:52:02

21 Q Yeah. 14:52:05

22 A -- in my declaration. 14:52:05

1	Q	In that exhibit that I handed you.	14:52:07
2	A	Okay.	14:52:08
3	Q	So that loose paper that I handed you.	14:52:09
4	A	Okay.	14:52:11
5	Q	Do you need a pen?	14:52:11
6		Okay. So let's start looking into it.	14:52:15
7		So let's -- I believe what I handed you or	14:52:17
8		I should have handed you is something that has	14:52:20
9		paragraph 0101.	14:52:23
10		Tell me if I'm wrong.	14:52:27
11	A	Yes, I have 0101.	14:52:38
12	Q	Okay. So let me orient myself now.	14:52:41
13		All right. Why don't you go ahead and read	14:52:55
14		that paragraph?	14:52:57
15	A	"The distance between the Metal-Chelate	14:52:57
16		moiety and the pyrrolidone moiety of the complex	14:53:00
17		represented by Formula I can be varied by altering	14:53:03
18		the tether and/or expanding the length of the tether	14:53:06
19		between them to modify the affinity and selectivity	14:53:10
20		of the complex for seprase," meaning FAP.	14:53:13
21		"The pharmacokinetic properties of the	14:53:20
22		complex may also be modified by incorporating	14:53:24

1 heteroatoms into the tethers. The following 14:53:28
2 structures represented by Formulas I-a to" -- or 14:53:30
3 "I-k are some" example -- "some exemplary 14:53:36
4 embodiments with different tethers and/or the length 14:53:39
5 of tethers." 14:53:42

6 Q Okay. And this is where I'm going to ask 14:53:44
7 you, in each Formula I-a through I-k, to mark the 14:53:48
8 tether, please? 14:53:55

9 A I-a through I-k. Okay. Mark the tether 14:53:57
10 only? 14:54:09

11 Q Mm-hmm. 14:54:09

12 A Okay. Just for the record, I feel like all 14:54:09
13 of this is captured in the paragraph below -- in 14:54:21
14 the -- oh, my gosh -- in the figure below paragraph 14:54:32
15 105. And so in the event that my pen slips here, it 14:54:35
16 is better captured there. 14:54:39

17 Which numbers did you tell me you wanted me 14:55:24
18 to do? 14:55:27

19 Q Well, it says I-a through I-k. 14:55:27

20 A G, H -- I don't think I have K. 14:55:33

21 DR. SHIWCHARAN: It stops at I. 14:55:36

22 BY DR. PARTINGTON: 14:55:38

1	Q	Oh, it stops at I. That's the patent.	14:55:38
2		If you -- let's just confirm so that you're	14:55:38
3		happy with this yourself.	14:55:39
4		If you'd go to the actual patent,	14:55:40
5		Exhibit 1004, the full exhibit, and if you'd go to	14:55:43
6		page 15 --	14:55:45
7	A	Can you tell me the -- oh, sorry.	14:55:47
8	Q	It's page 15 on the bottom. The patent	14:55:49
9		page is actually nine on top.	14:55:53
10	A	Sure.	14:55:57
11	Q	You can see -- you can orient yourself.	14:55:57
12		You can see that these structures do stop at I --	14:56:00
13		I-i. They don't go to I-k.	14:56:05
14	A	Okay. Okay.	14:56:11
15		Okay.	14:57:00
16	Q	Okay. I'm going to hand you next --	14:57:02
17		MR. KUSHAN: Hold on. So you're going to	14:57:05
18		use that as the exhibit?	14:57:07
19		THE WITNESS: Yes.	14:57:12
20		MR. KUSHAN: Wait. You've got an exhibit	14:57:16
21		number on that one. No, let her mark the exhibit.	14:57:18
22		THE WITNESS: Oh, I have to do this again	14:57:28

1	on this.	14:57:29
2	DR. PARTINGTON: Thank you, Jeff.	14:57:33
3	THE WITNESS: Might take a minute.	14:57:35
4	DR. PARTINGTON: Wonderful. Thank you.	14:59:04
5	Exhibit 2022.	14:59:09
6	- - -	14:59:09
7	(Deposition Exhibit 2022 was marked	14:59:09
8	for identification.)	14:59:09
9	- - -	14:59:13
10	BY DR. PARTINGTON:	14:59:13
11	Q And please mark that.	14:59:14
12	A Again, for what it's worth, I think it	14:59:15
13	is -- can I have the -- I think it is -- this is all	14:59:18
14	articulated in that figure when it wasn't being done	14:59:21
15	on the spot.	14:59:24
16	Q I understand.	14:59:24
17	MR. KUSHAN: I'm going to take his	14:59:39
18	marked -- unmarked and then the non-exhibit-label	14:59:41
19	marked version. There's no sticker on this one	14:59:45
20	(indicating).	14:59:49
21	DR. PARTINGTON: Yeah.	14:59:51
22	BY DR. PARTINGTON:	14:59:51

1	Q	So here I'm going to direct you to	14:59:52
2		paragraph 0130. And you can satisfy yourself that	14:59:54
3		this paragraph also uses the word "tether."	15:00:06
4	A	"Scheme 3 can also be utilized to	15:00:09
5		synthesize functionalized proline-M(+) (CO) (3)	15:00:12
6		complexes to explore the effect of more significant	15:00:17
7		variations of the distance of the metal chelator	15:00:21
8		from the proline moiety by incorporating a tether	15:00:26
9		into these structures. The tether may comprise	15:00:30
10		simple alkyl chain as shown, a PEG (CH(2)CH(2)O) (M),	15:00:33
11		a polyethylene amine...or the like. Terminal	15:00:39
12		aminoalkanoic acids (such as beta-alanine,	15:00:44
13		4-aminobutanoic acid, 5-aminopentanoic acid,	15:00:50
14		6-aminohexanoic acid and the 8-aminooctanoic acid)	15:00:58
15		or amino-PEG-acids" -- and then I'll spare the court	15:01:06
16		reporter. That word may be utilized as tethers	15:01:07
17		according to some embodiments.	15:01:10
18	Q	Okay. And so let's look at Scheme 3, and	15:01:12
19		Scheme 3 shows, at the bottom, a compound of Formula	15:01:22
20		I, correct?	15:01:30
21	A	What page is scheme 3 on?	15:01:31
22	Q	It's on the front.	15:01:33

1	A	The previous page?	15:01:34
2	Q	Yeah.	15:01:36
3	A	"Scheme 3: Synthesis of	15:01:44
4		boronoproline-M(+)(CO)(3) complex from preformed	15:01:46
5		M(+)(CO)(3) ligand."	15:01:46
6		Okay.	15:01:55
7	Q	In the bottom there is the compound of	15:01:55
8		Formula I, which is a complete radiotracer, correct?	15:01:58
9	A	Compound I-g?	15:02:03
10	Q	Mm-hmm.	15:02:06
11	A	Yes.	15:02:08
12	Q	Could you mark that, where the tether is?	15:02:08
13	A	Mark the tether in that compound?	15:02:13
14		Again, I feel like this is better done in	15:02:26
15		my figure.	15:02:28
16		Oh, I'm done --	15:02:44
17	Q	Okay. Great.	15:02:44
18	A	-- with that particular one. Do you want	15:02:45
19		me to do the others?	15:02:46
20	Q	No, just that one for now.	15:02:47
21		And then last is paragraph 0133. It should	15:02:47
22		be on the same exhibit.	15:02:50

1	Also, please satisfy yourself that that	15:02:51
2	paragraph contains the word "tether." You don't	15:02:53
3	have to read out loud as long as you confirm.	15:02:57
4	A Okay. It has the word tether.	15:03:01
5	Q Okay. And it talks about Scheme 4, right?	15:03:03
6	A That paragraph does not explicitly mention	15:03:15
7	Scheme 4, unless I'm looking at the wrong paragraph.	15:03:18
8	Q No, you're probably looking at the right	15:03:25
9	paragraph.	15:03:27
10	I'm sorry. It says: "The above reaction	15:03:29
11	scheme..."	15:03:32
12	You see that?	15:03:33
13	A Yes.	15:03:35
14	Q And the above reaction scheme was Scheme 4,	15:03:35
15	correct?	15:03:38
16	A Yeah. I wasn't trying to be difficult. I	15:03:38
17	was just trying to make sure I understand.	15:03:41
18	Q No. No.	15:03:42
19	All right. And, again, the assembled	15:03:44
20	radiotracer here is a compound of formula -- general	15:03:49
21	Formula I, correct?	15:03:53
22	A I-c.	15:03:55

1	Q	Mm-hmm. And just for completeness, please	15:03:58
2		label the tether there.	15:04:00
3	A	(Witness complied.)	15:04:02
4		Okay.	15:04:17
5	Q	Okay. In all of these figures that we just	15:04:18
6		looked -- all the structures that we looked that the	15:04:20
7		patent mentions the word "tether," it's always	15:04:22
8		mentioned in connection with compound of general	15:04:27
9		Formula I, correct?	15:04:29
10	A	I mean -- in the ones that I just circled?	15:04:33
11	Q	Mm-hmm. Yeah.	15:04:35
12	A	Yes, but there are compounds of general	15:04:36
13		type Formula II with tethers as well.	15:04:39
14	Q	I'm asking you with regard to the passages	15:04:41
15		that you read that has -- that have the	15:04:45
16		word "tether" in it always refers to compounds of	15:04:49
17		Formula I, correct?	15:04:53
18	A	Okay. To check that, may I please have	15:04:54
19		back the other one? Or once it's in, it's in.	15:04:59
20		Okay.	15:05:03
21		All of the ones that you have had me circle	15:05:14
22		in these instances have had metal chelates and,	15:05:16

1	therefore, are Formula Type I, but those are not the	15:05:19
2	only compounds that have tethers in '633.	15:05:24
3	Q Okay. So you identified example 13 in	15:05:45
4	US-633 as an example of: "...linking a radiometal	15:05:50
5	chelator to proline-derived boronic acid FAP	15:05:52
6	targeting moiety [sic]..."	15:05:55
7	A Can you show me where I identify that or	15:05:57
8	tell me?	15:05:59
9	Q Paragraph 120, I believe.	15:06:00
10	A Paragraph 120 reads: "US-633 describes the	15:06:30
11	use of a 'linker' or 'tether' to connect	15:06:34
12	proline-derived boronic acid FAP targeting moieties	15:06:36
13	to radiolabeling moieties. It describes these	15:06:41
14	'tethers' as being 'a chemical linking moiety	15:06:43
15	between a metal ion center and another chemical	15:06:46
16	moiety. It also illustrates examples of synthetic	15:06:49
17	procedures for constructing radiopharmaceuticals.	15:06:52
18	For example, it provides examples of linking a	15:06:54
19	radiometal chelator to proline-derived boronic acid	15:06:56
20	FAP targeting moieties (Example 13) and examples in	15:07:01
21	which a radiolabeled [sic] prosthetic group is	15:07:05
22	linked to its FAP targeting moiety (Example 14.)	15:07:09

1	Both use conventional chemical synthesis techniques	15:07:13
2	well-known to skilled artisans before 2017."	15:07:16
3	Q Great.	15:07:19
4	A Yes. Okay.	15:07:19
5	Q So let's look at example 13 first.	15:07:20
6	A Where I can find example 13?	15:07:22
7	Q It's somewhere in the patent. Let me find	15:07:25
8	it, and I will tell you.	15:07:29
9	It is on page 27.	15:07:45
10	I'm sorry. The top page says 27. The	15:07:48
11	bottom -- the GE labeled one says page 33. You see	15:07:51
12	how on the bottom -- yeah.	15:07:57
13	You see that there's a page number there?	15:08:00
14	A Okay.	15:08:02
15	Q Page 33.	15:08:04
16	A Sure.	15:08:05
17	Q Okay. See the Example 13?	15:08:05
18	A Okay.	15:08:07
19	Q All right.	15:08:08
20	So Example 13 -- and if you scan through	15:08:09
21	this example, you just will need to satisfy yourself	15:08:15
22	that example -- the structure discussed in Example	15:08:19

1	13 is shown in figure 4. So take a minute and look	15:08:21
2	at that full example.	15:08:27
3	A Figure 4 where?	15:08:28
4	Q Well, it's in the patent.	15:08:29
5	A I'm sorry.	15:08:32
6	Q It's all in the patent. So we're going to	15:08:32
7	stay with that Zimmerman. I guess it's a patent	15:08:34
8	publication.	15:08:38
9	A Okay.	15:08:38
10	Q We're going to stay with Zimmerman, Example	15:08:40
11	13 that you identified in your declaration. Please	15:08:43
12	confirm that the structure in Example 13 is shown in	15:09:02
13	figure 4.	15:09:08
14	A The structures in Example 13 -- I mean I	15:09:09
15	think the problem that I'm having here is I can't	15:09:15
16	tell, and it might be a typo in the declaration, but	15:09:17
17	it would only be a typo, if Example 13 is the	15:09:20
18	example of the general radiolabeling procedure	15:09:24
19	described in the proceeding paragraph or an example	15:09:27
20	of this structure that has 1050.	15:09:34
21	So the Example 13 on page 27 --	15:09:40
22	Q Mm-hmm.	15:09:40

1 A -- that's not a label, I don't think, for 15:09:43
2 the compound above. That's a descript- -- that is 15:09:46
3 saying the general radiolabeling procedure for 15:09:49
4 Example 13 -- 15:09:52
5 Q Oh, yeah. Don't -- 15:09:53
6 A -- is described below it. 15:09:55
7 Q Right. Right. Yeah. Don't look at the 15:09:57
8 figure above. 15:09:59
9 So let's just start with Example 13. 15:10:00
10 Example 13, right? So you read the Example 13. At 15:10:03
11 the very end, it says -- 15:10:06
12 A It says -- 15:10:06
13 Q -- "As shown in figure 4." 15:10:08
14 A Yes. 15:10:08
15 Q Do you see that? 15:10:10
16 A Okay. Yes, I understand. I'm sorry. I'm 15:10:10
17 confused. 15:10:13
18 Q Okay. That's okay. So let's go to figure 15:10:13
19 4. 15:10:15
20 A Sure. 15:10:16
21 Q It's going to be at the beginning of the -- 15:10:16
22 A Yes. 15:10:18

1	Q	You see figure 4. You see compound there,	15:10:18
2		right?	15:10:23
3	A	Mm-hmm.	15:10:23
4	Q	This is a compound of general Formula I,	15:10:24
5		correct?	15:10:26
6	A	Mm-hmm.	15:10:27
7	Q	And this compound has a tether --	15:10:27
8		correct? -- that separates a chelator from targeting	15:10:35
9		moiety?	15:10:40
10	A	Compound -- the compound shown in figure 4	15:10:40
11		does have a tether.	15:10:42
12	Q	Okay.	15:10:43
13		Could you please tell me how many bond	15:10:44
14		lengths separate targeting moiety from the reporter	15:10:53
15		moiety?	15:11:01
16	A	Okay.	15:11:02
17		As I have defined the tether in my diagram	15:11:21
18		below figure 105 -- paragraph 105 of the	15:11:26
19		declaration, that would be eight bond lengths.	15:11:32
20	Q	Could you explain to me how you're	15:12:00
21		counting?	15:12:02
22	A	Okay. So if you look at the picture --	15:12:02

1	Q	Mm-hmm.	15:12:08
2	A	-- on -- that we -- that I drew on -- below	15:12:08
3		paragraph 105, where it has the pyrrolidone unit --	15:12:15
4	Q	Okay. Hold on.	15:12:19
5	A	Yeah.	15:12:20
6	Q	Yeah.	15:12:20
7	A	-- then it has a carbonyl facing down.	15:12:25
8		Then it has a carbon with G --	15:12:28
9	Q	Mm-hmm.	15:12:31
10	A	-- and then from there on, the linker	15:12:32
11		starts.	15:12:34
12	Q	Mm-hmm. Got it.	15:12:35
13	A	And then the linker ends when you get to	15:12:36
14		the metal chelate.	15:12:38
15		So in this context, I would start right	15:12:39
16		after that carbon with the G substituent, one bond	15:12:43
17		to the amid, two bonds to the carbonyl carbon.	15:12:48
18		Then, as you move along the aliphatic chain --	15:12:51
19	Q	Mm-hmm.	15:12:51
20	A	-- three, four, five, six, seven, eight.	15:12:55
21	Q	Okay. Great.	15:12:58
22		Let's go to Example 14, please. So that	15:13:03

1	would be page 28 if you're looking at the top, page	15:13:16
2	34 if you're looking at the bottom.	15:13:19
3	A Oh, boy. You're confusing me with top and	15:13:21
4	bottom. Why don't we just do top?	15:13:24
5	Q Okay. 28.	15:13:27
6	A Thank you. Okay.	15:13:28
7	Q You've identified this example. We've	15:13:29
8	already established that.	15:13:32
9	A Okay.	15:13:34
10	Q And I want us to figure out which compound	15:13:34
11	is exemplified in Example 14, and I believe it is a	15:13:39
12	compound of figure 2, but please confirm.	15:13:43
13	A In the paragraph 182?	15:13:49
14	Q Yes.	15:13:53
15	A Yeah, 1024, figure 2.	15:14:01
16	Q Okay. Let's go to figure 2.	15:14:03
17	A Mm-hmm.	15:14:05
18	Q Are you there?	15:14:24
19	A Yeah.	15:14:25
20	Q This is a compound of general Formula II,	15:14:25
21	correct?	15:14:28
22	A That is a compound of general Formula II.	15:14:29

1 Q Okay. How many bond lengths separate the 15:14:33
2 reporter moiety from the targeting moiety here? 15:14:38

3 A The linker is the carbonyl, and so if you 15:14:42
4 look at my structure of the diagram below paragraph 15:14:45
5 105, the Type 2, you start with the boronic acid and 15:14:49
6 you travel out to the amide. Then you have the bond 15:14:53
7 to the carbonyl, and then you have the bond to the 15:14:56
8 subunit denoted Y sub Q. 15:15:00

9 Elsewhere in the US-633 there are compounds 15:15:03
10 with longer linkers where Q is a number. In this 15:15:07
11 case, Q looks like it's zero, so the number of bond 15:15:12
12 lengths between that and the radiolabeling moiety 15:15:15
13 that is based on the phenyl group would be two 15:15:17
14 bonds. 15:15:23

15 Q Okay. You can put that aside. 15:15:24

16 Let's go back to Exhibit 1007. 15:15:30

17 A This is the Jansen 2013 paper? 15:15:58

18 Q Mm-hmm. 15:16:02

19 We've already discussed this paper several 15:16:07
20 times. This paper relates to small molecule FAP 15:16:09
21 inhibitors, correct? 15:16:12

22 A Mm-hmm. 15:16:13

1 Q And this paper evaluates both FAP potency 15:16:13
2 and selectivity over PREP, correct? 15:16:17
3 A Mm-hmm. 15:16:19
4 Q Okay. And this paper identifies the N4 15:16:20
5 quinolinoyl scaffold as a particular promising 15:16:26
6 starting point for FAPI, correct? 15:16:29
7 A Where does it say that? 15:16:32
8 Q I'm just asking you: Do you know if this 15:16:34
9 paper identifies the N4 quinolinoyl scaffold as a 15:16:36
10 particular promising starting point for FAPI? 15:16:41
11 A This paper talks about -- it's in the 15:16:43
12 title: "Selective Inhibitors of Fibroblast 15:16:46
13 Activation Protein...with a (4-Quinolinoyl)" -- I'll 15:16:49
14 slow down -- "(4-Quinolinoyl)-glycyl-2- 15:16:50
15 cyanopyrrolidone Scaffold." 15:16:56
16 Q Okay. And this paper evaluates the effects 15:17:01
17 of substituents on the quinoline ring, correct? 15:17:04
18 A That is not the only thing that the paper 15:17:09
19 investigates, but that is one thing the paper 15:17:13
20 investigates. 15:17:15
21 Q And, in fact, it does that in Table 3 -- 15:17:18
22 or, rather, it reports the results within Table 3, 15:17:21

1	correct?	15:17:24
2	A Yes.	15:17:24
3	Q And those substituents on quinoline ring	15:17:26
4	include hydroxy group, methoxy group, and halogens,	15:17:30
5	correct?	15:17:35
6	A I'd have to take a moment.	15:17:35
7	Q Please do.	15:17:37
8	A Yes.	15:17:42
9	Q So let's focus on the halogen substitute	15:17:42
10	quinoline compounds, for example, the chloro and	15:17:49
11	bromo substituted quinolines, okay?	15:17:56
12	A Could you please tell me which? There's	15:17:59
13	several of those.	15:18:01
14	Q Yes, I will.	15:18:02
15	Let's look at Compound 25 --	15:18:04
16	A Okay.	15:18:23
17	Q -- and 26.	15:18:23
18	A Okay.	15:18:25
19	Q Just confirm that these are	15:18:25
20	halogen-substituted quinoline, correct?	15:18:27
21	A Those are halogen-substituted quinolines.	15:18:30
22	Q The authors of the paper confirm or	15:18:40

1	conclude, rather, bottom of page 493, left column:	15:18:46
2	"Introducing a chlorine or bromine substituent at	15:18:53
3	the 5-position of the quinoline ring such as in	15:18:56
4	analogues 25 and 26 has limited effect on FAP	15:19:01
5	potency. Most remarkably, the selectivity with	15:19:05
6	respect to PREP of these inhibitors sharply	15:19:09
7	increases (SI...> 1000), rendering them the most	15:19:12
8	favorable affinity/selectivity profile of all	15:19:18
9	FAP-inhibitors we have identified so far."	15:19:25
10	You see that?	15:19:27
11	A That is what those sentences read.	15:19:28
12	Q So as reported here, adding a halogen	15:19:30
13	substituent to the quinoline ring at position 5	15:19:35
14	significantly improved selectivity of FAPI over --	15:19:42
15	for PREP -- I'm sorry. Strike that. Let me start	15:19:47
16	over.	15:19:51
17	Adding a halogen substituent to the	15:19:51
18	quinoline ring at position five significantly	15:19:56
19	improved selectivity of the FAPIs to FAP over PREP,	15:20:01
20	correct?	15:20:05
21	MR. KUSHAN: Objection. Form.	15:20:06
22	THE WITNESS: In what position? Can you	15:20:10

1	say that question again? Sorry. The two	15:20:11
2	iterations, it got confusing.	15:20:14
3	BY DR. PARTINGTON:	15:20:15
4	Q That's okay.	15:20:15
5	Adding a halogen substituent to the	15:20:17
6	quinoline ring at position five significantly	15:20:19
7	improved selectivity of the FAPIs for FAP over PREP,	15:20:24
8	correct?	15:20:32
9	A No, not correct. In those particular	15:20:32
10	cases, it was a bromine or a chlorine, not any	15:20:35
11	halogen, those two halogens.	15:20:38
12	Q Okay. Fair enough.	15:20:40
13	In fact, the substitution at position five,	15:20:49
14	with chlorine and bromine, resulted in compounds	15:20:54
15	with the highest selectivity indices reported in	15:20:59
16	this particular study, correct?	15:21:02
17	A I'd have to look through every single one	15:21:04
18	of the compounds, but given what the authors say in	15:21:06
19	the first sentence of the left-hand column of page	15:21:10
20	494, I would say that is correct.	15:21:15
21	Q Okay.	15:21:20
22	A As I've said before, the selectivity and	15:21:20

1 affinity are not the only two things, and there are 15:21:24
2 more recent papers, Jansen 2014 for example, that 15:21:26
3 provide compounds with more complete and more 15:21:31
4 compelling datasets. 15:21:33

5 Q And Table 3 also shows that merely changing 15:21:37
6 the substituent or even its position on the 15:21:42
7 quinoline ring causes large selectivity changes, 15:21:45
8 correct? 15:21:49

9 A What sort of changes are you talking about? 15:21:51
10 That was -- that's an awfully broad statement that 15:21:54
11 I'm not sure I'm prepared to -- 15:21:57

12 Q Okay. Let's look at -- so we're going to 15:21:59
13 stay on this page, page 493, left column, first 15:22:01
14 complete paragraph starting with: "Next..." 15:22:06

15 You see that? 15:22:12

16 A Yes. 15:22:12

17 Q So: "Overall, none of the evaluated 15:22:21
18 substituents was able to improve FAP potency 15:22:25
19 significantly, with substituents in the 2- and 15:22:28
20 3-position of the quinoline ring as in compounds 15:22:32
21 19-24, having a clearly negative effect on this 15:22:37
22 parameter." 15:22:41

1	You see that?	15:22:42
2	A I see that.	15:22:42
3	Q All right.	15:22:43
4	Compound 19, does it have a substituent	15:22:44
5	quinoline ring?	15:22:51
6	A Is that a question or are you thinking out	15:22:56
7	loud?	15:22:58
8	Q It's a question.	15:22:58
9	Does Compound 19 have a substituent	15:22:59
10	quinoline ring?	15:23:02
11	A Yes, it has a methyl group in what I think	15:23:03
12	is the 2-position, but I'd have to brush up on my	15:23:07
13	quinoline ring numbering.	15:23:10
14	Q What about Compound 20?	15:23:11
15	A It has two substituents on the quinoline	15:23:13
16	ring.	15:23:18
17	Q Okay. It's adding hydroxy to the Compound	15:23:18
18	19, correct?	15:23:21
19	A It is saying it is -- it isn't doing	15:23:22
20	anything. Compound 20 has a hydroxy where Compound	15:23:27
21	19 has a hydrogen.	15:23:31
22	Q Okay. Compound 21, does it have --	15:23:34

1	A	Compound 21's no longer's a quinoline.	15:23:36
2	Q	Okay. Fair enough.	15:23:39
3		Compound 22, does it have a substituent	15:23:41
4		quinoline ring?	15:23:45
5	A	Yes, it has a phenyl methoxy group.	15:23:46
6	Q	Compound 23, does it have a substituent?	15:23:54
7	A	It's no longer a quinoline ring, but it has	15:23:57
8		an extra ring fused to the right side of the	15:24:00
9		quinoline.	15:24:02
10	Q	And Compound 24?	15:24:08
11	A	Compound 24 has a hydroxyl in positions 2	15:24:11
12		or 3.	15:24:17
13	Q	Mm-hmm.	15:24:18
14	A	Again, I would need to brush up on my	15:24:18
15		quinoline numbering.	15:24:21
16	Q	Are you saying -- I mean, I think I	15:24:22
17		understand what you're saying, whether it's starting	15:24:24
18		with nitrogen or a carbon next to it?	15:24:27
19	A	You mean the nitrogen is the four position,	15:24:30
20		hence four quinolinoyl.	15:24:34
21	Q	Got it.	15:24:34
22	A	I just -- it's been a little while since I	15:24:37

1 looked at a diagram of IUPAC-based quinoline 15:24:38
2 numbering. So, yes, 24 has a hydroxy group. 15:24:41

3 Q So then let me ask my question again, now 15:24:45
4 that we've looked at specific changes. 15:24:50

5 Table 3 shows that merely changing the 15:24:52
6 substituent or even its position on the quinoline 15:24:54
7 ring causes large changes in selectivity, correct? 15:24:57

8 A I mean, depends on what you mean by large, 15:25:01
9 but figure -- Table 3 shows that changing 15:25:04
10 substituents on the quinoline ring can change 15:25:08
11 selectivity for FAP over PREP. 15:25:13

12 Q Okay. 15:25:13

13 So Jansen -- this Jansen -- Exhibit 1007, 15:25:22
14 shows experimentally that selectivity is sensitive 15:25:27
15 to substitutions on the quinoline ring, correct? 15:25:32

16 A Jansen shows experimentally that the 15:25:37
17 selectivity of these quinolinyl FAP inhibitors -- 15:25:42
18 and, again, any paper is just within its context, so 15:25:47
19 specifically the compounds with the 15:25:51
20 dihydropyrrolidone -- cyano-pyrrolidone ring, 15:25:56
21 changing those substituents on the quinoline ring 15:25:59
22 can change the affinity for FAP and the affinity for 15:26:02

1	PREP.	15:26:06
2	Q And the best selectivity improvements were	15:26:19
3	observed with bromine and chlorine substituents in	15:26:22
4	the quinoline scaffold at position 5, correct?	15:26:26
5	A The best improvements relative to what?	15:26:37
6	You said the best improvements were seen with those,	15:26:42
7	but for me to measure an improvement, I would have	15:26:46
8	to have a baseline.	15:26:48
9	Q I'm guessing Compound 19 -- oh, I'm sorry.	15:26:51
10	No, not 19.	15:26:55
11	A I don't think so.	15:26:57
12	Q Probably 3. I'm guessing Compound 3. And	15:27:01
13	feel free to agree or disagree.	15:27:08
14	A I mean, I would need a calculator to do the	15:27:10
15	actual selectivity index, but I think that Compounds	15:27:13
16	25 and 26 are more selective for FAP over PREP in	15:27:16
17	Compound 3, but Compound 3 is an entirely different	15:27:21
18	family. So I'm not sure that comparison is germane.	15:27:24
19	Q How is Compound 3 in an entirely different	15:27:28
20	family?	15:27:34
21	A It lacks the glycyl subunit.	15:27:34
22	THE COURT REPORTER: Say it again.	15:27:34

1	THE WITNESS: It lacks the glycyl subunit.	15:27:34
2	Compound 3 also is a naphthalene without a	15:27:39
3	nitrogen -- nitrogen.	15:27:39
4	BY DR. PARTINGTON:	15:27:43
5	Q Oh, I see that. How about Compound 7?	15:27:43
6	A Compound 7, that's dividing -- .86 divided	15:27:46
7	by 0.01. I can't do that in my head, but, also, the	15:27:49
8	group at the top of the column is different between	15:28:00
9	the two.	15:28:03
10	Q But, Doctor --	15:28:04
11	A Yeah.	15:28:06
12	Q -- the Compound 7 has a quinoline and then	15:28:06
13	an amide attached to it, right?	15:28:10
14	A Uh-huh.	15:28:10
15	Q So the top group where -- that's connected	15:28:13
16	to amide where it says R -- you see that?	15:28:17
17	A Mm-hmm.	15:28:20
18	Q -- that is -- that is the substituent that	15:28:20
19	is attached to the amide of Compound 7; agree?	15:28:27
20	A Yes.	15:28:30
21	Q Okay.	15:28:31
22	A I see that.	15:28:31

1 Q Okay. And so then, now, let's look at 15:28:32
2 Compound 25. 15:28:35
3 What Compound 25 is showing here is just 15:28:36
4 the quinoline component of it -- 15:28:41
5 A Yes. 15:28:43
6 Q -- and the rest of the structure is up on 15:28:43
7 top, correct? 15:28:46
8 A Yeah, I'm just a little hesitant to -- 15:28:47
9 there's a reason that the authors put them in 15:28:49
10 separate columns -- 15:28:52
11 Q Okay. But -- 15:28:52
12 A -- and short of drawing -- short of taking 15:28:53
13 five minutes to make sure I draw them and making 15:28:55
14 sure they're exactly the same, I'm hesitant to 15:28:56
15 compare the two. 15:28:58
16 Compounds 25 and Compounds 26 have higher 15:29:00
17 FAP over PREP selectivity than several other 15:29:07
18 compounds in Table 2 and Table 3. I'm just trying 15:29:10
19 to make sure I'm exact, and I don't want to compare 15:29:17
20 things to Compound 3 because it's a naphthyl group. 15:29:20
21 Q That's fine. I corrected myself. We're 15:29:26
22 comparing to Compound 7. Anyways, I think -- I 15:29:30

1	think we're on the same page.	15:29:35
2	A Okay.	15:29:37
3	DR. PARTINGTON: Do you know what time we	15:30:58
4	started this session?	15:30:59
5	MR. BHATLA: 2:32.	15:31:02
6	THE WITNESS: 1 hour and 21 minutes -- no,	15:31:04
7	1 hour and 3 minutes ago.	15:31:07
8	BY DR. PARTINGTON:	15:31:09
9	Q Let's take a break. Let's do five minutes	15:31:09
10	if that's okay with you, Doctor.	15:31:11
11	A Fine with me.	15:31:13
12	(Recessed at 3:31 p.m.)	15:31:15
13	(Reconvened at 3:43 p.m.)	15:43:00
14	BY DR. PARTINGTON:	15:43:04
15	Q Dr. Zeglis, we've taken a number of breaks	15:43:05
16	today. Did you discuss the substance of your	15:43:09
17	testimony today with your counsel during breaks?	15:43:11
18	A No.	15:43:13
19	Q I don't have any further questions for you.	15:43:14
20	Thank you very much.	15:43:15
21	DR. PARTINGTON: I'm going to pass the	15:43:17
22	witness.	15:43:19

Transcript of Brian Zeglis, Ph.D.
Conducted on March 11, 2026

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1	MR. KUSHAN: Why don't we take about a	15:43:20
2	five-minute break, and then we'll resume.	15:43:22
3	(Recessed at 3:43 p.m.)	15:43:26
4	(Reconvened at 3:46 p.m.)	15:46:47
5	MR. KUSHAN: We have no questions.	15:46:48
6	THE COURT REPORTER: Mr. Kushan, are you	15:46:51
7	purchasing a copy of the transcript?	15:46:55
8	MR. KUSHAN: I've never had a question	15:47:01
9	asked that way. Usually it's -- we will get -- we	15:47:02
10	want a copy of the transcript. It's usually do we	15:47:06
11	want to pay more money to get it faster. We don't.	15:47:09
12	No. You're paying for faster?	15:47:15
13	DR. PARTINGTON: Yes, just until Friday.	15:47:18
14	THE COURT REPORTER: Do you want the rough	15:47:24
15	draft?	15:47:26
16	MR. KUSHAN: Rough would be great.	15:47:29
17	(Signature having not been discussed,	15:47:31
18	the deposition of Brian Matthew Zeglis, Ph.D. was	
19	concluded at 3:47 p.m. EDT.)	
20		
21		
22		

1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

2
3 I, JOAN V. CAIN, court reporter and Notary
4 Public within and for the District of Columbia do
5 hereby certify:

6
7 That Brian Matthew Zeglis, Ph.D.,
8 the witness whose deposition is hereinbefore set
9 forth, was duly sworn by me before the commencement
10 of such deposition and that such deposition was
11 taken before me and is a true record of the
12 testimony given by such witness.

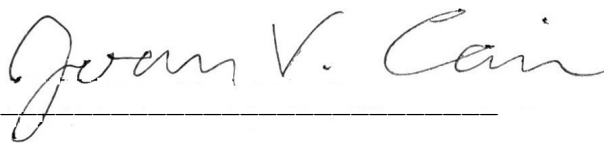
13
14 I further certify that the adverse
15 party, GE HEALTHCARE, LTD., was represented by
16 counsel at the deposition.

17
18 I further certify that the deposition of
19 Brian Matthew Zeglis, Ph.D., occurred at the offices
20 of Sidley Austin, LLP, 1501 K Street, Northwest,
21 Washington, D.C. 20005, on Wednesday,
22 March 11, 2026, commencing at 9:06 a.m. to 3:47 p.m.

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

7
8 IN WITNESS WHEREOF, I have hereunto set
9 my hand and affixed my notarial seal this 12th day
10 of March 2026.

11
12 My Commission Expires: July 31, 2029

13
14 
15 _____

16 NOTARY PUBLIC IN AND FOR

17 THE DISTRICT OF COLUMBIA
18
19
20
21
22

A			
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