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

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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
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C O N T E N T S

EXAMINATION OF BRIAN MATTHEW ZEGLIS, PH.D. PAGE

By Dr. Partington 11

E X H I B I T S

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EXHIBIT 2019 Article: Radiopharmaceuticals for Imaging in Oncology with Special Emphasis on Positron-Emitting Agents, by Zeglis, et al. 120

1 E X H I B I T S C O N T I N U E D
2 (Attached to the Transcript.)

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

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

2 PREVIOUSLY MARKED EXHIBITS REFERENCED

3 EXHIBIT 1007 American Chemical Society 136
4 Article: Selective
5 Inhibitors of Fibroblast
6 Activation Protein (FAP)
7 with a (4-Quinolinoyl)
8 -Glycyl-2-Cyanopyrrolidine
9 Scaffold, by Jansen, et al.
10 EXHIBIT 1008 Molecules' Article: 159
11 Evaluation of the
12 Radiolabeled Boronic
13 Acid-Based FAP Inhibitor
14 MIP-1232 for
15 Atherosclerotic Plaque
16 Imaging, by Meletta, et al.

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

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EXHIBIT 1044	Patent Application Publication No. US 2014/0357650 A1	132
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1 P R O C E E D I N G S
2 - - -
3 9:06 a.m., EDT
4 March 11, 2026
5 - - -
6 Whereupon,
7 BRIAN MATTHEW ZEGLIS, PH.D.,
8 having been duly sworn under penalties of perjury by
9 the Notary Public, was examined and did testify as
10 follows:
11 EXAMINATION BY COUNSEL FOR PATENT OWNER 09:06:57
12 BY DR. PARTINGTON: 09:06:57
13 Q Good morning, Dr. Zeglis. 09:06:57
14 A Good morning. 09:06:59
15 Q My name is Olga Partington with Sterne, 09:06:59
16 Kessler. Could you please state and -- 09:07:01
17 MR. KUSHAN: Sorry. Sorry. Appearances? 09:07:08
18 DR. PARTINGTON: She has them. 09:07:10
19 THE COURT REPORTER: I do have appearances 09:07:10
20 noted. 09:07:15
21 MR. KUSHAN: You already have them? 09:07:15
22 Go ahead. Go ahead. 09:07:15

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 09:15:42
2 your declaration? 09:15:48
3 A Over the last two days. 09:15:51
4 Q And how did you discover those errors? 09:15:52
5 A During deposition training, looking at the 09:15:55
6 structures, and looking at the footnotes. 09:15:59
7 Q Did you discover them yourself, or did your 09:16:05
8 counsel point you to them? 09:16:07
9 A The first one I discovered myself. The 09:16:13
10 second one counsel and I both discovered. 09:16:16
11 Q Did you talk to anyone besides counsel 09:16:27
12 regarding the substance of your deposition today? 09:16:29
13 A No. 09:16:33
14 Q So you stated that you reviewed every 09:16:44
15 exhibit that is cited in Appendix C of your 09:16:48
16 declaration in preparation for your deposition 09:16:53
17 today. 09:16:57
18 Did you review any documents not mentioned 09:16:57
19 in your declaration? 09:17:01
20 A Only documents that I read within the 09:17:11
21 context of my job, which are other -- I mean, there 09:17:14
22 are other papers about optical PET and SPECT imaging 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 -- 09:17:37
6 in preparation for your deposition today, did you 09:17:41
7 review anything else outside of what's listed in 09:17:44
8 your declaration? 09:17:47
9 A Over time, I may have looked at abstracts 09:17:48
10 on papers on PubMed that are -- that relate to the 09:17:56
11 topic at hand, but that are not necessarily in the 09:18:01
12 declaration, just in the course of being interested 09:18:05
13 in things. 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 09:18:08
16 much. 09:18:12
17 Q Is it fair to say that because you did not 09:18:12
18 include those abstracts in your declaration you did 09:18:16
19 not find them important for making your conclusions 09:18:20
20 that are described in your declaration? 09:18:26
21 A I'm not sure that's fair to say. They may 09:18:30
22 have made redundant points that are covered by other 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 09:18:46
3 declaration said gallium-68 is a good PET imaging 09:18:50
4 agent, I have looked at other papers that also say 09:18:56
5 gallium-68 is a good radionuclide that I would not 09:18:59
6 have felt compelled to put in the declaration 09:19:03
7 because it is a redundant point. 09:19:06
8 Q So let me make sure I understand. The only 09:19:09
9 reason you would not have included a reference in 09:19:12
10 your declaration is because it provided information 09:19:16
11 that is already found in something -- some other 09:19:21
12 reference that is cited in your declaration, 09:19:26
13 correct? 09:19:28
14 A Or if I read the paper after the 09:19:28
15 declaration was finalized. 09:19:32
16 Q Were there documents -- were there papers 09:19:36
17 that you read after the declaration was finalized 09:19:38
18 that you would deem to be important for your 09:19:42
19 opinion? 09:19:47
20 A None that I can think of right here and 09:19:50
21 now. 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

terms that you remember, but there may have been 09:24:37
others; is that correct? 09:24:39
A There were surely others; I just can't 09:24:40
remember them. 09:24:43
Q Okay. Besides counsel, did you communicate 09:24:58
with anyone in order to prepare your declaration? 09:25:01
A No. 09:25:07
Q Your current rate is $900 per hour, 09:25:11
correct? 09:25:13
A Yes. 09:25:15
Q How much have you billed so far in this 09:25:16
case? 09:25:22
A I can't tell you exactly because I don't 09:25:22
have my invoicing software in front of me, but in 09:25:24
light of the previous question you asked, that was 09:25:31
between 50 and a hundred hours and 50 a hundred 09:25:36
hours, presumably between 100 total times $900 an 09:25:39
hour -- I'm not good at mental math -- and 200 times 09:25:45
$900 an hour, so somewhere in there. 09:25:50
Q Okay. And are you owed any additional 09:25:55
money for this case? 09:25:58
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 09:27:46
2 healthcare division, but I don't remember 09:27:54
3 specifically that it was GE. It might have been a 09:27:56
4 similarly blue-logoed medical tech company. I just 09:27:59
5 don't remember. I give so many lectures that it's 09:28:04
6 hard to remember. 09:28:07
7 But, no, nothing -- nothing recently. 09:28:07
8 Nothing within the last decade. 09:28:11
9 Q Okay. Do you remember if you were paid for 09:28:13
10 that lecture that you referred to? 09:28:15
11 A Oh, definitely not. No. 09:28:17
12 Q Do you have an ownership share in GE? 09:28:20
13 A A mutual fund that I own may have a small 09:28:28
14 ownership share in GE, but I own no securities on an 09:28:32
15 independent basis in GE. 09:28:39
16 Q And is your compensation here contingent on 09:28:41
17 the outcome of these proceedings? 09:28:47
18 A No. I am being compensated to give my 09:28:49
19 scientific opinion. 09:28:52
20 Q So let's talk about your scientific 09:29:03
21 opinion. 09:29:07
22 In your declaration, you provided opinions 09:29:09

1 on patentability of the claims of the '233 patent, 09:29:11
2 and, specifically, you provided opinions regarding 09:29:17
3 obviousness of the patent claims, and my question 09:29:20
4 for you is: In assessing obviousness, what did you 09:29:24
5 analyze first? 09:29:29
6 A The exact temporal ordering of what I 09:29:36
7 analyzed first is hard to remember, given that it 09:29:41
8 was a long time ago, but the overarching conclusion 09:29:47
9 was that the claims were obvious. I mean, we can go 09:29:51
10 to -- 09:29:56
11 Q We can go to your declaration in a minute. 09:30:00
12 I'm just curious about your methodology that you 09:30:02
13 applied here. 09:30:06
14 So you were approached by Sidley counsel, 09:30:07
15 given the patent, presumably. So my question for 09:30:13
16 you is: How did you start assessing obviousness of 09:30:16
17 the claims at issue here? 09:30:21
18 A I was not given the patent to start. 09:30:23
19 Q What -- 09:30:29
20 A The first -- the first thing, independent 09:30:30
21 of the patent, never having seen the patent, was an 09:30:37
22 analysis of FAP-targeting pharmacophores, and based 09:30:41

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 09:32:29
2 have downloaded or I did download Jansen '14 and 09:32:33
3 Meletta. 09:32:39
4 I don't remember the exact file transfer 09:32:40
5 with regard to US-633, but they would have been 09:32:41
6 plainly obvious to look into for a skilled artisan 09:32:44
7 in 2017. 09:32:47
8 Q And how did you zero in on these three 09:32:48
9 papers? 09:32:51
10 A A -- how did I -- okay. 09:32:54
11 So I did this because -- thinking about -- 09:32:56
12 thinking within the framework of a skilled artisan 09:32:58
13 in 2017 trying to develop a new FAP-targeted 09:33:01
14 radiopharmaceutical or thinking about FAP-targeted 09:33:10
15 radiopharmaceuticals in general, the Meletta paper 09:33:13
16 and other literature at the time, and a person -- a 09:33:17
17 skilled artisan at that time would have known that 09:33:21
18 FAP was a very enticing target for optical nuclear 09:33:24
19 imaging. 09:33:28
20 So a skilled artisan would have known that 09:33:33
21 FAP is an enticing target. The Meletta paper lays 09:33:35
22 out one potential FAP-targeting radiotracer -- I can 09:33:39

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 09:34:58
2 agent, but you had also testified that you had not 09:35:04
3 seen the patent when you were doing this analysis 09:35:05
4 and when you were researching papers. 09:35:08
5 So my question for you is -- 09:35:10
6 A Which patent do you mean? I'm sorry. I 09:35:11
7 interrupted. 09:35:13
8 Q I'm talking about the challenged patent 09:35:13
9 here, the '233 patent. 09:35:15
10 So my question for you here is: How did 09:35:17
11 you know what the level of skill in the art is here, 09:35:19
12 i.e., who is a POSA here, if you never saw the 09:35:27
13 patent before you started your analysis? 09:35:31
14 A Okay. A -- well, counsel explained to me 09:35:34
15 what a POSA is, and so that we're all on the same 09:35:43
16 page, I can read it. 09:35:52
17 So paragraph 21 of the declaration: "I 09:36:16
18 have been informed that one requirement for 09:36:22
19 patentability is that an invention must not have 09:36:24
20 been obvious to a person of ordinary skill in the 09:36:27
21 art in view" -- "in view of what was known in the 09:36:30
22 prior art before the filing date of the patent. I 09:36:34

1 also have been informed that if a patent claim 09:36:36
2 encompasses a compound that would have been obvious 09:36:39
3 in light of the prior art, that claim is 09:36:40
4 unpatentable." 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 09:36:55
10 counsel that a person of ordinary skill in the art 09:36:57
11 is a hypothetical person who is presumed to have the 09:36:59
12 typical skills and knowledge of someone working in 09:37:02
13 the field of the invention. Based on my review of 09:37:05
14 the patent and my experience, I believe a person of 09:37:08
15 ordinary skill in the art (who I may refer to as 'a 09:37:12
16 skilled artisan') would have had an undergraduate 09:37:14
17 degree and a Ph.D. in chemistry, biochemistry, 09:37:17
18 medicinal chemistry or a comparable field. The 09:37:20
19 person would have had experience with and/or 09:37:24
20 knowledge of chemical synthesis methods...assessment 09:37:26
21 of cellular targets for" -- 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, 09:44:26
2 testing and/or evaluation of radiopharmaceuticals. 09:44:28
3 The person would" have always -- "also been familiar 09:44:31
4 with" radiopharmaceutical -- "how 09:44:34
5 radiopharmaceuticals are distributed and used in 09:44:35
6 patients to perform therapy or nuclear imaging 09:44:37
7 diseases, including cancer." 09:44:40
8 None of -- that understanding, what a 09:44:42
9 skilled artisan in molecular imaging would have been 09:44:46
10 in 2017, does not require any knowledge of the '233 09:44:51
11 patent. 09:45:04
12 Q Do you have an understanding of how a 09:45:04
13 person of ordinary skill in the art is determined? 09:45:09
14 A I understand, as represented here in 09:45:14
15 paragraph 15, what a person of ordinary skill in the 09:45:17
16 art is. I describe that in paragraph 15. 09:45:24
17 How that benchmark is created, I'm not sure 09:45:31
18 I understand what you mean by the process by which 09:45:42
19 definition of a skilled artisan. I understand the 09:45:44
20 definition of the term, as I lay out in -- in 09:45:46
21 paragraph 15. 09:45:50
22 Q And where -- how did you determine that 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 09:46:00
3 skilled artisan in molecular imaging chemistry would 09:46:06
4 have been in 2017, what would a skilled artisan know 09:46:11
5 about? They would know about these things. 09:46:15
6 Q So fair to say you did not consider 09:46:19
7 educational level and specialty of the inventors, 09:46:22
8 correct? 09:46:26
9 MR. KUSHAN: Objection. Foundation. 09:46:27
10 THE WITNESS: My definition -- no. My 09:46:35
11 opinion on what a skilled artisan is, is here and 09:46:39
12 doesn't refer to any of what you just mentioned. 09:46:47
13 The definition of what a skilled artisan is, as I 09:46:51
14 understand it, is in paragraph 15. 09:46:54
15 BY DR. PARTINGTON: 09:46:56
16 Q And you proffered this definition in 09:47:34
17 paragraph 15 without reviewing the patent, correct? 09:47:41
18 MR. KUSHAN: Objection. Foundation. 09:47:44
19 THE WITNESS: The paragraph 15 is included 09:47:50
20 in the declaration which was written -- which was 09:47:52
21 finalized on July 13th, 2025. Between when all this 09:47:57
22 started and when this declaration was finalized, I 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, 09:48:23
5 Meletta, and US-633, correct? 09:48:27
6 A I identified those as part of my analysis 09:48:29
7 of obviousness prior to reading the patent in 09:48:32
8 question, '233. 09:48:37
9 Q What were you tasked with doing that -- 09:49:06
10 what -- strike that. 09:49:09
11 What were you tasked with doing that led 09:49:11
12 you to identify these references? 09:49:15
13 A I don't remember the specific directive 09:49:25
14 because, again, it's quite a long time ago. But, 09:49:28
15 generally speaking, tasked with deciding how I, in 09:49:34
16 2017, would have approached making a FAP-targeted 09:49:41
17 molecular imaging agent in light of the literature 09:49:50
18 available to me in 2017. 09:49:53
19 Q So in assessing obviousness, you believe 09:50:03
20 that the problem facing a person of ordinary skill 09:50:05
21 in the art was the design of FAP-targeting radio for 09:50:08
22 tumor imaging, correct? 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 09:51:44
3 but did not include them in your declaration, those 09:51:47
4 papers were not important for your opinion in this 09:51:50
5 declaration, correct? 09:51:56
6 A No, not not important, but created a point 09:51:57
7 that might have been redundant, given other papers 09:52:03
8 cited in the declaration. 09:52:08
9 Q At the time you offered your obviousness 09:52:16
10 opinion regarding the claims of the '233 patent, you 09:52:18
11 did not understand that evidence of copying by 09:52:23
12 others can be relevant in that obviousness, correct? 09:52:26
13 MR. KUSHAN: Objection. Foundation. Also 09:52:32
14 objection to form. 09:52:33
15 THE WITNESS: It seems like there might 09:52:34
16 have even been a double negative in that question. 09:52:37
17 Could you simplify it for me? It was a 09:52:40
18 little long, and I have trouble understanding what 09:52:43
19 to answer. 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 09:52:58
2 others is relevant to obviousness analysis, correct? 09:53:02
3 A I'm having trouble with your 09:53:09
4 phrase "evidence of copying." What do you mean by 09:53:12
5 that? 09:53:15
6 I mean, copying could mean, like, Xeroxing, 09:53:17
7 like -- like -- and, again, I don't think you mean 09:53:21
8 Xeroxing, but I'm having trouble understanding that 09:53:23
9 particular word in the context of the question. 09:53:26
10 Q Do you have an understanding of copying in 09:53:32
11 the context of obviousness? 09:53:34
12 A Again, the word "copying" is giving me 09:53:38
13 trouble in that question. Is there a different way 09:53:43
14 you could phrase it so that I understand it better? 09:53:45
15 Q In forming your obviousness opinion 09:53:54
16 regarding the '233 patent, did you inquire whether 09:53:56
17 there was any evidence that others copied the 09:53:59
18 invention claimed in the '233 patent? 09:54:03
19 A I still don't understand exactly what you 09:54:09
20 mean by "copied." It's -- it isn't a word that 09:54:12
21 we -- that I use in the declaration, and it has 09:54:22
22 several meanings. So if there's a synonym or 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 09:55:39
3 invention, somebody takes the invention disclosed 09:55:41
4 and makes a duplicate of it, that's what I mean by 09:55:45
5 copying. 09:55:54
6 So my question -- does that clarify it for 09:55:55
7 you? 09:55:57
8 A Not really. My opinion is that the claims 09:56:00
9 in '233 -- and the opinion is laid out here in a way 09:56:07
10 that does not use, to my remembering, the 09:56:13
11 word "copying," the claims in '233 would have been 09:56:19
12 obvious -- are obvious. 09:56:26
13 Q Okay. Did you make any investigation into 09:56:27
14 the following: Whether a third party looked at the 09:56:31
15 '233 patent, looked at the claims of the '233 09:56:34
16 patent, and made a duplicate of the invention 09:56:37
17 disclosed in the '233 patent? So let me repeat that 09:56:41
18 slowly. 09:56:48
19 Did you make any investigation into whether 09:56:49
20 a third party looked at the '233 patent, looked at 09:56:54
21 the claims of the '233 patent, and made a duplicate 09:56:59
22 of the invention disclosed in the '233 patent? 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 10:17:58
3 amount of experimentation would be needed to figure 10:18:00
4 out -- to make all those compounds and to figure out 10:18:02
5 whether they -- and to use them for optical or 10:18:08
6 nuclear imaging. 10:18:14
7 Q Doctor, I'm not asking what your opinions 10:18:14
8 are. 10:18:16
9 A Okay. 10:18:16
10 Q I can -- I've read your declaration, 10:18:17
11 believe it or not. 10:18:19
12 A Okay. 10:18:19
13 Q I'm asking what methodology you used in 10:18:21
14 conducting your analysis. 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 10:18:38
19 written description and enablement, what did you 10:18:41
20 analyze first? 10:18:46
21 A The temporal arrangement of the acts is too 10:18:50
22 far in the past for me to remember, but with respect 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 10:25:09
2 in the declaration that describes some other line of 10:25:13
3 thinking than the ones I've laid out, but, again, 10:25:17
4 what I've described is the general thought process 10:25:20
5 behind that analysis. 10:25:26
6 Q Doctor, is it your understanding that a 10:26:06
7 patent specification needs to redescribe things that 10:26:09
8 were already well-known in the art in order to 10:26:11
9 satisfy written description? 10:26:14
10 MR. KUSHAN: Objection to form. 10:26:19
11 THE WITNESS: I am not a lawyer, but I can 10:26:23
12 read to you my understanding of written description. 10:26:26
13 BY DR. PARTINGTON: 10:26:34
14 Q You don't need to read the -- I'm just 10:26:42
15 asking you if your understanding is that a patent 10:26:46
16 specification needs to describe things that were 10:26:51
17 already well-known in the art to satisfy written 10:26:55
18 description. 10:26:58
19 MR. KUSHAN: Objection. Form. 10:26:58
20 THE WITNESS: Again, I'm not a lawyer. 10:26:59
21 What I know is that many common prosthetic groups 10:27:00
22 and many common chelators were not described in the 10:27:04

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 10:38:32
2 primary one. 10:38:34
3 Q Affinity and specificity are particularly 10:38:38
4 valuable in cancer imaging and therapy, correct? 10:38:41
5 Strike that. Let me rephrase. That was a bad 10:38:50
6 question. 10:38:52
7 Affinity and specificity of imaging agents 10:38:52
8 are particularly valuable in cancer imaging and 10:38:56
9 therapy, correct? 10:38:58
10 A Well, affinity and specificity of an 10:39:00
11 imaging agent is invaluable for therapy, which was 10:39:02
12 what -- if I said, "correct," to your question, I 10:39:07
13 would have said, "correct," to that sentence, which 10:39:09
14 is not correct. 10:39:12
15 Q Let me clarify the record. 10:39:13
16 A I'm sorry. 10:39:15
17 Q It was not a good question. 10:39:16
18 Is affinity and specificity particularly 10:39:17
19 valuable in cancer imaging? 10:39:20
20 MR. KUSHAN: Objection. Form. 10:39:25
21 THE WITNESS: In vitro or in vivo imaging? 10:39:26
22 BY DR. PARTINGTON: 10:39:31

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, 10:40:57
2 specificity or selectivity is very important, and 10:41:05
3 affinity is very important. But, again, those are 10:41:08
4 not the only two important things." 10:41:11
5 A Yeah. 10:41:13
6 Q So what do you mean by "important"? 10:41:13
7 A I cover that here. So on page 30 -- or 10:41:15
8 sorry -- paragraph 54 of my declaration -- that's 10:41:42
9 under subsection E -- I talk about considerations 10:41:49
10 influencing the development of radiopharmaceuticals 10:41:53
11 and optical imaging agents. 10:41:55
12 And so I say: "There are [sic] a number of 10:41:57
13 functional and practical considerations influence 10:42:00
14 the design of a radiopharmaceutical, particularly 10:42:02
15 for one intended for use in nuclear imaging. I 10:42:05
16 summarize these considerations below, many of which 10:42:07
17 also apply to optical imaging" -- and many of which 10:42:10
18 also apply to in vitro imaging agents. 10:42:13
19 So first is selectivity and affinity, as we 10:42:17
20 talked about. I can read that but -- 10:42:19
21 Q You don't have to read that. 10:42:21
22 A Second is the stability of the probe, the 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 10:46:58
3 that, but, again, selectivity, though very, very 10:47:01
4 important, is not the only concern in this context. 10:47:04
5 Q I understand that. 10:47:15
6 The field of radiopharmaceuticals is not 10:47:21
7 limited to antibodies, correct? 10:47:23
8 A No. There are other vectors that are used 10:47:31
9 in radiopharmaceuticals that are not immunoglobulins 10:47:33
10 or full-length antibodies. 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 10:47:54
16 choice, correct? 10:47:57
17 A Yes. 10:47:58
18 Q And even within the antibodies, we can talk 10:48:02
19 about full-length antibodies or antibody fragments 10:48:04
20 or engineered proteins, correct? 10:48:09
21 A I'm not sure I know what you mean by 10:48:10
22 engineered proteins, but, yes, antibody fragments 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 -- 10:56:37
2 would be a different subset of radiopharmaceutical. 10:56:39
3 Q Okay. Okay. So then, on the next page, 10:56:45
4 you're talking about: "'Reporter moiety' refers to 10:56:55
5 the portion of the radiopharmaceutical" -- 10:57:00
6 A Hold on, please, so I can -- 10:57:02
7 Q Oh, sorry. 10:57:04
8 A Thank you. 10:57:05
9 Q Under (i), you see that? 10:57:09
10 A Yes. 10:57:12
11 Q So: "'Reporter moiety' refers to the 10:57:13
12 portion of the radiopharmaceutical or optical 10:57:17
13 imaging agent that sends a signal that can be 10:57:18
14 detected by a device to generate an image," and 10:57:21
15 then, right under that, you have: "'Radiolabeling 10:57:25
16 moiety' refers to the portion of a 10:57:29
17 radiopharmaceutical that is covalently linked to or 10:57:33
18 non-covalently complexed with a radionuclide." 10:57:37
19 Again, this might be a silly question for 10:57:43
20 you, but I'm trying to understand what is the 10:57:45
21 difference between a reporter moiety and 10:57:48
22 radiolabeling moiety. 10:57:50

1 A It's hard for me to explain this better 10:57:54
2 because I've laid it out right here, but one way to 10:57:58
3 understand that is that one subset of reporter 10:58:04
4 moieties is an optical -- is an optical dye, and 10:58:09
5 obvious in that would not be included within 10:58:16
6 radiolabeling moiety. 10:58:19
7 Q That's a perfect explanation. Thank you. 10:58:21
8 And imaging agent -- let me see if I get 10:58:38
9 this correctly. An imaging agent is a subset of 10:58:40
10 radiopharmaceutical? 10:58:44
11 A No. In (l): "'Imaging agent' is" -- I'm 10:58:48
12 quoting now -- "'Imaging agent' is a general term 10:58:52
13 that includes both optical imaging agents and 10:58:55
14 radiotracers, and may be used interchangeably with 10:58:58
15 'molecular imaging agent.'" 10:59:02
16 Q So is it kind of like a Venn diagram then, 10:59:04
17 between radiopharmaceutical and imaging agent? 10:59:07
18 A They are related words that are defined 10:59:13
19 here. Whether -- I don't have a -- I'm not equipped 10:59:15
20 to draw a Venn diagram right now, but it's defined 10:59:19
21 right in (l). 10:59:24
22 Q Can you give me an example of a 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 11:09:25
2 that were developed as imaging agents, but that is 11:09:28
3 possible prior to 2017. 11:09:33
4 Q And before signing your declaration, did 11:09:34
5 you, Dr. Zeglis -- 11:09:38
6 A Mm-hmm. 11:09:38
7 Q -- consider whether the field developed 11:09:42
8 imaging agents targeting FAP using anti-FAP 11:09:45
9 antibodies before 2017? 11:09:51
10 A The declaration represents all of my 11:09:57
11 opinions on this matter. What I considered or did 11:10:00
12 not consider prior to signing it is -- is -- I 11:10:03
13 cannot possibly tell you everything I did or did not 11:10:12
14 consider prior to signing it, but it represents all 11:10:14
15 of my opinions on the matter. 11:10:18
16 I don't know if I cited an anti-FAP 11:10:19
17 antibody reported before 2017. If there's one you'd 11:10:22
18 like me to speak about, you can -- I'm happy to look 11:10:26
19 at a paper. 11:10:28
20 Q Dr. Zeglis, in the field of 11:10:32
21 radiopharmaceuticals, there were both metallic 11:10:34
22 radionuclides and nonmetallic radionuclides known in 11:10:38

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 isotopolgous 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 11:45:05
2 them equally when creating a new 11:45:08
3 radiopharmaceutical. 11:45:10
4 Q Understand. 11:45:11
5 All right. So putting it all together, an 11:45:14
6 imaging agent or making an imaging agent can involve 11:45:21
7 using metallic or nonmetallic radionuclides 11:45:24
8 incorporated either directly or via chelator or 11:45:28
9 prosthetic group, correct? 11:45:32
10 A A metallic radionuclide could not be 11:45:33
11 incorporated directly. So the full scope of the 11:45:36
12 question you just asked is not the case. 11:45:43
13 Q I understand. 11:45:46
14 So nonmetallic radionuclides can be 11:45:53
15 incorporated either directly or via prosthetic 11:45:57
16 group, correct? 11:46:00
17 A Yes. 11:46:02
18 Q And metallic nuclides can be incorporated 11:46:03
19 via a chelator, correct? 11:46:07
20 A Yes, but both those prosthetic groups and 11:46:10
21 the chelators require a linker to the targeting 11:46:12
22 vector. 11:46:16

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 Isotopolgous 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 isotopolgous substitution minimally -- 12:08:42
22 strike that. 12:08:49

1 Isotopolgous 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 12:19:12
2 small molecule tracers, the radionuclide most often 12:19:15
3 replaces an isotopologue..." These are talking 12:19:19
4 about very, very, very small molecules, acetate and 12:19:21
5 water, also ammonia. 12:19:25
6 In those cases, literally on the 12:19:28
7 cyclotron -- the cyclotron replaces the atom in the 12:19:31
8 middle of the ammonia -- that is not used to label 12:19:35
9 antibodies. But the guiding principles of how to 12:19:38
10 radiolabel a molecule are the same for small 12:19:42
11 molecules, especially small molecules that target 12:19:47
12 specific proteins and antigens and immunoglobulins. 12:19:49
13 And many of the same ways that are used to label 12:19:55
14 large molecules can be used and have been used to 12:19:58
15 great effect to label small molecules. 12:20:02
16 DR. PARTINGTON: I would like to mark as 12:20:37
17 Exhibit, I believe, 2019. 12:20:39
18 - - - 12:20:39
19 (Deposition Exhibit 2019 was marked 12:20:39
20 for identification.) 12:20:39
21 - - - 12:21:02
22 BY DR. PARTINGTON: 12:21:02

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 isotopolgous 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 tile, 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 13:16:34
3 different from the ones that we had just looked at 13:16:37
4 in the previous exhibit, correct? 13:16:39
5 A The previous exhibit used a xanthine 13:16:43
6 scaffold. Since it's been a little while, I'm not 13:16:48
7 entirely comfortable reconstructing the scaffold 13:16:57
8 here, but presumably these are the scaffolds. So, 13:17:05
9 yes, these are different -- these are different FAP 13:17:08
10 inhibitors. 13:17:11
11 Q Okay. Let's look at Table 4 of the same 13:17:11
12 exhibit, please. This table also lists more FAPIs, 13:17:15
13 correct? 13:17:23
14 A Yes. Correct. 13:17:49
15 Q Okay. And these are also different from 13:17:50
16 the xanthine FAPIs, correct? 13:17:52
17 A Again, I'm not entirely comfortable having 13:18:00
18 this in front of me and knowing the R(5), R(6) -- I 13:18:02
19 presume the R(5), R(6) is denoted in that structure, 13:18:06
20 and the star is denoting -- let me just take a 13:18:11
21 moment to make sure -- I'm having trouble finding 13:18:19
22 the identity of the asterisk structure, but based on 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 13:30:07
3 target. Selectivity in the context of most of the 13:30:09
4 FAP inhibitors we've discussed here is relative to a 13:30:13
5 different enzyme, the prolyl oligopeptidase PREP. 13:30:18
6 Q Okay. So just to make the record clear, 13:30:26
7 when you use the term "selectivity," you mean the 13:30:29
8 ability of a ligand to bind FAP preferentially over 13:30:33
9 PREP, correct? 13:30:38
10 MR. KUSHAN: Objection. Foundation. 13:30:39
11 THE WITNESS: That's not what I mean every 13:30:40
12 time you use the word "selectivity." 13:30:42
13 In the context of the declaration, when we 13:30:46
14 specifically speak about FAP over PREP selectivity, 13:30:48
15 that's what I many by the word "selectivity." 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 13:31:01
19 the desired target and minimal binding to off 13:31:05
20 target, correct? 13:31:11
21 A You -- selectivity is simply a ratio of the 13:31:12
22 binding to the intended target protein over the 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 13:35:41
2 factor because the radiopharmaceutical is intended 13:35:44
3 to report on the specific biological target, 13:35:45
4 correct? 13:35:48
5 A I'm much more comfortable explaining why I 13:35:48
6 think selectivity is important by reading exactly 13:35:51
7 how -- why I say it's important in the declaration. 13:35:54
8 Q I realize, Doctor, that you're much more 13:35:58
9 comfortable referring to your declaration, but if 13:36:03
10 you recall, at the beginning of the deposition you 13:36:05
11 agreed that you're going to answer my questions the 13:36:07
12 way I ask them. So could you please answer the 13:36:10
13 question the way I ask it, without -- 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 13:36:19
17 your declaration? Let me rephrase the question 13:36:22
18 again. 13:36:25
19 A Okay. 13:36:26
20 Q You describe selectivity as the most 13:36:26
21 important factor because a radiopharmaceutical is 13:36:29
22 intended to report on the specific biological 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 13:38:58
2 without knowing the entire lump sum of all small 13:39:00
3 molecule interactions and all antibody interactions. 13:39:04
4 Myself would not worry about selectivity more with a 13:39:07
5 small molecule than an antibody, per se, because 13:39:13
6 selectivity is always important within the context 13:39:19
7 of radiopharmaceuticals, optical imaging agents, in 13:39:22
8 vitro imaging agents across the board. 13:39:27
9 Q And does your answer regarding the 13:39:32
10 importance of selectivity depend on whether it's 13:39:36
11 imaging agent versus therapeutic agent? 13:39:39
12 A Selectivity is important for 13:39:44
13 radiopharmaceuticals, the entire group, and optical 13:39:46
14 imaging agents, all of them. Selectivity is always 13:39:52
15 important. 13:39:55
16 Q And this means that starting with a small 13:39:56
17 molecule that already has a high selectivity is 13:40:01
18 critical for developing a successful 13:40:04
19 radiopharmaceutical, correct? 13:40:06
20 MR. KUSHAN: Objection. Foundation. 13:40:08
21 THE WITNESS: Having a molecule, as I say 13:40:15
22 here -- I mean, I'll just read it here. "When 13:40:18

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 13:56:09
2 that might be in the literature, but allow me to 13:56:14
3 look through the exhibit list just to make sure. 13:56:21
4 There are several papers that identify FAP 13:56:49
5 as a potential target in cancer. 13:56:51
6 Q That wasn't quite my question. 13:56:55
7 A I know. I'm -- I feel like that's 13:56:56
8 important context. 13:56:59
9 I mean, Exhibit No. 1035, Marquis, et al., 13:57:19
10 targeting tumor micro- -- 13:57:24
11 THE COURT REPORTER: I'm sorry. Say that 13:57:24
12 slower. "Targeting tumor"? 13:57:24
13 THE WITNESS: I apologize. 13:57:24
14 Exhibit 1035, Marquis, et al., Abstract No. 13:57:30
15 4467: Targeting Tumor Microenvironment With 13:57:37
16 Radiolabeled Inhibitors of Seprase. 13:57:44
17 BY DR. PARTINGTON: 13:57:47
18 Q Do you know if this is the same -- strike 13:57:47
19 that. 13:57:47
20 Do you know if this is the abstract that 13:57:51
21 you previously referred to from the Meletta group? 13:57:53
22 A Off the top of my head, I don't know. 13:57:56

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 14:04:41
2 core, the pyrrolidone boronic acid, a short linker, 14:04:47
3 and then the prosthetic group of the phenyl group 14:04:51
4 and iodine. 14:04:56
5 Q Okay. Thank you for your -- for providing 14:04:58
6 your chemical instincts. That's not what Meletta 14:05:01
7 says, though -- correct? -- what you just explained? 14:05:04
8 MR. KUSHAN: Objection. Foundation. 14:05:07
9 THE WITNESS: I think we would need to look 14:05:12
10 in Marquis and look and read the Marquis that they 14:05:13
11 cite at the beginning of that paragraph to glean 14:05:21
12 their intent with making MIP-1232. 14:05:24
13 BY DR. PARTINGTON: 14:05:29
14 Q Have you read Marquis? 14:05:29
15 A I've looked at Marquis, but it's been a 14:05:31
16 while since I looked at Marquis. 14:05:36
17 Q Did you look at Marquis before signing your 14:05:37
18 declaration? 14:05:41
19 A I don't know which Marquis paper they're 14:05:44
20 talking about there. Is that a Marquis paper? Is 14:05:46
21 that the exhibit? I don't know. 14:05:49
22 Q Well, let's look. It's reference 29. 14:05:50

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 14:36:25
3 functional language describing how compound B-L-A 14:36:28
4 behaves in the body, correct? 14:36:32
5 MR. KUSHAN: Objection. Foundation. 14:36:35
6 THE WITNESS: All of that language, the 14:36:37
7 functional language that would apply to B applies to 14:36:40
8 the combination of those elements in B-L-A. The 14:36:43
9 definition -- the functional language that covers B 14:36:48
10 states its function as part of the B-L-A construct. 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 14:37:03
14 functional language in the claims is B is any 14:37:17
15 optical or radiolabeled functional group suitable 14:37:21
16 for all those types of imaging, and then B, that's 14:37:24
17 the functional language describing what B must be, 14:37:29
18 and then B is part of B-L-A; therefore, B must still 14:37:32
19 have that function within the context of B-L-A. 14:37:38
20 Beyond that, I understand the claims in the 14:37:41
21 context of the specifications of the patent, which 14:37:45
22 lay out, right at the beginning, imaging and 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 commuted 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

on this. 14:57:29

DR. PARTINGTON: Thank you, Jeff. 14:57:33

THE WITNESS: Might take a minute. 14:57:35

DR. PARTINGTON: Wonderful. Thank you. 14:59:04

Exhibit 2022. 14:59:09

- - - 14:59:09

(Deposition Exhibit 2022 was marked 14:59:09

for identification.) 14:59:09

- - - 14:59:13

BY DR. PARTINGTON: 14:59:13

Q And please mark that. 14:59:14

A Again, for what it's worth, I think it 14:59:15

is -- can I have the -- I think it is -- this is all 14:59:18

articulated in that figure when it wasn't being done 14:59:21

on the spot. 14:59:24

Q I understand. 14:59:24

MR. KUSHAN: I'm going to take his 14:59:39

marked -- unmarked and then the non-exhibit-label 14:59:41

marked version. There's no sticker on this one 14:59:45

(indicating). 14:59:49

DR. PARTINGTON: Yeah. 14:59:51

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

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

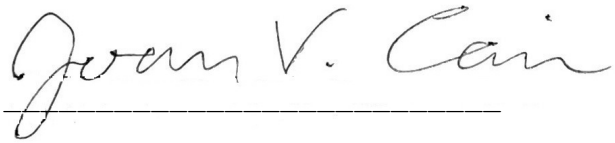
1 MR. KUSHAN: Why don't we take about a 15:43:20
2 five-minute break, and then we'll resume. 15:43:22
3 (Recessed at 3:43 p.m.) 15:43:26
4 (Reconvened at 3:46 p.m.) 15:46:47
5 MR. KUSHAN: We have no questions. 15:46:48
6 THE COURT REPORTER: Mr. Kushan, are you 15:46:51
7 purchasing a copy of the transcript? 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.

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

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

My Commission Expires: July 31, 2029



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THE DISTRICT OF COLUMBIA

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