

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD
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4 _____
5 SHANGHAI HONGENE BIOTECH)
6 CORPORATION,)
7 Petitioner,) IPR2023-00490
8 vs.) US Patent No.
9 CHEMGENES CORPORATION,) 9,884,885 B2
10 Patent Owner.)
11 _____)

12 VIDEO DEPOSITION OF PHIL S. BARAN, Ph.D.

13 SEPTEMBER 13, 2023

14 SAN DIEGO, CALIFORNIA
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22 Job No. 505051

23 Pages 1 - 189

24 Reported by

25 Cynthia J. Vega, RMR, RDR, CSR 6640, CCRR 95

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Yann Thillier (Remote appearance)

The Technician:

Melody Adair (Remote appearance)

The Videographer:

Ryan LaFond

* * * * *

The video deposition of Phil S. Baran,
Ph.D., a Witness herein, taken on behalf of Patent
Owner, on Wednesday, September 13, 2023, before
Cynthia J. Vega, CSR 6640, beginning at the hour of
8:04 a.m., at 12544 High Bluff Drive, Suite 300, in
the City of San Diego, County of San Diego, State of
California.

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WITNESS

Phil S. Baran, Ph.D.

EXAMINATION

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By Mr. Shores

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EXHIBITS

EXHIBIT

DESCRIPTION

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Exhibit 2001

Research paper titled "A P(V)
platform for oligonucleotide
synthesis"

42

Exhibit 2002

Israel Journal of Chemistry
Review article titled "DNA
Encoded Libraries: A Visitor's
Guide"

53

Exhibit 2003

Journal of the American Chemical
Society article titled
"Expanding Reactivity in
DNA-Encoded Library Synthesis
via Reversible Binding of DNA to
an Inert Quaternary Ammonium
Support"

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EXHIBITS		
EXHIBIT	DESCRIPTION	PAGE
Exhibit 2006	Review article titled "Current Challenges in Nucleic Acid Synthesis"	154
(Exhibits 1001, 1003, 1007, 1017, 1018, 1019, 1020, and 1028 were previously marked and attached for reference.)		

Transcript of Phil S. Baran, Ph.D.
Conducted on September 13, 2023

6

SAN DIEGO, CALIFORNIA

WEDNESDAY, SEPTEMBER 13, 2023, 8:04 A.M.

THE VIDEOGRAPHER: Good morning. We are on the record. This is the video-recorded deposition of Dr. Phil Baran in the matter of Shanghai Hongene Biotech Corporation versus ChemGenes Corporation. This case is filed in the United States Patent and Trademark Office.

Today's date is September 13, 2023. The time on the record is 8:04 a.m. Pacific time.

My name is Ryan LaFond. I am the videographer. Our court reporter today is Cindy Vega. We represent Planet Depos.

Would counsel please identify yourself and state whom you represent.

MR. SHORES: Yes. I'm Dan Shores. I am with Rothwell Figg, and I represent the patent owner, ChemGenes Corporation. And with me also from our firm is Aydin Harston. He's in our -- I'm in Rothwell Figg's Boston office, and Aydin is my colleague and another attorney at Rothwell Figg and he's located in Rothwell Figg's DC office.

MR. EDWARDS: This is Jeremy Edwards from Procopio on behalf of petitioner and the witness.

08:03:57
08:03:57
08:04:01
08:04:07
08:04:11
08:04:13
08:04:16
08:04:18
08:04:25
08:04:28
08:04:31
08:04:34
08:04:37
08:04:39
08:04:41
08:04:46
08:04:50
08:04:54
08:04:58
08:05:01
08:05:07
08:05:10

1 Dan, could you also please identify for us 08:05:16
2 on the record who else is attending. 08:05:18

3 MR. SHORES: Yes. Also attending is Kevin 08:05:25
4 O'Connor. He's the general counsel for ChemGenes 08:05:27
5 Corporation. And with Kevin is Anuj Mohan, Jeremy 08:05:30
6 Little, and Yann Thillier, T-h-i-l-l-i-e-r. They 08:05:38
7 are also with ChemGenes Corporation. 08:05:43

8 MR. O'CONNOR: Dan, it's Anuj Srivastava. 08:05:47

9 MR. SHORES: Excuse me. Kevin, maybe you 08:05:51
10 can clarify titles as well. 08:05:53

11 MR. O'CONNOR: Sure. So it's Anuj 08:05:58
12 Srivastava is the chief operating officer of 08:05:59
13 ChemGenes. Dr. Jeremy Little is the head of the 08:06:05
14 oligonucleotide unit of ChemGenes. And Yann 08:06:10
15 Thillier is a scientific officer of ChemGenes. 08:06:12

16 MR. SHORES: Then also on the call on this 08:06:21
17 deposition is Dr. Patrick Hrdlicka. And Dr. Patrick 08:06:22
18 Hrdlicka is an expert consultant for ChemGenes 08:06:30
19 Corporation in connection with this IPR. 08:06:32

20 MR. EDWARDS: And I think we should get the 08:06:38
21 IPR number on the record. It's IPR2023-00490. 08:06:40

22 MR. SHORES: Just to clarify too, I'm 08:06:56
23 having a little difficulty hearing you, Jeremy. 08:06:59
24 It's a little muffled. 08:07:01

25 MR. EDWARDS: How about now? 08:07:03

Transcript of Phil S. Baran, Ph.D.
Conducted on September 13, 2023

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1	MR. SHORES: I'm sorry?	08:07:08
2	MR. EDWARDS: How about now?	08:07:10
3	MR. SHORES: Yeah, that's better. Thank	08:07:11
4	you.	08:07:13
5	MR. EDWARDS: Sure.	08:07:14
6	THE VIDEOGRAPHER: All right. Thank you.	08:07:29
7	Would the reporter please swear in the	08:07:29
8	witness.	08:07:31
9		
10	PHIL S. BARAN, PhD,	
11	Witness herein, being first duly sworn, testifies as	
12	follows:	
13		
14	EXAMINATION	
15	BY MR. SHORES:	
16	Q. Good morning, Dr. Baran. How are you?	08:07:45
17	A. Good morning, Counsel. Good. How you	08:07:47
18	doing?	08:07:49
19	Q. Very well. Thank you.	08:07:50
20	So you were just sworn in. You	08:07:51
21	understand -- so you understand that you are under	08:07:54
22	oath in this deposition; right?	08:07:57
23	A. Yes, sir.	08:07:58
24	Q. And you understand that the court reporter,	08:08:00
25	who is present in the room with you, is making a	08:08:04

1	written record of all of my questions and all of	08:08:07
2	your answers; right?	08:08:11
3	A. Yes, sir.	08:08:12
4	Q. And you understand that the court reporter	08:08:14
5	is not able to take down nonverbal gestures like	08:08:17
6	head nods; right?	08:08:23
7	A. Yes, sir.	08:08:24
8	Q. Okay. So during the course of this	08:08:25
9	deposition, could you please give verbal answers to	08:08:27
10	all of my questions?	08:08:32
11	A. Absolutely.	08:08:33
12	Q. Okay. Thank you.	08:08:34
13	And you understand that this deposition is	08:08:36
14	being videotaped; correct?	08:08:39
15	A. Yes, sir.	08:08:40
16	Q. And you also understand that Mr. Edwards,	08:08:42
17	which is petitioner's counsel, is entitled to make	08:08:46
18	concise objections to my questions; right?	08:08:50
19	A. Yes, sir.	08:08:53
20	Q. And you understand that petitioner's	08:08:55
21	counsel is not allowed to make speaking objections	08:08:57
22	or to coach you on your answers; right?	08:09:01
23	A. Yes, sir.	08:09:05
24	Q. And you also understand that petitioner's	08:09:07
25	counsel is not allowed to act as an intermediary	08:09:09

1	between you and me; right?	08:09:15
2	A. Yes, sir.	08:09:16
3	Q. Okay. So, for example, if -- petitioner's	08:09:17
4	counsel is not allowed to interpret questions and	08:09:21
5	decide which questions you should answer or help you	08:09:26
6	formulate your answers while testifying.	08:09:29
7	Understand?	08:09:31
8	A. Yes, sir.	08:09:32
9	Q. Okay. And unless Mr. Edwards instructs you	08:09:33
10	not to answer, you must answer my questions	08:09:42
11	regardless of the objections that the counsel may	08:09:45
12	make. Do you understand that?	08:09:49
13	A. Understood.	08:09:50
14	Q. And during the deposition, counsel is not	08:09:52
15	allowed to consult or confer with you regarding the	08:09:56
16	substance of your testimony already given except for	08:10:01
17	the purposes of conferring on whether to assert a	08:10:05
18	privilege against testifying or how to comply with	08:10:09
19	the board order. Understand?	08:10:13
20	A. Yes.	08:10:17
21	Q. And then counsel is also not allowed to	08:10:17
22	suggest to you in any manner in which any of my	08:10:19
23	questions should be answered; right?	08:10:22
24	A. Yes, sir.	08:10:26
25	Q. Okay. Or counsel is also not allowed to	08:10:26

1 initiate a private conference with you or call for a 08:10:30
2 break in the proceedings while a question is pending 08:10:34
3 except for purposes of determining whether a 08:10:38
4 privilege should be asserted. Do you understand 08:10:41
5 that? 08:10:43

6 A. Yes, sir. 08:10:43

7 Q. Okay. And given that this is a remote 08:10:43
8 deposition, you know, I'm not physically present in 08:10:48
9 the room. I want to ask some other questions. 08:10:51

10 So you're being represented by your counsel 08:10:54
11 today, Mr. Edwards; right? 08:10:56

12 A. Yes, sir. 08:10:58

13 Q. Hongene's counsel, Mr. Edwards; right? 08:11:03

14 A. Yes, sir. 08:11:05

15 Q. And who else is in the room with you today? 08:11:06

16 A. We have the folks from Depo -- Planet Depos 08:11:12
17 and counsel. That's it. 08:11:18

18 Q. And no other counsel is present with you 08:11:21
19 today; correct? 08:11:23

20 A. No. Just a total of three people here. 08:11:25

21 Q. Okay. Thank you. 08:11:26

22 And you understand that no notes are to be 08:11:30
23 passed between you and counsel during this 08:11:31
24 deposition? 08:11:33

25 A. Yes, sir. 08:11:34

1	Q.	And that you're not allowed to pass notes	08:11:38
2		to Mr. Edwards, and Mr. Edwards is not allowed to	08:11:40
3		pass notes to you; right?	08:11:43
4	A.	Yes, sir. Understood.	08:11:44
5	Q.	Okay. And you understand that there is no	08:11:45
6		verbal and nonverbal communication between you and	08:11:50
7		counsel during this deposition. You understand?	08:11:52
8	A.	Yes, sir.	08:11:54
9	Q.	Okay. So if you need to take a break at	08:11:55
10		all at any point today, just let me know. Depending	08:11:58
11		on how this goes, it could go long, it could go	08:12:03
12		short, but we'll see how it goes. And -- but if you	08:12:07
13		do need to take a break, you know, just, again,	08:12:09
14		advise me and we'll take the appropriate break.	08:12:11
15	A.	Thank you.	08:12:17
16	Q.	So is there -- you're welcome.	08:12:18
17		Is there any reason why you would not be	08:12:20
18		able to provide full, truthful, and complete	08:12:22
19		testimony today?	08:12:25
20	A.	No. Absolutely not.	08:12:26
21	Q.	Are you currently taking any medications	08:12:29
22		that would cause you not to be able to provide full,	08:12:30
23		truthful, or complete testimony today?	08:12:32
24	A.	No. Absolutely not.	08:12:34
25	Q.	Excuse me?	08:12:37

1	A. Absolutely not.	08:12:38
2	Q. Okay. So there is no reason that would	08:12:39
3	cause you not to be able to provide full, truthful,	08:12:41
4	and complete testimony today; right?	08:12:44
5	A. No, sir.	08:12:48
6	Q. Okay. If the technician could put up	08:12:48
7	petitioner's previously marked Exhibit 1003.	08:12:53
8	THE REPORTER: And, Counsel, to be clear,	08:13:07
9	previously marked, you don't want me to re-mark it	08:13:07
10	today?	08:13:07
11	MR. SHORES: That's correct. Yeah.	08:13:09
12	Unless, Jeremy, you have a reason why you want to	08:13:09
13	re-mark these. I certainly don't. But we will	08:13:12
14	stick with the marking system that's consistent with	08:13:15
15	the rules in the IPR.	08:13:19
16	MR. EDWARDS: That's fine.	08:13:21
17	THE WITNESS: Mr. Shores?	08:13:23
18	BY MR. SHORES:	08:13:24
19	Q. Yes, sir.	08:13:25
20	A. I did want to alert you that I have an	08:13:25
21	unmarked copy of the document you're showing at the	08:13:28
22	top. Am I allowed to have this with me? There is	08:13:30
23	no marking on it.	08:13:32
24	Q. In the lower right-hand corner, is there a	08:13:35
25	mark?	08:13:38

Transcript of Phil S. Baran, Ph.D.
Conducted on September 13, 2023

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1	THE WITNESS: Cindy, is there anything?	08:13:39
2	THE REPORTER: No.	08:13:41
3	MR. EDWARDS: May I see it?	08:13:43
4	THE WITNESS: It was just sitting up here	08:13:44
5	in front of me when I walked in.	08:13:45
6	MR. EDWARDS: So on the cover page, there	08:13:47
7	is no footer, but every subsequent page has a footer	08:13:48
8	that says Shanghai Hongene Exhibit 1003.	08:13:54
9	MR. SHORES: Right. So it is just not	08:13:59
10	marked in the cover page, but the rest of the pages	08:14:00
11	are marked in the document that Dr. Baran's looking	08:14:03
12	at?	08:14:09
13	MR. EDWARDS: Yes.	08:14:10
14	BY MR. SHORES:	08:14:10
15	Q. Okay. So looking at Exhibit 1003, if you	08:14:11
16	turn to page 77.	08:14:15
17	Technician can go to 77.	08:14:21
18	This reads, "I declare under the	08:14:31
19	penalty" -- actually could you read that into the	08:14:32
20	record?	08:14:34
21	A. It says, "I declare under penalty of	08:14:35
22	perjury under the laws of the United States of	08:14:37
23	America that the foregoing is true and correct."	08:14:39
24	Q. And that's dated January 18, 2023; correct?	08:14:42
25	A. Yes.	08:14:45

1	Q.	And that's your signature; correct?	08:14:46
2	A.	Yes.	08:14:48
3	Q.	Thank you.	08:14:51
4		If we can go to page -- to paragraphs 40 --	08:14:58
5		to paragraph 40 in this document, please.	08:15:02
6	A.	Mr. Shores?	08:15:06
7	Q.	Yes, sir.	08:15:07
8	A.	When I was reviewing this document over the	08:15:08
9		past couple weeks, I did notice a small typo. I	08:15:10
10		don't know if that matters or not.	08:15:14
11	Q.	Which typo?	08:15:19
12	A.	Well, on page 66. I did all the figures	08:15:21
13		for this report obviously and I noticed that I	08:15:26
14		pasted in the wrong figure on page 66. That figure	08:15:31
15		shows cytosine but it should show guanine, but -- or	08:15:36
16		guanosine, but there is no difference to the	08:15:41
17		conclusion. It's just I put the wrong structure in.	08:15:43
18		So sorry about that.	08:15:46
19	Q.	Thank you for putting -- thank you for	08:15:49
20		letting me know.	08:15:52
21	A.	Yeah.	08:15:54
22		Sorry. Where were we? Page -- what page	08:15:55
23		did you want to go to?	08:15:57
24	Q.	Give me one second, Dr. Baran.	08:16:04
25		Dr. Baran, on paragraph 40 of your expert	08:16:15

1	declaration in Exhibit 1003, you testified that	08:16:18
2	nucleotides are the molecular building blocks of DNA	08:16:25
3	and RNA; right?	08:16:29
4	A. Correct.	08:16:30
5	Q. And then down in paragraph 43 -- so if the	08:16:32
6	technician would move to paragraph 43 -- you also	08:16:38
7	testified that those nucleotides have identifiable	08:16:44
8	substructures like in figure 2; right?	08:16:49
9	A. Correct.	08:16:53
10	Q. And just -- what I'm doing here is I just	08:16:53
11	want to clarify some of the terminology so that when	08:16:57
12	we have our discussion today, we're sort of on the	08:17:00
13	same page with regard to the terminology.	08:17:03
14	A. Okay.	08:17:05
15	Q. So I'm going to walk through some of these	08:17:06
16	sections in your report to ensure that we're on the	08:17:08
17	same page.	08:17:11
18	A. Okay.	08:17:12
19	Q. So on paragraph 43, you testified that	08:17:12
20	nucleotides have identifiable substructures. And my	08:17:16
21	question is: Those substructures include a	08:17:21
22	five-membered carbon sugar ring; right?	08:17:24
23	A. Correct.	08:17:28
24	Q. A phosphate group; right?	08:17:29
25	A. Correct.	08:17:31

1	Q. And one of four major nucleobases; correct?	08:17:31
2	A. Correct.	08:17:36
3	Q. And then in paragraph 45 -- if the	08:17:36
4	technician would scroll to paragraph 45 -- and I	08:17:41
5	understand this is academic for you, but to confirm	08:17:46
6	for the record, the four major nucleobases are	08:17:51
7	DNA -- before DNA are adenine, thymine, cytosine,	08:17:55
8	and guanine; right?	08:17:59
9	A. Yes, sir.	08:18:02
10	Q. And the four major nucleobases for RNA are	08:18:03
11	adenine, uracil, cytosine, and guanine; correct?	08:18:06
12	A. Yes.	08:18:08
13	(Reporter clarification with counsel.)	08:18:17
14	Q. And this is in the report.	08:18:19
15	So it's -- RNA is adenine, uracil,	08:18:24
16	cytosine, and guanine.	08:18:30
17	(Reporter clarification with counsel.)	08:18:41
18	Q. In paragraph 46, you identified the	08:18:47
19	numbering system for the five-membered carbon sugar	08:18:50
20	ring of the nucleotide; right?	08:18:58
21	A. Yes, sir.	08:19:00
22	Q. And this is shown in figure 3. So if we	08:19:02
23	can move to figure 3, which I believe is on the next	08:19:05
24	page. And up in that -- I guess you can use the top	08:19:08
25	structure. 1 prime is in the -- the 1 prime	08:19:18

1	position of the sugar ring is in the upper	08:19:22
2	right-hand corner; correct?	08:19:25
3	A. Yes, sir.	08:19:27
4	Q. 2 prime is in the lower right-hand corner;	08:19:29
5	correct?	08:19:30
6	A. Yes, sir.	08:19:32
7	Q. 3 prime in the lower left-hand corner;	08:19:33
8	correct?	08:19:37
9	A. Yes.	08:19:38
10	Q. 4 prime is in the upper left-hand corner.	08:19:38
11	And then 5 prime is -- extends from that; correct?	08:19:40
12	A. Yes, sir.	08:19:45
13	Q. Okay. Thank you.	08:19:45
14	So during today's deposition when we refer	08:19:48
15	to 1 prime, 2 prime, 3 prime, 5 prime, et cetera, of	08:19:50
16	the sugar rings of nucleotides, nucleosides, and	08:19:55
17	phosphoramidites, we'll be referring to this	08:19:58
18	1 prime, 2 prime, 3 prime, 4 prime, 5 prime system.	08:20:02
19	Is that fair?	08:20:07
20	A. That would be great.	08:20:08
21	Q. Works for you? Okay. Good.	08:20:09
22	And then similarly if we jump to	08:20:11
23	paragraph 50 of the report -- or the expert	08:20:13
24	declaration. Excuse me. So we go to paragraph 50.	08:20:18
25	You testified that the sugar rings and nucleobase	08:20:27

1	rings of nucleotides have reactive hydroxyl and	08:20:33
2	amino and NH2 functional groups, which could result	08:20:38
3	in undesirable side reactions during solid phase	08:20:45
4	oligonucleotide synthesis; right?	08:20:50
5	A. Yes, sir.	08:20:53
6	Q. When you refer here to nucleobase rings,	08:20:54
7	you're referring to the structure of the bases we	08:20:57
8	discussed earlier; right?	08:21:01
9	A. That's correct.	08:21:02
10	Q. And so if we turn to page -- to paragraph	08:21:05
11	115, page 47.	08:21:07
12	Page 47, paragraph 115, the technician.	08:21:17
13	Okay.	08:21:23
14	You provided a figure of a guanosine	08:21:27
15	phosphoramidite here; right?	08:21:27
16	A. Yes, sir.	08:21:33
17	Q. And the nucleobase attached to the 1 prime	08:21:33
18	position of the sugar ring of this guanosine	08:21:37
19	phosphoramidite is guanine; right?	08:21:40
20	A. Correct.	08:21:43
21	Q. And here the guanine is protected with	08:21:44
22	isobutyryl; correct?	08:21:46
23	A. Correct.	08:21:48
24	Q. And there is a numbering system relating to	08:21:49
25	the positions on the guanine structure; right?	08:21:52

1	A. Correct.	08:21:55
2	Q. And you can see that on this structure --	08:21:58
3	we already said that isobutyryl is connected to this	08:22:00
4	guanine. And here the isobutyryl is -- protecting	08:22:06
5	group is connected to guanine at the N2 position of	08:22:12
6	the guanine ring; correct?	08:22:15
7	A. Correct.	08:22:17
8	Q. So today -- during today's deposition when	08:22:18
9	we refer to N2 position of guanine, we will be	08:22:20
10	referring to this position of the guanine ring shown	08:22:25
11	here. Does that sound good?	08:22:27
12	A. That sounds great.	08:22:29
13	Q. Okay. Thank you.	08:22:30
14	If you turn to paragraph 47, so jumping	08:22:34
15	back to paragraph 47, you testified that in a single	08:22:37
16	strand of DNA or RNA, nucleotides are connected by	08:22:50
17	covalent bonds between the sugar of one nucleotide	08:22:56
18	and the phosphate of the next nucleotide; right?	08:22:59
19	A. Yes.	08:23:03
20	Q. And that's shown in figure 3?	08:23:04
21	A. Yes.	08:23:06
22	Q. So that's what you mean when you say	08:23:08
23	nucleotides -- you also say in your report that	08:23:12
24	nucleotides are the molecular building blocks of DNA	08:23:14
25	and RNA. So is that what you mean when you say	08:23:18

1	nucleotides are the molecular building blocks of DNA	08:23:23
2	and RNA?	08:23:27
3	A. Yes, sir.	08:23:27
4	Q. Okay. And each strand of DNA and RNA will	08:23:28
5	be comprised of a number of these nucleotide	08:23:34
6	building blocks as you referred to them; correct?	08:23:39
7	A. Yes, sir.	08:23:42
8	Q. And your testimony is that oligonucleotides	08:23:43
9	are comprised of short chains of nucleotides; right?	08:23:49
10	A. Yes, sir.	08:23:55
11	Q. So nucleotides are -- and as you refer to	08:23:57
12	them in your report in connection with this case,	08:24:03
13	your testimony is that nucleotides are also the	08:24:07
14	molecular building blocks -- nucleotides are also	08:24:12
15	the molecular building blocks of oligonucleotides;	08:24:15
16	right?	08:24:19
17	A. Yes, sir.	08:24:20
18	Q. Okay. So if we go to paragraph 52, you	08:24:20
19	testified that modern oligonucleotide synthesis	08:24:32
20	employs molecules known as nucleoside	08:24:39
21	phosphoramidites, or commonly referred to as just	08:24:43
22	phosphoramidites; right?	08:24:47
23	A. Correct.	08:24:49
24	Q. So a nucleoside as you've testified is just	08:24:49
25	a nucleotide without a phosphate group; correct?	08:24:54

1	A. Correct.	08:24:58
2	Q. So when we refer to just phosphoramidites	08:24:59
3	today, it's understood that we'll be referring to	08:25:02
4	nucleoside phosphoramidites. Is that fair?	08:25:07
5	A. Yes, sir.	08:25:10
6	Q. Okay. And you also say that	08:25:11
7	phosphoramidites are used as key reagents during	08:25:15
8	solid phase oligonucleotide synthesis; is that	08:25:19
9	right?	08:25:27
10	A. Yes, sir.	08:25:27
11	Q. And then you've also referred to the	08:25:28
12	shorthand for oligonucleotide synthesis as SPOS;	08:25:29
13	right? Excuse me. As for solid phase	08:25:34
14	oligonucleotide synthesis as SPOS, S-P-O-S; correct?	08:25:39
15	A. S-P-O-S, yes. Yes, sir.	08:25:43
16	Q. An acronym?	08:25:45
17	A. Yes.	08:25:46
18	Q. And you also in your report -- so we talked	08:25:46
19	about where nucleotides are building blocks of RNA,	08:25:49
20	DNA, and oligonucleotides. But you also refer to	08:25:58
21	phosphoramidites as building blocks; right?	08:26:03
22	A. Yes, sir.	08:26:05
23	Q. But you also said earlier that -- you also	08:26:09
24	testified that phosphoramidites are reagents; right?	08:26:12
25	A. They're both.	08:26:16

1	Q. They're both. Okay. So -- but are	08:26:17
2	phosphoramidites are not themselves building blocks	08:26:24
3	in oligonucleotide chain; right?	08:26:28
4	A. No. It's about the context. So if you're	08:26:30
5	talking about solid phase oligonucleotide synthesis	08:26:34
6	from the point of view of the practitioner, then the	08:26:38
7	phosphoramidite is your building block that allows	08:26:42
8	you to construct the oligonucleotide. But when you	08:26:44
9	talk about structures of nature or the	08:26:47
10	oligonucleotide itself, then the building blocks are	08:26:49
11	the nucleotides within them.	08:26:53
12	So it is just a vantage point of context.	08:26:59
13	If you're making them and you're a synthetic	08:27:00
14	chemist, you think of -- if you're using P(III) as	08:27:02
15	your mode of synthesis, you think of the	08:27:06
16	phosphoramidites as your building blocks for	08:27:10
17	reagents -- your building blocks for the synthesis.	08:27:15
18	Whereas if you're a student or you're looking at the	08:27:17
19	finished oligonucleotide product, you view the	08:27:23
20	individual nucleotides as the building blocks of the	08:27:27
21	oligo. Does that make sense?	08:27:31
22	Q. So your testimony is that the building	08:27:33
23	blocks are -- it's more of a general term that	08:27:35
24	encompasses nucleotides, nucleosides, and	08:27:39
25	phosphoramidites; is that right?	08:27:44

1 A. Well, what I'm -- my testimony is that,
2 which is what is the convention in the community, is
3 that if you look at a piece of RNA or DNA, for
4 example, a student will refer to the individual ATGC
5 as the nucleotide building blocks. Or you can even
6 call them -- you know, the people often interconvert
7 the use of nucleoside or nucleotide as a building
8 block that is made up -- that makes up the chain.

9 But when you're talking about
10 phosphoramidites, obviously those are not building
11 blocks of the final DNA because you don't have
12 phosphoramidite in DNA. But those are the building
13 blocks that you use in an unnatural setting. Nature
14 doesn't use phosphoramidites. Humans use them for
15 solid phase oligo synthesis that eventually, after
16 oxidation and deprotection, become the final oligo
17 product.

18 Q. Thank you, Dr. Baran.

19 I guess what I'm trying to just confirm is
20 the term building blocks are being used in your
21 testimony. You've used building blocks in your
22 testimony. So I'm just -- in connection with both
23 nucleotides and nucleosides and phosphoramidites.
24 And so I'm just confirming, when you say building
25 blocks, that's more of a -- that's a broader term

1	that encompasses nucleotides, nucleosides, and	08:29:55
2	phosphoramidites; right?	08:29:59
3	A. All in different context, correct.	08:30:02
4	Q. When we say building -- you say	08:30:04
5	phosphoramidite, that's a building block. I mean,	08:30:06
6	you put on record what your view is as to the	08:30:09
7	context for that. But you would refer to	08:30:12
8	phosphoramidites -- your testimony is that	08:30:14
9	phosphoramidites are building blocks, nucleotides;	08:30:18
10	right?	08:30:21
11	So phosphoramidites are building blocks;	08:30:21
12	right?	08:30:23
13	A. And they're reagents too, yes.	08:30:23
14	Q. Phosphoramidites are also reagents?	08:30:27
15	A. Yes.	08:30:28
16	Q. Nucleotides are building blocks; correct?	08:30:30
17	A. Are building blocks that, you know,	08:30:34
18	people -- that nature expresses.	08:30:37
19	Q. And nucleosides are building blocks as	08:30:42
20	well?	08:30:44
21	A. Correct. And they can be reagents too	08:30:45
22	actually.	08:30:48
23	Q. Sides can be reagents. Okay. That's fair.	08:30:50
24	Thank you for your testimony.	08:30:53
25	A. Sure.	08:30:54

1	Q. Moving to paragraph 57. You testified that	08:30:55
2	phosphoramidite chemistry encompassing not only the	08:31:04
3	P(III) reactive center but also the accompanying	08:31:10
4	protecting groups, activating agents, and	08:31:14
5	adaptations for automated oligonucleotide synthesis	08:31:18
6	is the gold standard method for DNA synthesis that	08:31:24
7	has been used in the industry for almost 35 years;	08:31:30
8	right?	08:31:34
9	A. Correct.	08:31:34
10	Q. And you also testified that phosphoramidite	08:31:34
11	chemistry is also highly flexible and can be used to	08:31:39
12	produce oligonucleotides and their conjugates with	08:31:45
13	diverse chemical modifications; right?	08:31:49
14	A. Correct.	08:31:53
15	Q. And you agree that there are a large number	08:31:55
16	of different chemically modified phosphoramidites	08:31:59
17	that exist; right?	08:32:04
18	A. Yes.	08:32:05
19	Q. And you'd agree that there are a large	08:32:08
20	number of chemically modified phosphoramidites that	08:32:12
21	existed in the 2009 time frame; is that correct?	08:32:15
22	A. Yes.	08:32:19
23	Q. Would you say hundreds of -- hundreds of	08:32:22
24	different chemically modified phosphoramidites?	08:32:26
25	MR. EDWARDS: Object to form.	08:32:31

1	THE WITNESS: I mean, it would be	08:32:31
2	conjecture, but certainly one could easily identify	08:32:32
3	hundreds in the literature at that time. Sure.	08:32:38
4	BY MR. SHORES:	08:32:41
5	Q. Thousands?	08:32:42
6	A. Perhaps.	08:32:43
7	Q. Okay. And then if we go to paragraph 58,	08:32:45
8	you testified that a canonical cycle for the	08:32:49
9	phosphoramidite method of modern SPOS is depicted in	08:32:59
10	figure 5; is that correct?	08:33:07
11	A. Yes, sir.	08:33:09
12	Q. And you see in the 1 prime group in	08:33:10
13	figure 5, the 1 prime group, there is a letter B of	08:33:15
14	the molecule, and figure 5 and the molecule -- I say	08:33:22
15	start in the upper left-hand corner.	08:33:27
16	A. Yes. Yes.	08:33:31
17	Q. Right. And that -- and that B stands for	08:33:32
18	the base group; correct?	08:33:36
19	A. Correct.	08:33:37
20	Q. And in this canonical cycle, the base	08:33:39
21	groups are protected; is that right?	08:33:45
22	A. Most often they are. Almost always.	08:33:50
23	Q. Most often?	08:33:53
24	A. Yes.	08:33:53
25	Q. Okay. Most often the base group is	08:33:53

1	protected. So in the situations where a base group	08:33:56
2	is protected, and the base group is protected and in	08:34:02
3	this cycle -- let me take a step back.	08:34:14
4	So in this canonical cycle that you show	08:34:15
5	here, this depicts the synthesis of an	08:34:19
6	oligonucleotide; correct?	08:34:26
7	A. Yes, sir.	08:34:27
8	Q. Where a -- you know, building blocks are	08:34:29
9	added onto each other during each cycle; is that	08:34:35
10	correct?	08:34:39
11	A. Yes.	08:34:40
12	Q. So when it goes through one cycle, one	08:34:41
13	building block is added to make a two-building block	08:34:44
14	oligonucleotide; right?	08:34:48
15	A. Well, that is true, but there are	08:34:50
16	exceptions. Sometimes people will add two monomeric	08:34:54
17	units -- I mean, there are obviously exceptions to	08:34:59
18	this, but --	08:35:02
19	Q. Okay.	08:35:02
20	A. -- in the 99 percent of the time, what you	08:35:02
21	normally see is one at a time as depicted here.	08:35:06
22	Q. So in that circumstance -- understanding	08:35:09
23	that there are exceptions -- in the 99 percent of	08:35:13
24	the time, the -- every cycle in a new building block	08:35:15
25	is added to the oligonucleotide; right?	08:35:21

1	A. Yes, sir.	08:35:23
2	Q. And then during the cycles where these --	08:35:25
3	during each step in the cycle, each cycle where	08:35:32
4	another building block is added to the	08:35:36
5	oligonucleotide chain, the base protecting group	08:35:39
6	never changes; right? That's not deprotected during	08:35:47
7	that process; is that correct?	08:35:50
8	A. You do not desire the base protected group	08:35:54
9	to come off, that's correct.	08:35:57
10	Q. Right. And so is it correct that if there	08:36:00
11	are ten cycles to build a ten-building block chain,	08:36:05
12	oligonucleotide chain, that at no point during	08:36:13
13	that -- those cycles does the protecting group on	08:36:17
14	the base, does that come off, does that get	08:36:23
15	deprotected?	08:36:27
16	A. You definitely do not want it to come off.	08:36:29
17	Q. Okay.	08:36:31
18	A. And if the protecting group is, you know,	08:36:31
19	affixed correctly and is the proper one, it will not	08:36:35
20	come off.	08:36:38
21	Q. And in your experience, how long do these	08:36:40
22	oligo -- can these oligonucleotide chains be,	08:36:45
23	become?	08:36:49
24	A. They can be very big. People have made,	08:36:49
25	you know, ones that are, you know, 100 in length.	08:36:55

1 They're usually shorter than that, but they can be 08:37:00
2 very large. 08:37:03

3 Q. And can you put a number on it? 08:37:06

4 A. No. They can be very large. I mean, I 08:37:08
5 don't know what the world record is as of 2009 08:37:12
6 versus today, but when you get into really, really 08:37:16
7 big ones, people often pivot to a convergent 08:37:18
8 approach where you, let's say, take two large oligos 08:37:24
9 and you ligate them together with an enzyme. 08:37:27
10 Because at a certain point your yield drops and the 08:37:30
11 coupling efficiency drops when you get to really, 08:37:34
12 really large oligonucleotides using SPOS. 08:37:37

13 Q. When you say "yield," what do you mean by 08:37:42
14 that? 08:37:46

15 A. Well, the overall amount of product you get 08:37:46
16 is your yield. And if it was 100 percent yield, it 08:37:54
17 would mean that every -- for every one building 08:38:00
18 block you put in this cycle, 100 percent of that 08:38:02
19 building block is coupled. And for every step in 08:38:06
20 the sequence oxidation, deprotection, and whatnot, 08:38:10
21 the quantity you get out is 100 percent of what you 08:38:15
22 would expect. 08:38:19

23 Now, in the real world, you don't often 08:38:20
24 get -- you know, it's very difficult to get 08:38:22
25 100 percent. You get, you know, 99 percent plus 08:38:25

1 using this chemistry. Sometimes it drops a little 08:38:29
2 bit. But due to the law of numbers, if you're 08:38:31
3 making something very big and the yield is 08:38:35
4 99 percent for each coupling step, after 20 or 30 08:38:38
5 couplings, your yield actually pretty -- starts 08:38:44
6 getting low. 08:38:47
7 Q. Okay. So an example, if you had -- under 08:38:49
8 base protecting group, if you used isobutyryl, if 08:38:56
9 isobutyryl was the protecting group on the -- at the 08:39:00
10 N2 position of guanine, for example, so this is 08:39:05
11 guanosine, and you went through 100 cycles, the 08:39:08
12 isobutyryl would -- during the cycles would not be 08:39:13
13 removed; right? 08:39:17
14 A. One would not expect them to be removed, 08:39:18
15 correct. 08:39:20
16 Q. But at what point -- but at some point the 08:39:21
17 isobutyryl protecting group would be removed; right? 08:39:29
18 A. That's correct. 08:39:32
19 Q. And at what point does that happen? 08:39:33
20 A. At the very end. 08:39:35
21 Q. When you say "At the very end," you mean 08:39:38
22 what? 08:39:41
23 A. When you're done with all the coupling 08:39:42
24 cycles and you're ready to release it from the solid 08:39:45
25 phase resin, that's the end. 08:39:47

1	Q.	Is there a step in there where the	08:39:52
2		oligonucleotide is also cleaved from the solid	08:39:57
3		support?	08:40:00
4	A.	That is the same step.	08:40:00
5	Q.	So your testimony is that the deprotection	08:40:02
6		step occurs at the same time as the cleavage from	08:40:06
7		the solid support?	08:40:12
8	A.	No. There are -- people have published	08:40:13
9		different modifications, but the canonical coupling	08:40:15
10		cycle and cleavage from the resin involves a base	08:40:21
11		treatment, sometimes an amine, where everything is	08:40:25
12		deprotected, the cyanoethyl group comes off, the	08:40:29
13		removal from the solid phase resin by attack of the	08:40:34
14		succinyl, s-u-c-c-i-n-y-l, group usually comes off	08:40:42
15		as well liberating it from the resin. And also the	08:40:50
16		base protecting groups will come off liberating the	08:40:53
17		free oligonucleotide.	08:41:00
18	Q.	Thank you.	08:41:05
19		Okay. If we can please pull up	08:41:07
20		Exhibit 1001.	08:41:11
21		And you see this exhibit, Dr. Baran?	08:41:24
22	A.	Yes, sir.	08:41:28
23	Q.	And this is the US Patent Number 9,884,885;	08:41:29
24		correct?	08:41:35
25	A.	Yes.	08:41:35

1	Q.	And you understand that this is the patent	08:41:36
2		at issue in this IPR; correct?	08:41:38
3	A.	Yes, sir.	08:41:41
4	Q.	Okay. So if we -- if the technician can	08:41:41
5		move -- please move down to the claims, which are	08:41:43
6		probably on page 31, 30 or 31. 31. Maybe we can	08:41:50
7		zoom in a little bit.	08:42:04
8		So these are the -- this -- page 31 on the	08:42:06
9		PDF, which is column 25 -- columns 25 and 26 of the	08:42:11
10		'885 patent show the five patent claims that are at	08:42:16
11		issue in this case; correct?	08:42:20
12	A.	Yes, sir.	08:42:21
13	Q.	Okay. If we look at claim 1, claim 1 is	08:42:22
14		directed to a group of -- let me take a step back.	08:42:26
15		You understand in your report that the	08:42:33
16		concept in patent law are relating to Markush	08:42:37
17		groups; right?	08:42:40
18	A.	Yes, sir.	08:42:43
19	Q.	And so when you see the language consisting	08:42:43
20		of and a number of compounds following that, you	08:42:44
21		understand that the claim can be directed to	08:42:47
22		multiple -- multiple compounds; is that right?	08:42:53
23	A.	Yes, sir.	08:42:57
24	Q.	And when we look at claim 1 -- if the	08:43:00
25		technician can scroll down a little bit -- the --	08:43:05

1	claim 1 is directed to -- claim 1 is directed to a	08:43:07
2	group of phosphoramidite compounds; correct?	08:43:11
3	A. Yes, sir.	08:43:16
4	Q. And claim 2 is also directed to a group of	08:43:19
5	phosphoramidite compounds; right?	08:43:22
6	A. If we can just scroll up.	08:43:25
7	Q. Scroll a little bit.	08:43:29
8	A. There it is. Yes.	08:43:29
9	Q. And your testimony is that claim 3 is	08:43:33
10	directed to a group of nucleosides, succinates, and	08:43:37
11	solid supports; right?	08:43:41
12	A. Yes.	08:43:42
13	Q. And claim 4 is also directed to a group of	08:43:44
14	nucleosides, succinates, and solid supports; right?	08:43:47
15	A. Yes.	08:43:50
16	Q. And your testimony is that claim 5 is also	08:43:51
17	directed to a group of nucleosides, succinates, and	08:43:55
18	solid supports; right?	08:44:00
19	A. Yes.	08:44:01
20	Q. None of these claims are directed to a	08:44:02
21	method of treatment; correct?	08:44:06
22	A. That's correct.	08:44:11
23	Q. And none of these claims are directed to	08:44:13
24	how these molecules are ultimately used; correct?	08:44:16
25	A. Correct.	08:44:20

1	Q.	So these claims are directed to the	08:44:23
2		molecules themselves; correct?	08:44:24
3	A.	Yes.	08:44:26
4	Q.	And then your understanding is that these	08:44:28
5		molecules can be used as building blocks for	08:44:29
6		oligonucleotide synthesis; is that right?	08:44:36
7	A.	Yes, sir.	08:44:40
8	Q.	Okay. Okay. I'd like to now go back to --	08:44:40
9	A.	Could I just correct that?	08:44:48
10	Q.	Sure.	08:44:54
11	A.	One doesn't necessarily need to use all of	08:44:57
12		these as building blocks for oligonucleotide	08:44:59
13		synthesis, not necessarily. One could use these	08:45:03
14		phosphoramidite reagents or succinates or	08:45:09
15		nucleosides for potentially other things as well.	08:45:13
16	Q.	But none of these claims are directed to	08:45:18
17		the use of these compounds; correct?	08:45:19
18	A.	That's correct.	08:45:22
19	Q.	Okay. Thank you.	08:45:26
20		Now if we go back to Exhibit 1003 and we go	08:45:27
21		to paragraph 2.	08:45:48
22		Here your testimony is that you graduated	08:45:59
23		from New York University in 1997 with a bachelor of	08:46:00
24		science with honors in chemistry. After college you	08:46:05
25		obtained a PhD in chemistry in 2001 from the Scripps	08:46:09

1	Research Institute where you worked under	08:46:11
2	Professor KC Nicolaou.	08:46:15
3	A. Nicolaou.	08:46:20
4	Q. Excuse me?	08:46:21
5	A. Nicolaou.	08:46:22
6	Q. Nicolaou. Excuse me. I can't see the PDF	08:46:23
7	very well here.	08:46:26
8	"After that, I did a National Institute of	08:46:27
9	Health postdoctoral fellowship at Harvard University	08:46:28
10	from 2001 to 2003." And here you say you worked	08:46:33
11	under Professor EJ Corey; right?	08:46:38
12	A. Yes, sir.	08:46:40
13	Q. During the period of 1997 to 2003 you	08:46:45
14	didn't work in the area of nucleotide synthesis; is	08:46:50
15	that correct?	08:46:54
16	A. My first exposure to nucleoside chemistry	08:46:59
17	was as an undergraduate in 19 -- it was around	08:47:03
18	middle of 1996. While I was an undergrad I	08:47:10
19	published six publications in the group I was in,	08:47:14
20	and there was some nucleoside chemistry.	08:47:17
21	Q. I have trouble hearing you. You published?	08:47:20
22	A. Numerous papers as an undergraduate. And	08:47:23
23	as part of some of those studies, I was doing	08:47:25
24	nucleoside derivatization chemistry. When I was a	08:47:30
25	PhD student with Professor Nicolaou, I did not work	08:47:37

1	on nucleosides.	08:47:42
2	Q. Which papers? You testified that when you	08:47:46
3	were an undergraduate you published papers that	08:47:50
4	related to nucleotide synthesis; is that correct?	08:47:54
5	A. Not nucleotide. I had some intermediates	08:47:59
6	that I was working on explorative studies to see if	08:48:04
7	I could couple a particular nucleoside framework	08:48:07
8	with Buckminsterfullerene, C60.	08:48:12
9	Q. And tell me all the details surrounding	08:48:20
10	that work.	08:48:22
11	A. It was mainly protecting group chemistry,	08:48:24
12	manipulations, trying to get precise derivative that	08:48:28
13	I could couple to C60. That was my first sort of	08:48:32
14	experience diving into the literature of	08:48:38
15	nucleosides, nucleotides, and, you know, working	08:48:42
16	with those sugar molecules containing purine basis.	08:48:46
17	That was the first time I had ever read that	08:48:50
18	literature and done anything with my hands on that.	08:48:53
19	Q. Did you publish any papers that related to	08:48:57
20	nucleotide synthesis?	08:49:00
21	A. Not nucleotide.	08:49:02
22	Q. Okay. Nucleoside synthesis, did you	08:49:07
23	publish any papers when you were an undergraduate	08:49:10
24	relating to nucleoside synthesis?	08:49:13
25	A. I might have. I need to look at my	08:49:16

1	publication record. I'm just trying to remember if	08:49:21
2	those papers were published. I did a lot. If you	08:49:23
3	let me...	08:49:28
4	Q. Yes. Please. Take your time.	08:49:30
5	A. I don't see it here. There may be. I need	08:49:49
6	to look. But maybe publication 246 was published	08:49:57
7	after I left, but I was on the paper where they did	08:50:04
8	it. I'd have to look. But, yeah, you're looking	08:50:07
9	for -- it was, as I remember, AZT-linked structures	08:50:10
10	to fullerene. But that was my first clear	08:50:16
11	recollection of the whole world of nucleoside	08:50:21
12	chemistry, first exposed to it then as an	08:50:25
13	undergraduate.	08:50:27
14	Q. And did any of that work involve	08:50:30
15	phosphoramidite synthesis?	08:50:33
16	A. No.	08:50:35
17	Q. So your testimony is that -- clarifying	08:50:36
18	your testimony, when you were an undergraduate, you	08:50:39
19	did some work relating to --	08:50:44
20	A. Nucleosides.	08:50:51
21	Q. -- nucleoside synthesis?	08:50:52
22	A. Correct.	08:50:55
23	Q. And your testimony is that you may have	08:50:58
24	published -- you may have been listed on a paper	08:51:01
25	that was published relating to the work on	08:51:05

1	nucleoside synthesis?	08:51:10
2	A. Yes. And I may not -- I have to go back	08:51:12
3	and study. There may be other papers that I have	08:51:15
4	from that work that I did as an undergrad. But to	08:51:18
5	be clear, there was no phosphoramidite chemistry	08:51:26
6	then, and I did not make oligonucleotides then, just	08:51:30
7	to be clear.	08:51:35
8	Q. And then when you went on to -- I guess you	08:51:37
9	went on to graduate school and a PhD program. Did	08:51:43
10	you conduct any work on nucleoside synthesis during	08:51:49
11	your PhD studies?	08:51:56
12	A. No.	08:51:57
13	Q. Did you conduct any work on oligonucleotide	08:52:01
14	synthesis during your PhD studies?	08:52:07
15	A. No.	08:52:09
16	Q. Did you perform any work relating to	08:52:11
17	oligonucleotide synthesis during your PhD studies?	08:52:15
18	A. No.	08:52:19
19	Q. And you didn't publish any papers relating	08:52:21
20	to oligonucleotide synthesis during your PhD	08:52:23
21	studies?	08:52:29
22	A. No.	08:52:29
23	Q. You didn't publish any papers relating to	08:52:30
24	oligo nucleoside synthesis during your PhD studies;	08:52:31
25	correct?	08:52:39

1	A.	I'm trying to think. I had about 35 papers	08:52:39
2		in my PhD.	08:52:42
3	Q.	Okay.	08:52:46
4	A.	There may have -- in some of the	08:52:46
5		methodologies that I worked on, there may have been	08:52:48
6		examples, and I'd have to go back and look at all of	08:52:51
7		them, where nucleosides were part of the substrate	08:52:54
8		scope of that methodology, but there was not any	08:52:59
9		phosphoramidite chemistry nor was there	08:53:05
10		oligonucleotide chemistry.	08:53:07
11	Q.	And in paragraph 3 of your declaration, you	08:53:14
12		testified that you started teaching at Scripps in	08:53:18
13		June 2003 as an assistant professor of chemistry;	08:53:21
14		right?	08:53:25
15	A.	Yes.	08:53:25
16	Q.	And in July of 2006 you earned tenure at	08:53:27
17		Scripps and became an associate professor of	08:53:30
18		chemistry; correct?	08:53:32
19	A.	Yes.	08:53:33
20	Q.	And then you were promoted to professor of	08:53:34
21		chemistry in June 2008; correct?	08:53:36
22	A.	Yes.	08:53:38
23	Q.	And then since January 2013, you've held	08:53:40
24		the Darlene Shiley chair in chemistry at Scripps;	08:53:43
25		right?	08:53:47

1	A. Yes.	08:53:47
2	Q. And then you've also been a member of the	08:53:48
3	Skaggs Institute for chemical biology since April	08:53:50
4	2009; right?	08:53:56
5	A. Correct.	08:53:59
6	Q. During the period of -- during the period	08:53:59
7	of June 2003 through 2009, you did not work in the	08:54:03
8	area of nucleotide synthesis; is that correct?	08:54:13
9	A. The lab did not, but in my classes that I	08:54:17
10	taught and in consulting that I did with companies,	08:54:22
11	I was -- you know, had to learn a lot about the	08:54:24
12	area.	08:54:29
13	Q. During the period June 2003 through 2009,	08:54:32
14	you did not publish any articles or you were not	08:54:37
15	listed as an author on any articles that related to	08:54:41
16	nucleotide synthesis; correct?	08:54:45
17	A. Not that I recall.	08:54:47
18	Q. And then during the period of June 2003	08:54:49
19	through 2009, you didn't publish any articles in the	08:54:53
20	area of nucleoside synthesis; correct?	08:54:58
21	A. Not that I recall.	08:55:02
22	Q. During the period of June 2003 through	08:55:05
23	2009, you did not publish any papers in the area of	08:55:08
24	phosphoramidite synthesis; correct?	08:55:17
25	A. That's correct.	08:55:18

1	Q.	And then during the period of June 2003	08:55:20
2		through 2009, you did not publish any papers	08:55:23
3		relating to oligonucleotide synthesis; correct?	08:55:28
4	A.	That's correct.	08:55:30
5	Q.	If we move to paragraph 6, you list three	08:55:41
6		papers that you published on oligonucleotide	08:55:48
7		synthesis; correct?	08:55:52
8	A.	Yes.	08:55:53
9	Q.	Your testimony is that all of these papers	08:55:57
10		relate to oligonucleotide synthesis; correct?	08:56:00
11	A.	Correct.	08:56:02
12	Q.	And you cited to a paper titled "A	08:56:04
13		P(V)-Platform for Oligonucleotide Synthesis," dated	08:56:09
14		2021; right?	08:56:13
15	A.	Yeah. That paper is a follow-up to our	08:56:14
16		Science paper we had in 2018 on a similar topic.	08:56:18
17	MR. SHORES:	Okay. And if the technician	08:56:22
18		can put up patent owners Exhibit 2001.	08:56:26
19		(Exhibit 2001 marked for identification.)	08:56:30
20	BY MR. SHORES:		08:57:08
21	Q.	Does this look -- Doctor, does this look	08:57:09
22		like the paper that we're referring to, the title of	08:57:12
23		"A P(V) platform for oligonucleotide synthesis"?	08:57:16
24	A.	Yes, sir.	08:57:21
25	Q.	This paper does not discuss nucleotide	08:57:22

1	synthesis; correct?	08:57:26
2	A. Does not discuss nucleotide -- well, in	08:57:32
3	this paper we make nucleotides building blocks that	08:57:36
4	are connected to P(V) reagents. It's similar to a	08:57:40
5	phosphoramidite but a different oxidation state, and	08:57:45
6	then those are put together to make	08:57:48
7	oligonucleotides.	08:57:50
8	Q. My question was: The paper does not	08:57:52
9	discuss the synthesis of those nucleotides; right?	08:57:55
10	A. In the supporting information, all of the	08:58:00
11	synthesis is discussed for those building blocks.	08:58:03
12	Yes.	08:58:05
13	Q. Okay. Show me on the paper where the	08:58:06
14	synthesis of the nucleotides is discussed.	08:58:10
15	A. Can you give me the paper?	08:58:14
16	Q. It's on the screen.	08:58:20
17	A. I don't have a paper copy?	08:58:22
18	Okay. If you keep going -- if you keep	08:58:23
19	going down.	08:58:26
20	MR. EDWARDS: I may be able to pull out a	08:58:33
21	paper copy, if that helps folks.	08:58:35
22	THE WITNESS: Keep going down. Next page.	08:58:40
23	Next page. No, no. Stay there.	08:58:47
24	Yeah. So because it's a paper in Science	08:59:01
25	magazine, which is, I guess, along with Nature, the	08:59:05

1 most impactful scientific journal on the planet, a 08:59:08
2 lot of data is thrown into the SI, supporting 08:59:14
3 information, because they -- the page limit is 08:59:19
4 rather strict for this journal. 08:59:23

5 So if you look into the supporting 08:59:26
6 information of this paper, which is I think many 08:59:28
7 hundreds of pages long, you'll find that the 08:59:32
8 synthesis of the nucleotides that have these P(V) 08:59:35
9 base coupling agents connected to them is all 08:59:41
10 described. 08:59:45

11 BY MR. SHORES: 08:59:48

12 Q. But the synthesis of -- but synthesis of 08:59:48
13 nucleotides is not discussed within the body of the 08:59:52
14 paper. You're referencing footnotes. But the paper 08:59:55
15 itself, the work that was produced by you and the 08:59:58
16 other authors, does not discuss anywhere the 09:00:02
17 synthesis of nucleotides; is that right? 09:00:06

18 MR. EDWARDS: Object to form. 09:00:11

19 THE WITNESS: Well, it's inherent. It's 09:00:12
20 inherently there because you can't make these 09:00:14
21 oligonucleotides without making the nucleotide 09:00:17
22 building blocks, and that's found in the supporting 09:00:19
23 information. 09:00:21

24 BY MR. SHORES: 09:00:23

25 Q. So you were involved -- directly involved 09:00:24

1 with the synthesis of nucleotides in connection with 09:00:26
2 this paper? 09:00:30

3 A. Of course. 09:00:31

4 Q. Please describe that work that you did in 09:00:33
5 connection with this paper and synthesizing 09:00:38
6 nucleotides. 09:00:42

7 A. Sure. If you go down to the next page, 09:00:43
8 you'll see here a number of examples of, you know, 09:00:47
9 nucleotide-related -- this is just sort of showing 09:00:55
10 the difference between P(III) and P(V) and the 09:00:58
11 advantage of using the P(V) approach over P(III). 09:01:02

12 If we go to the next -- I think the next 09:01:06
13 page. 09:01:09

14 MR. EDWARDS: For the sake of the record, 09:01:10
15 what are you looking at? You're saying this is 09:01:12
16 showing something. What is -- 09:01:16

17 MR. SHORES: Understand, Counsel. This is 09:01:20
18 Exhibit 2001. And if the witness can point to the 09:01:22
19 specific areas that he's referring to, I think that 09:01:30
20 would be helpful for the record. 09:01:32

21 MR. EDWARDS: Right. That's all I was 09:01:34
22 getting at, is Dr. Baran was saying this shows 09:01:35
23 something, and I'm not sure what he's pointing us 09:01:38
24 to. 09:01:41

25 MR. SHORES: Okay, Jeremy. Thank you. 09:01:42

1	THE WITNESS: The previous figure, if you	09:01:43
2	look at the previous figure on the other page, shows	09:01:45
3	the difference in rate when you do a coupling. So	09:01:51
4	let's look at figure C in the bottom there.	09:01:57
5	There is a P-monomer, which I guess you	09:02:02
6	could consider to be a nucleoside that has either a	09:02:04
7	phosphoramidite connected to it or a phosphotriester	09:02:10
8	or the P(V) reagents attached to it. So that would	09:02:14
9	be a nucleotide because it has the phosphorous	09:02:17
10	connected to it.	09:02:19
11	So we had to make all of those monomers to	09:02:20
12	compare the rate. So dozens of monomers were made	09:02:23
13	with nucleosides connected to the phosphorous atom.	09:02:29
14	And then those --	09:02:33
15	BY MR. SHORES:	09:02:35
16	Q. Excuse me. Sorry. Go ahead.	09:02:35
17	A. And then those monomers, P-monomers, which	09:02:36
18	you could refer to as nucleotides, were used in a	09:02:41
19	solid phase organic synthesis regime on a machine as	09:02:44
20	depicted in the next figure to make	09:02:49
21	oligonucleotides. This was done both in this work	09:02:52
22	as well as the 2018 Science paper where we, again,	09:02:58
23	made a bunch of nucleotides and nucleosides and	09:03:03
24	oligonucleotides.	09:03:06
25	Q. So on this page 3 of Exhibit 2001, and we	09:03:09

1	were talking about under section C of the figure 2,	09:03:14
2	which shows the -- what you described as a monomer,	09:03:19
3	then it is shown here, if I can see it correctly, is	09:03:22
4	the P-monomer.	09:03:26
5	A. Uh-huh.	09:03:28
6	Q. Your testimony is that you synthesized that	09:03:28
7	molecule?	09:03:32
8	A. I believe all of these were -- all of -- I	09:03:35
9	believe all of these were made, yes, in our lab.	09:03:40
10	Q. I understand that they were made. I'm	09:03:43
11	asking if you, Dr. Baran, if you synthesized that	09:03:44
12	P-monomer.	09:03:49
13	A. Oh, with my own hands?	09:03:50
14	Q. If you were directly involved with it.	09:03:53
15	A. Of course. I'm the corresponding author of	09:03:55
16	the paper. So since -- to be clear, I run a lab of	09:03:56
17	around 40 people. And in some cases I'll go into	09:04:01
18	the lab and do the chemistry with my own hands, but	09:04:06
19	it's the large amount -- largely the work that gets	09:04:10
20	done in the lab, as with every, I think, normal	09:04:16
21	university, is done by your postdocs and your	09:04:19
22	graduate students, and they're reporting to exactly	09:04:22
23	what they do. And I review their lab notebook and	09:04:25
24	so I write the paper. So yeah. Yeah. This -- the	09:04:29
25	content of this figure was not done with my own	09:04:34

1	hands.	09:04:36
2	Q. So you did not synthesize that P-monomer?	09:04:41
3	A. Personally, no, but my students did under	09:04:46
4	my supervision.	09:04:50
5	Q. And did you personally synthesize any of	09:04:53
6	the monomers in this paper?	09:04:57
7	A. Personally, not with my own hands, no.	09:04:59
8	Q. So you weren't -- you didn't have direct	09:05:02
9	involvement with the synthesis of the monomers	09:05:05
10	disclosed in Exhibit 2001; correct?	09:05:08
11	A. I have direct involvement in everything	09:05:10
12	that's published in my papers.	09:05:12
13	Q. Excuse me?	09:05:14
14	A. I have direct involvement in everything	09:05:15
15	that's published in my papers. Doesn't mean that	09:05:17
16	I'm in the fume hood mixing chemicals with them.	09:05:20
17	Q. Right.	09:05:24
18	A. That's not how academics works.	09:05:25
19	Q. And this paper -- this paper does not	09:05:35
20	discuss the synthesis of that monomer; correct?	09:05:42
21	A. I believe it's in the supporting	09:05:47
22	information, either of this paper or the 2018	09:05:48
23	Science paper.	09:05:51
24	Q. My question is: In the body of this paper,	09:05:53
25	not including the references but in the body of this	09:05:57

1	paper, the synthesis of that monomer is not	09:06:00
2	disclosed; correct?	09:06:10
3	A. You can't divorce -- it's not found in a	09:06:15
4	reference. It's found in the supporting	09:06:19
5	information. And that is part of the paper. So the	09:06:21
6	way academic papers work is that you've got the main	09:06:25
7	body, and then you've got the supporting	09:06:29
8	information, which is a continuation of the paper	09:06:31
9	that contains a number of technical details that	09:06:34
10	allow people to -- that enable the work, to use your	09:06:39
11	language, that allow people to reproduce the	09:06:42
12	findings and know exactly where everything came	09:06:45
13	from.	09:06:47
14	So the supporting information and the main	09:06:47
15	body for the purposes of my testimony are the same	09:06:50
16	thing because you can't divorce them. It's not a	09:06:55
17	reference. It's part of the paper.	09:06:58
18	Q. I can take that as a refusal to answer.	09:07:08
19	I'm asking you -- let's go page by page.	09:07:12
20	Let's go to page 1.	09:07:15
21	A. Well, the question, with all due respect,	09:07:20
22	doesn't make sense to me because we're speaking a	09:07:22
23	different language. I consider a publication to be	09:07:25
24	all encompassing, including the supporting -- as	09:07:28
25	does the referee. I was the editor of the Journal	09:07:31

1 of the American Chemical Society for almost five 09:07:34
2 years. The supporting information and the paper are 09:07:37
3 one and the same. You cannot disconnect them. 09:07:41

4 So we may not be able to find in the body 09:07:44
5 a -- of this paper an experimental protocol showing 09:07:48
6 how the monomers and nucleotides were made and nor 09:07:52
7 would you expect to find that. That's why 09:07:56
8 supporting information exists. It's available for 09:07:59
9 free. There is no pay wall. So in many cases 09:08:01
10 people who don't have access to the journal will 09:08:05
11 only download the supporting information to find out 09:08:08
12 what they need to do. 09:08:11

13 So in some ways you can think of the 09:08:13
14 supporting information as even more important than 09:08:15
15 the main body, because they actually give the 09:08:18
16 practitioner the enablement details. 09:08:22

17 Q. Can we go to page 1, please. 09:08:25

18 Dr. Baran, isn't it correct that nothing on 09:08:33
19 page 1 discloses the synthesis of a building block? 09:08:37

20 A. I don't know. 09:08:44

21 Q. Take your time. Read the document. 09:08:48

22 A. Do you have a paper copy? 09:08:51

23 MR. EDWARDS: I do, if examining counsel 09:08:53
24 would consent to me providing it. I don't think it 09:08:59
25 is in the same format as the marked exhibit, but I 09:09:01

1	do believe it's the same paper.	09:09:05
2	And you can interrogate that if you'd like,	09:09:07
3	Dan.	09:09:10
4	MR. SHORES: Yes, please. Absolutely,	09:09:11
5	Dr. Baran. Please take a look at the paper copy.	09:09:14
6	THE WITNESS: Okay. Great.	09:09:16
7	MR. EDWARDS: So I've got to fish it out.	09:09:17
8	So this might be a good time to take a break, or	09:09:19
9	not. It's up to you. It's your time, Dan.	09:09:22
10	MR. SHORES: Yeah. That's fine.	09:09:25
11	MR. EDWARDS: You want to take a break?	09:09:27
12	MR. SHORES: Yes. That sounds good.	09:09:30
13	MR. EDWARDS: Okay.	09:09:33
14	THE VIDEOGRAPHER: Off the record at	09:09:35
15	9:09 a.m.	09:09:35
16	(Recess, 9:09 a.m. to 9:26 a.m.)	09:09:37
17	THE VIDEOGRAPHER: Back on the record at	09:26:09
18	9:25 a.m.	09:26:09
19	THE WITNESS: Okay.	09:26:15
20	BY MR. SHORES:	09:26:16
21	Q. Dr. Baran, we were talking about	09:26:17
22	Exhibit 2001 before we took the break. Do you	09:26:19
23	recall that?	09:26:24
24	A. Yes, sir.	09:26:25
25	Q. And we were discussing -- and if the	09:26:25

1	technician can please scroll down to figure 1 --	09:26:30
2	actually figure 2.	09:26:32
3	And we were using as an example the	09:26:36
4	P-monomer shown under section C of figure 2. Do you	09:26:39
5	recall that?	09:26:43
6	A. Yes.	09:26:44
7	Q. And your testimony is that your team	09:26:47
8	synthesized that P-monomer; is that correct?	09:26:55
9	A. Yes.	09:26:58
10	Q. And your testimony is that you were not	09:26:59
11	directly involved in the synthesis of that	09:27:01
12	P-monomer; correct?	09:27:04
13	A. No. I -- it really depends on what the	09:27:05
14	word "direct" means. I think that we should be	09:27:09
15	precise with the language and say I did not do it	09:27:12
16	with my own hands, but I was directly involved in	09:27:15
17	all the work of the paper.	09:27:18
18	Q. Is it your testimony that your team	09:27:20
19	synthesized all of the monomers that are disclosed	09:27:24
20	in this Exhibit 2001?	09:27:27
21	A. Most, if not all. Perhaps there was	09:27:34
22	something that was commercial. I'm not sure. But	09:27:36
23	most of them, yes.	09:27:39
24	Q. Okay. And your team wouldn't have	09:27:41
25	purchased these monomers; correct?	09:28:07

1 A. They may have. Some of them. Maybe some
2 phosphoramidites were purchased. I would have to
3 look at the supporting information.

4 Q. So sitting here, you just -- you don't
5 know?

6 A. I don't recall. It's a very large paper.

7 Q. But you do recall that your team
8 synthesized most of the monomers; correct?

9 A. Correct.

10 MR. SHORES: If we can move on to
11 Exhibit 2002, which, Counsel, you should have a copy
12 of that as well.

13 (Exhibit 2002 marked for identification.)

14 MR. EDWARDS: I have an electronic copy
15 that you sent me, yes.

16 MR. SHORES: Have you printed that out, or
17 has that been printed out, Counsel?

18 MR. EDWARDS: I may be able to fish out
19 what appears to be the same paper. I haven't just
20 printed it out. It is what I had -- I had obtained
21 this on my own, not the one you sent me, but it may
22 be the same one.

23 THE WITNESS: Looks like the same.

24 MR. EDWARDS: I'm looking to compare it.

25 MR. SHORES: Counsel, if I can just

1	suggest -- Jeremy, if I can suggest that, you know,	09:29:45
2	that everything that I have emailed you over the	09:29:50
3	previous break, that those be printed out.	09:29:53
4	MR. EDWARDS: Oh, sure. We can try and get	09:29:56
5	that done.	09:29:58
6	MR. SHORES: Okay.	09:29:59
7	MR. EDWARDS: You want to proceed or do you	09:30:04
8	want me to do that first?	09:30:05
9	MR. SHORES: We can proceed under the	09:30:08
10	electronic version, but I just for -- if the witness	09:30:10
11	wanted to look at a paper copy, which is what I	09:30:15
12	understood.	09:30:17
13	THE WITNESS: It depends what the question	09:30:19
14	is, so maybe just go ahead and...	09:30:19
15	MR. SHORES: You know, if the witness wants	09:30:24
16	to look at a paper copy, then I would suggest	09:30:25
17	printing them out. But if Dr. Baran is okay looking	09:30:28
18	at an electronic copy, then we can look at the	09:30:32
19	electronic copy up on the screen.	09:30:37
20	THE WITNESS: Sure. For this review	09:30:39
21	article, that's fine.	09:30:39
22	MR. SHORES: The electronic copy?	09:30:42
23	THE WITNESS: Sure. For now, yeah.	09:30:43
24	BY MR. SHORES:	09:30:45
25	Q. Okay. Dr. Baran, you recognize this	09:30:45

1	article "DNA Encoded Libraries: A Visitor's Guide"?	09:30:49
2	A. Yes, sir.	09:30:56
3	Q. And this paper does not discuss nucleotide	09:30:59
4	synthesis; correct?	09:31:02
5	A. Well, it's inherent. It may, but it's a	09:31:02
6	review article. That's the nature of it. So it is	09:31:11
7	reviewing all the literature associated with how to	09:31:13
8	do a certain type of discovery science involving	09:31:18
9	labeling small molecules or other molecules with DNA	09:31:23
10	in order to encode them.	09:31:28
11	And as part of that, what is discussed in	09:31:30
12	this review is sort of the how-to of making the	09:31:33
13	libraries, derivatizing them, the chemistry that is	09:31:39
14	compatible with them, and then developments in the	09:31:44
15	area using DNA encoded libraries to discover new	09:31:47
16	medicine.	09:31:53
17	Q. Dr. Baran, this Exhibit 2002 does not	09:31:54
18	disclose synthesis scheme for a nucleotide; correct?	09:31:59
19	A. Then I need the paper copy to make sure,	09:32:05
20	which I can see Jeremy is holding in his hand.	09:32:09
21	MR. EDWARDS: Right. To be clear, what	09:32:11
22	I've got is the version of this -- what I think is	09:32:12
23	the version of this exhibit --	09:32:18
24	THE WITNESS: Same thing.	09:32:19
25	MR. EDWARDS: -- this paper that I	09:32:20

1 previously obtained, not the one you just emailed 09:32:21
2 me. 09:32:23

3 THE WITNESS: They're identical. 09:32:26

4 MR. EDWARDS: Dan, do you want me to hand 09:32:30
5 them the one that I previously obtained, or do you 09:32:32
6 want me to print the one that you just sent me? 09:32:34

7 MR. SHORES: Well, let me ask you this. 09:32:35
8 Are those documents that I sent to you being printed 09:32:36
9 off? 09:32:40

10 MR. EDWARDS: I'm working on it. You just 09:32:41
11 sent them to me. 09:32:43

12 MR. SHORES: I understand. I understand. 09:32:44
13 I'm just asking because I think that's going to make 09:32:46
14 things go more smoothly if we have those paper 09:32:49
15 copies of what I sent to you, because I think in 09:32:53
16 some circumstances there are, you know, some -- your 09:32:54
17 version may not be the same as the version that I 09:33:01
18 sent to you because they come out in different 09:33:05
19 formats. 09:33:07

20 MR. EDWARDS: Okay. Well, let's take 09:33:08
21 another quick break. I'm in the midst of printing 09:33:09
22 these. It should be only a couple minutes unless 09:33:12
23 there is a printer problem. 09:33:15

24 MR. SHORES: Thank you. 09:33:16

25 THE VIDEOGRAPHER: Off the record at 09:33:17

1	9:33 a.m.	09:33:18
2	(Recess, 9:33 a.m. to 9:42 a.m.)	09:33:20
3	THE VIDEOGRAPHER: Back on the record at	09:42:33
4	9:42 a.m.	09:42:34
5	BY MR. SHORES:	09:42:39
6	Q. Dr. Baran, you recall before the break we	09:42:40
7	were discussing owner's Exhibit 2002?	09:42:41
8	A. Yes, sir.	09:42:46
9	Q. This document is an article titled "DNA	09:42:47
10	Encoded Libraries: A Visitor's Guide"; correct?	09:42:51
11	A. It is a review, yes.	09:42:55
12	Q. The document is titled "DNA Encoded	09:42:56
13	Libraries: A Visitor's Guide"; correct?	09:42:59
14	A. Correct.	09:43:01
15	Q. And you are an author on this paper?	09:43:06
16	A. Correct.	09:43:08
17	Q. This paper does not discuss nucleotide	09:43:08
18	synthesis; correct?	09:43:11
19	A. That's what I need a minute to look up.	09:43:14
20	Well, if I can direct your attention to	09:43:46
21	page 269, when -- and to be clear, this is a review	09:44:17
22	so nothing new is disclosed in the review. It's	09:44:23
23	just an analysis of the literature that has been	09:44:28
24	published and an introduction for people that have	09:44:34
25	never done this before.	09:44:37

1 And so if you look at page 269, second
2 paragraph, "The typical DEL is assembled (figure 1C)
3 through a series of DNA encodings followed by
4 chemical diversification (although these steps can
5 be inverted). Usually, the DEL starts as a small
6 DNA (single or double stranded) structure, referred
7 to as a headpiece, linked to a free amine group, or
8 other functional handle, by a spacer."

09:44:39
09:44:42
09:44:47
09:44:50
09:44:53
09:44:57
09:45:00
09:45:04

9 Now, in there is a reference to the
10 protocols that the practitioner would use to prepare
11 those oligonucleotides.

09:45:10
09:45:12
09:45:16

12 So that's my answer to the question.

09:45:21

13 Q. Well, it was a yes-or-no question.

09:45:26

14 So my question is: This paper does not
15 discuss nucleotide synthesis; correct?

09:45:29
09:45:31

16 A. Well, it does because in order to make the
17 DNA headpiece in the bar code you need to look up
18 the references that teach how to do that.

09:45:36
09:45:38
09:45:42

19 Q. But that's not in the four corners of this
20 document, though; correct?

09:45:46
09:45:48

21 A. Not in the four corners of the document.

09:45:51

22 Q. On pages 1 through 13, there is no
23 synthesis scheme for a building block; is that
24 correct?

09:45:54
09:45:58
09:46:00

25 A. Well, if you look at figure 2 on page 271,

09:46:21

1 part A, it shows how people would make the 09:46:25
2 oligonucleotide. It says, "DNA-Templated Synthesis. 09:46:30
3 DNA templates are synthesized followed by the 09:46:34
4 addition of building blocks attached (via cleavable 09:46:38
5 linker) to complementary oligonucleotides." 09:46:40

6 Q. Dr. Baran, so take a step back here. 09:46:45

7 You agree and you testified that -- and 09:46:47
8 it's your testimony that this case -- the claims of 09:46:50
9 the '885 patent relate to phosphoramidites and 09:46:54
10 nucleosides; correct? 09:47:02

11 A. That is one aspect of what this is about, 09:47:07
12 yes. 09:47:09

13 Q. But these are chemical compounds where the 09:47:10
14 claims at issue in this case relate to chemical 09:47:15
15 compounds, which are the building blocks that we 09:47:20
16 referred to earlier; correct? 09:47:23

17 A. That's correct. In essence, it's far more 09:47:26
18 simple than the oligonucleotide itself. But I think 09:47:29
19 a key claim or point that is implicit in this case 09:47:35
20 is the claiming of novelty when there is no novelty 09:47:41
21 with regards to oligonucleotide synthesis. 09:47:46

22 MR. SHORES: Move to strike the answer. 09:47:49
23 This is -- that was not -- that was not my question. 09:47:50
24 So I move to strike the witness's answer. 09:47:55

25 THE WITNESS: Do you want to ask the 09:48:04

1	question again?	09:48:05
2	BY MR. SHORES:	09:48:06
3	Q. The '885 patent claims are directed to	09:48:09
4	chemical compounds which are the building blocks for	09:48:19
5	solid phase of oligonucleotide synthesis; correct?	09:48:27
6	A. Well, there is the word claim --	09:48:30
7	Q. Yes or no? With all due respect --	09:48:36
8	MR. EDWARDS: No. Hang on a second.	09:48:38
9	You've got to stop interrupting this witness when	09:48:39
10	he's trying to answer your questions.	09:48:41
11	MR. SHORES: He's not answering the	09:48:42
12	question.	09:48:43
13	MR. EDWARDS: How would you know? He got	09:48:43
14	three words out and you cut him off for the second	09:48:45
15	time in a row. Let the witness answer the question.	09:48:47
16	If you want to move to strike thereafter, that's up	09:48:50
17	to you.	09:48:53
18	MR. SHORES: Making a speech on the record,	09:48:53
19	there is no need to get hot under the collar. I'm	09:48:54
20	just asking a yes-or-no question and the witness is	09:48:59
21	not answering my questions.	09:49:01
22	MR. EDWARDS: He's attempting to answer	09:49:03
23	your questions, and you are cutting him off now	09:49:04
24	twice in a row.	09:49:07
25	MR. SHORES: I am not.	09:49:07

1	MR. EDWARDS: Go ahead and ask another	09:49:09
2	question, see what happens.	09:49:10
3	MR. SHORES: Counsel, and your objections	09:49:12
4	are improper. Your speaking objections are	09:49:13
5	improper.	09:49:15
6	So it's a very straightforward question.	09:49:16
7	BY MR. SHORES:	09:49:19
8	Q. Let's move back to the '885 patent. So	09:49:20
9	let's go back to Exhibit 1001. And this -- by the	09:49:21
10	way, this is testimony that he's already put on the	09:49:27
11	record, but let's confirm this.	09:49:29
12	Claims 1 -- Dr. Baran, claims 1 through 5	09:49:43
13	are directed to chemical compounds; is that correct?	09:49:47
14	A. The word claim used in this context on this	09:49:51
15	page, that's correct.	09:49:54
16	Q. So claim 1 is directed to a chemical	09:49:57
17	compound; correct?	09:50:00
18	A. On this page, yes.	09:50:00
19	Q. Claim 2 is directed to a chemical compound;	09:50:03
20	correct?	09:50:06
21	A. On this page, correct.	09:50:07
22	Q. Claim 3 is directed to a chemical compound;	09:50:09
23	correct?	09:50:12
24	A. On this page, correct.	09:50:13
25	Q. Claim 4 is directed to a chemical compound;	09:50:15

1	correct?	09:50:17
2	A. On this page, correct.	09:50:19
3	Q. Claim 5 is directed to a chemical compound;	09:50:21
4	correct?	09:50:23
5	A. On this page, correct.	09:50:24
6	Q. And in your previous answers when you say	09:50:26
7	"on this page," you're referring to the last page of	09:50:28
8	the '885 patent that lists the patent claims;	09:50:32
9	correct?	09:50:34
10	A. Correct.	09:50:35
11	Q. So we were talking about your prior	09:50:43
12	publications. And my questions with respect to	09:50:47
13	those prior publications was that those prior	09:50:54
14	publications did not discuss the synthesis of	09:50:57
15	compounds like the compounds shown in claims 1	09:51:04
16	through 5; right?	09:51:10
17	MR. EDWARDS: Object to form.	09:51:12
18	THE WITNESS: Incorrect.	09:51:13
19	BY MR. SHORES:	09:51:18
20	Q. So your testimony is that your prior	09:51:18
21	articles that we reviewed, Exhibits 2001 and 2002,	09:51:23
22	do disclose the synthesis of chemical compounds like	09:51:26
23	the compounds shown in Exhibit -- shown in claims 1	09:51:34
24	through 5 of the '885 patent; correct?	09:51:40
25	MR. EDWARDS: Object to form.	09:51:43

1 THE WITNESS: It's not a yes-or-no
2 question. So you showed two different articles.
3 The one which is a review in the Israeli Journal of
4 Chemistry does not disclose phosphoramidites,
5 succinates of the type shown on this page that is
6 shown in the screen right now of the claim page of
7 the patent.

8 However, the first paper we discussed, the
9 one in Science as well as its preceding article in
10 2018, does show the synthesis of phosphoramidites
11 and even succinate derivatives of nucleosides.

12 BY MR. SHORES:

13 Q. That's your testimony?

14 A. Yes, sir.

15 Q. And your testimony is that your team --
16 excuse me.

17 Your testimony is that you were not
18 personally involved in the synthesis of the building
19 blocks disclosed in Exhibits 2001 and 2002; correct?

20 A. Again, that's not a yes-or-no question. So
21 you used the word "personally involved." I was
22 personally involved in everything. The only
23 granular detail we can say is that my hands didn't
24 actually do the chemistry, but I was personally
25 involved in every aspect of the work.

1	Q.	And so you supervised the work?	09:53:13
2	A.	Correct.	09:53:15
3	Q.	And when you supervised the work -- let's	09:53:16
4		go back to Exhibit 2001.	09:53:21
5		So is it your testimony that you supervised	09:53:36
6		your team synthesizing the P-monomer in section C of	09:53:37
7		figure 2 of the Exhibit 2001?	09:53:44
8	A.	Yes.	09:53:48
9	Q.	Tell me about that.	09:53:50
10	A.	Well, like all the work in this paper, the	09:53:52
11		students would design experiments, we would meet	09:53:56
12		sometimes daily, in some cases every hour, to look	09:53:59
13		at how the reactions were run, what the protocol	09:54:05
14		that was used, what the results were, and direct	09:54:08
15		experimental data was shown to me. Sometimes I	09:54:13
16		would walk to the fume hood and watch them do	09:54:15
17		particular reactions. So every aspect of this was	09:54:19
18		scrutinized by myself before signing off on it that	09:54:25
19		it was done properly.	09:54:29
20	Q.	And your testimony is that every aspect of	09:54:33
21		your -- supervising your team synthesizing the	09:54:34
22		building blocks disclosed in this paper in	09:54:38
23		Exhibit 2001; right?	09:54:41
24	A.	That goes for almost everything that's	09:54:44
25		published from my lab.	09:54:46

1 Q. But for this particular project when you 09:54:49
2 supervised your team synthesizing the building 09:54:53
3 blocks disclosed in this paper, your testimony is 09:54:58
4 that you did supervise them; correct? 09:55:01

5 A. Correct. 09:55:05

6 MR. SHORES: All right. Let's pull up 09:55:08
7 Exhibit 2003. 09:55:11

8 MR. EDWARDS: Hang on a sec. Do you want 09:55:23
9 the paper copy at this point, Dan? 09:55:25

10 MR. SHORES: Yes. I'd like the paper copy 09:55:30
11 to match what's on the screen just so -- as I 09:55:31
12 discussed earlier, so we have consistency. 09:55:33

13 And, Jeremy, you have a paper copy? 09:55:36

14 MR. EDWARDS: Yeah. I printed what you 09:55:39
15 sent me. That was -- the file name was 09:55:40
16 Exhibit 2003, and it looks to be what you have on 09:55:45
17 the screen, except for the yellow exhibit sticker, 09:55:47
18 which I believe was just attached by the reporter. 09:55:50

19 MR. SHORES: Right. 09:55:54

20 (Exhibit 2003 marked for identification.) 09:55:54

21 BY MR. SHORES: 09:56:00

22 Q. Dr. Baran, you see this document, this 09:56:01
23 Exhibit 2003? 09:56:04

24 A. Yes, sir. 09:56:05

25 Q. And this is titled "Expanding Reactivity in 09:56:06

1	DNA-Encoded Library Synthesis via Reversible Binding	09:56:10
2	of DNA to an Inert Quaternary Ammonium Support"; is	09:56:14
3	that correct?	09:56:19
4	A. Yes, sir.	09:56:20
5	Q. You are listed as an author on this	09:56:20
6	article; is that correct?	09:56:25
7	A. Correct.	09:56:25
8	Q. Dr. Baran, this paper does not discuss	09:56:29
9	nucleotide synthesis; correct?	09:56:33
10	A. In the supporting information it shows	09:56:36
11	nucleotide synthesis because that's what was needed	09:56:38
12	in order to make the components of this paper.	09:56:42
13	Q. This paper does not discuss nucleoside	09:56:46
14	synthesis; correct?	09:56:50
15	A. There may be -- I'm not sure. Probably the	09:56:52
16	nucleosides were purchased, and then they were	09:56:56
17	converted into nucleotides and oligonucleotides in	09:57:01
18	the supporting information.	09:57:04
19	Q. This paper does not discuss	09:57:07
20	phosphoramidites synthesis; correct?	09:57:10
21	A. I think phosphoramidites were used, but I	09:57:12
22	have to check the supporting information. I think	09:57:16
23	they were used to make the pieces of DNA, I believe.	09:57:18
24	Q. This paper does not discuss oligonucleotide	09:57:26
25	synthesis; correct?	09:57:30

1 A. Well, of course it has oligonucleotides in
2 it. And the synthesis thereof, I believe, is in the
3 supporting information because you have -- in a DNA
4 encoded library, you need oligonucleotides to encode
5 the library.

6 Q. And is it your testimony that you
7 supervised your team to synthesize nucleotides in
8 connection with the work on this paper?

9 A. Yes.

10 Q. Is it your testimony that you supervised
11 your team that synthesized nucleosides that were
12 used in connection with this paper?

13 A. Like I said, the nucleosides may have been
14 purchased -- that is the sugar with the free
15 alcohol -- and subsequently used in phosphoramidite
16 chemistry to make the oligonucleotide fragments that
17 would serve as a bar code for the library.

18 Q. Your testimony is that you supervised your
19 team that synthesized phosphoramidites in connection
20 with this paper?

21 A. If there were -- I believe there were
22 phosphoramidites used if they were commercial and
23 there was no synthesis needed. But if they were
24 made, then definitely I signed off on it and had to
25 know what was going on and supervise them.

1	Q. And your testimony is that you supervised	09:59:02
2	your team that synthesized oligonucleotides in	09:59:06
3	connection with this paper; correct?	09:59:11
4	A. Yes.	09:59:12
5	Q. So in the last three papers that we just	09:59:16
6	reviewed, Exhibits 1001 -- excuse me --	09:59:19
7	Exhibits 2001, 2002, and 2003, you did not have any	09:59:23
8	direct involvement in synthesizing any nucleosides;	09:59:34
9	right?	09:59:42
10	A. Well, again, you're using language that I	09:59:42
11	don't agree with. So if you'd, instead of using the	09:59:45
12	word direct involvement, use maybe a phrase like	09:59:51
13	with your own hands in a chemical fume hood, then I	09:59:55
14	can agree with that.	09:59:59
15	Q. That's not my question.	10:00:00
16	A. Well, then the question is incorrect. Then	10:00:02
17	I don't agree with it.	10:00:04
18	Q. Then you -- so your testimony is that you	10:00:06
19	did have direct involvement?	10:00:09
20	A. Direct involvement as I defined it before.	10:00:11
21	Q. In connection with -- if we go back to	10:00:21
22	Exhibit 2001 and scroll to the top.	10:00:24
23	In this article, a P(V) platform for	10:00:40
24	oligonucleotide synthesis, did you create a	10:00:42
25	synthesis scheme for any nucleosides?	10:00:46

1	A. Sure. Of course.	10:00:50
2	Q. Is that disclosed in this paper?	10:00:57
3	A. Of course.	10:00:59
4	Q. Where is it disclosed in this paper, the	10:01:02
5	synthesis?	10:01:06
6	A. You can look just at the first figure	10:01:06
7	after --	10:01:10
8	Q. The synthesis scheme for the nucleoside.	10:01:13
9	A. That would be -- figure 2 would be an	10:01:19
10	example. Figure 3 is another example. And then, as	10:01:21
11	I mentioned, the supporting information has got tons	10:01:29
12	and tons of nucleoside/nucleotide chemistry.	10:01:32
13	Q. What about with regard to nucleotides?	10:01:37
14	A. Of course. I mean, anytime the nucleoside	10:01:41
15	is connected to a phosphorous atom, you can either	10:01:43
16	refer to it, as we talked about before, as a	10:01:47
17	reagent. It can be a phosphoramidite. It could be	10:01:50
18	a P(V) reagent. But some people consider a	10:01:52
19	nucleotide as any nucleoside connected to a	10:01:58
20	phosphorous atom.	10:02:01
21	Q. How many papers -- so we looked at three	10:02:23
22	papers that, your testimony is, relates to	10:02:25
23	oligonucleotide synthesis; correct?	10:02:29
24	A. Yes, sir.	10:02:32
25	Q. How many more papers have you published	10:02:37

1	that relates to oligonucleotide synthesis?	10:02:41
2	A. Many. The initial 2018 work, for example,	10:02:45
3	was recently recognized with the highest prize that	10:02:50
4	is given for a patent. It won the Edison award for	10:02:56
5	inventorship just a few months ago. That 2018	10:03:00
6	Science paper was also patent -- also led to a	10:03:03
7	patent.	10:03:06
8	But, yeah, we can check my CV and I can	10:03:08
9	count, but my estimation would be -- I don't know.	10:03:10
10	Maybe there is ten papers on oligonucleotide	10:03:13
11	chemistry and then dozens of talks on the topic.	10:03:17
12	And I founded two companies on oligonucleotide	10:03:18
13	chemistry. So, yeah, I've been doing this for a	10:03:23
14	while.	10:03:25
15	Q. It's your testimony that ten out of your	10:03:28
16	250-plus papers that you've published relate to	10:03:32
17	oligonucleotide synthesis?	10:03:37
18	A. At least, yeah.	10:03:40
19	Q. Well, how many?	10:03:41
20	MR. EDWARDS: Object to form.	10:03:47
21	If you look at the transcript, I don't	10:03:48
22	think it caught your question, Dan, not completely	10:03:51
23	at least.	10:03:58
24	BY MR. SHORES:	10:03:59
25	Q. My question is: How many papers,	10:04:00

1	Dr. Baran, how many papers have you published -- let	10:04:01
2	me strike that question.	10:04:08
3	How many papers have you been named as an	10:04:11
4	author, how many of those papers relate to	10:04:13
5	oligonucleotide synthesis?	10:04:22
6	A. It's probably ten or more.	10:04:25
7	Q. I'm looking for an answer. Probably ten or	10:04:30
8	more does not really answer it. I mean, do you	10:04:32
9	know -- do you know how many?	10:04:34
10	A. I don't know off the top of my head, but if	10:04:38
11	you want me to start counting on the CV, I can do	10:04:40
12	that.	10:04:44
13	Q. I'd like you to, yes. I'd like you to	10:04:44
14	identify the papers in your CV that relate to	10:04:45
15	oligonucleotide synthesis.	10:04:50
16	A. Certainly.	10:04:52
17	Q. Identify them for the record.	10:04:52
18	A. Okay.	10:04:54
19	Okay. Is it easier for you, Counsel, to	10:05:37
20	just use the numbers in my CV?	10:06:49
21	Q. Yes. If you can refer to the paragraph	10:06:52
22	numbers or the number of, you know, whatever the	10:06:55
23	reference is and the page number, I'd appreciate	10:06:58
24	that.	10:07:01
25	A. Okay. This is publication number 63.	10:07:01

1	Q.	Okay. And that's dated 2018?	10:07:11
2	A.	Correct.	10:07:17
3	Q.	Okay.	10:07:21
4	A.	Publication 59.	10:07:27
5	Q.	Okay. That's dated 2018?	10:07:33
6	A.	Publication 46.	10:07:36
7	Q.	And that's dated 2019; correct?	10:07:44
8	A.	Uh-huh.	10:07:46
9		Publication number 36.	10:07:47
10	Q.	That's dated 2020; correct?	10:07:53
11	A.	Uh-huh.	10:07:55
12		Publication 39.	10:07:56
13	Q.	And that's dated 2020; correct?	10:08:00
14	A.	Uh-huh.	10:08:02
15		Publication number 40.	10:08:03
16	Q.	That's dated 2020; correct?	10:08:08
17	A.	Uh-huh.	10:08:10
18		Publication 41.	10:08:11
19	Q.	And that's dated 2020; correct?	10:08:14
20	A.	Uh-huh.	10:08:16
21		Publication 29.	10:08:22
22	Q.	29?	10:08:26
23	A.	Correct.	10:08:27
24	Q.	And that's dated 2020; correct?	10:08:28
25	A.	Uh-huh.	10:08:31

1	Publication 19.	10:08:41
2	Q. And that's dated 2021; correct?	10:08:46
3	A. Uh-huh.	10:08:49
4	Publication number 20.	10:08:50
5	Q. Okay. And that's dated 2021; correct?	10:08:52
6	A. Uh-huh.	10:08:56
7	Publication number 14.	10:09:07
8	Q. And that's dated 2021; correct?	10:09:12
9	A. Uh-huh.	10:09:14
10	Publication number 16.	10:09:15
11	Q. And that's dated 2021; correct?	10:09:20
12	A. Uh-huh.	10:09:22
13	And there are two more papers that	10:09:30
14	unfortunately were not here when this was submitted	10:09:33
15	in January. So there is two more papers, one of	10:09:37
16	which appeared in the Journal of American Chemical	10:09:43
17	Society. One of which is -- it's in the archive but	10:09:46
18	is appearing in Nature Chemistry. So that and we	10:09:51
19	have a bunch of ongoing work. As of now, 14	10:09:55
20	publications as of today.	10:09:59
21	Q. And the earliest of those publications is	10:10:01
22	dated 2018; correct?	10:10:03
23	A. That's correct.	10:10:05
24	Q. So is it fair to say that you're rather a	10:10:06
25	late entrant to the oligonucleotide space?	10:10:10

1	A. Define "entrant."	10:10:15
2	Q. Well, you didn't start your career in	10:10:17
3	oligonucleotide synthesis; right?	10:10:20
4	A. That's correct.	10:10:21
5	Q. You didn't start your career in synthesis	10:10:23
6	of nucleosides; right?	10:10:27
7	A. I had exposure to nucleosides even as early	10:10:33
8	as my undergraduate training.	10:10:36
9	Q. That wasn't part of your career?	10:10:43
10	A. I don't understand. What do you --	10:10:48
11	Q. Well, you know, you've cited over 250	10:10:50
12	papers in organic chemistry, and you're -- you've	10:10:54
13	received awards, but you're here testifying about	10:10:58
14	the synthesis of nucleosides, nucleotides, and	10:11:05
15	oligonucleotides. And the earliest publication that	10:11:08
16	you have is in 2018; correct?	10:11:13
17	A. Where our lab is focused on that topic,	10:11:18
18	yes.	10:11:20
19	Q. Focused on the synthesis of	10:11:22
20	oligonucleotides, the earliest paper that you have	10:11:25
21	published -- that you published that you are named	10:11:29
22	as an author on is 2018; correct?	10:11:31
23	A. Correct.	10:11:34
24	Q. And sitting here, you've -- in your CV	10:11:34
25	you've identified over 250 publications that you've	10:11:38

1	published throughout your career; right?	10:11:42
2	A. Yes.	10:11:45
3	Q. You testified to that?	10:11:47
4	A. Yes.	10:11:49
5	Q. But only 14 -- about 14 of those -- of your	10:11:50
6	papers relate to -- only 14 of the over 250 papers	10:11:57
7	that you published relate to the issues in this	10:12:06
8	case; right?	10:12:08
9	A. No. Now, while the publications may not	10:12:12
10	have an oligonucleotide -- prior to that may not	10:12:19
11	have an oligonucleotide focus, the issues of chemo	10:12:21
12	selectivity, protecting group manipulations, redox	10:12:25
13	fluctuations, things I've taught in class, you know,	10:12:31
14	made me well aware of the trials and tribulations	10:12:37
15	and intricacies of the field, not to mention the	10:12:40
16	many consulting sessions with companies I've had on	10:12:44
17	the topic that don't relate -- that don't make their	10:12:47
18	way into a publication.	10:12:50
19	So to characterize me as a late entry into	10:12:52
20	the field is only to take a myopic view of my career	10:12:57
21	only through the lens of a publication.	10:13:01
22	Q. But only 14 of your over 250 papers relate	10:13:17
23	to oligonucleotide synthesis; correct?	10:13:20
24	A. Yeah. That's correct.	10:13:26
25	Q. Only 14 -- of those 14 papers that you	10:13:30

1	testified relate to oligonucleotide synthesis, none	10:13:37
2	of those papers provides synthesis schemes for	10:13:41
3	nucleosides; correct?	10:13:48
4	A. Incorrect.	10:13:49
5	Q. None of those papers provide synthesis	10:13:51
6	schemes for phosphoramidites; correct?	10:13:54
7	A. Incorrect.	10:13:56
8	Q. None of those papers discloses synthesis	10:13:57
9	schemes for nucleotides; correct?	10:14:01
10	A. All of what you're saying is incorrect.	10:14:05
11	Q. You talked about your -- well, let me just	10:14:09
12	ask this. How many chemically modified	10:14:15
13	phosphoramidites has your group synthesized over	10:14:18
14	your career?	10:14:24
15	A. I don't know that number.	10:14:25
16	Q. Have you ever personally -- strike that.	10:14:35
17	We talked about your work history -- or	10:14:45
18	actually I'd like to talk a little bit about your	10:14:46
19	work history. You brought it up earlier. It's in	10:14:49
20	your affidavit. It's in your declaration.	10:14:52
21	You're a co-founder of a company called	10:14:57
22	Elsie; correct?	10:15:01
23	A. Correct.	10:15:01
24	Q. What is your role there at Elsie?	10:15:02
25	A. Co-founder, consultant, board member.	10:15:06

1	Q.	Co-founder?	10:15:11
2	A.	Co-founder, consultant, and board member.	10:15:12
3	Q.	You own shares in Elsie?	10:15:19
4	A.	Correct.	10:15:21
5	Q.	Elsie is in the oligonucleotide space;	10:15:24
6		right?	10:15:27
7	A.	Correct.	10:15:28
8	Q.	Elsie synthesizes oligonucleotides?	10:15:32
9	A.	Correct.	10:15:34
10	Q.	How does it do that?	10:15:37
11	A.	It does it by either using phosphoramidites	10:15:38
12		or using P(V) chemistry of the type depicted right	10:15:40
13		now on the screen.	10:15:46
14	Q.	You can take the exhibit down.	10:15:50
15		So does Elsie -- does Elsie use AI-driven	10:15:58
16		technology to synthesize or -- excuse me.	10:16:05
17		Does Elsie use AI-driven technology in	10:16:09
18		connection with its program?	10:16:15
19	A.	The use of AI is aspirational. At this	10:16:18
20		moment we don't use AI.	10:16:21
21	Q.	So does Elsie actually synthesize the --	10:16:26
22		synthesize phosphoramidites?	10:16:29
23	A.	Synthesize phosphoramidites, synthesize	10:16:33
24		nucleosides, oligonucleotides. We have our own	10:16:34
25		oligonucleotide synthesizer. We make almost	10:16:39

1	everything in-house.	10:16:43
2	Q. So there is a chemistry -- a chemistry team	10:16:45
3	in Elsie that performs those development functions?	10:16:53
4	A. Yes, sir.	10:16:57
5	Q. And do you work with those folks?	10:16:58
6	A. Constantly.	10:17:02
7	Q. And have you ever -- I'm sorry.	10:17:10
8	Does Elsie manufacture commercial scale	10:17:13
9	oligonucleotides?	10:17:22
10	A. I hope one day.	10:17:24
11	Q. That's your goal?	10:17:26
12	A. That's the goal.	10:17:27
13	Q. And that -- in your -- who would your	10:17:29
14	customers be?	10:17:31
15	A. Well, patients.	10:17:32
16	Q. Well, okay. Would you supply -- the	10:17:37
17	oligonucleotides that you manufacture, would you	10:17:45
18	sell them to a pharmaceutical company, for example?	10:17:48
19	A. No. I can tell you about what Elsie does	10:17:52
20	if you want, but it's not -- we're not a contract	10:17:55
21	research organization.	10:17:58
22	Q. Okay. So your plan would -- Elsie's plan	10:18:00
23	would not be to sell oligonucleotides that it	10:18:05
24	synthesizes to pharmaceutical companies; correct?	10:18:11
25	A. Well, not necessarily. I mean, the	10:18:14

1 question is nuanced, and it can be answered many
2 ways. So, for example, if Elsie invents its own
3 proprietary therapeutic, the eventual client or
4 purchaser of that would be the patient who would
5 benefit from it.

6 If on the other hand a large pharma company
7 said, "We love this asset that you've got. We would
8 like to purchase it from you. Could you please make
9 it?" Then in that case Elsie would make the API,
10 and then the pharmaceutical company would formulate
11 it perhaps and then they would sell it to a patient.

12 It's a typical biotech model where the
13 aspiration is you're going to make your own medicine
14 that's going to be given to patients, but as often
15 happens in the biotech space, you end up selling it
16 to a pharmaceutical company, a big one, and then
17 they take care of the further development and
18 formulation. Does that make sense?

19 Q. You have a pipeline that -- Elsie is
20 developing its own pipeline; is that correct?

21 A. Correct.

22 Q. And you testified earlier that Elsie
23 synthesizes oligonucleotides; right?

24 A. Correct.

25 Q. Does Elsie purchase reagents from any

10:18:17

10:18:21

10:18:25

10:18:28

10:18:32

10:18:33

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10:18:42

10:18:47

10:18:50

10:18:54

10:18:58

10:19:00

10:19:04

10:19:08

10:19:10

10:19:13

10:19:15

10:19:18

10:19:21

10:19:21

10:19:26

10:19:28

10:19:29

1	companies to assist in its oligonucleotide	10:19:36
2	synthesis?	10:19:39
3	A. Of course.	10:19:40
4	Q. And does Elsie purchase from Hongene?	10:19:42
5	A. I don't know where the -- I'm sure they	10:19:45
6	probably -- maybe they do, but I have no idea where	10:19:47
7	they get the actual -- if they order stuff.	10:19:50
8	Q. Your answer is you don't know whether Elsie	10:19:54
9	purchases from Hongene or not?	10:19:57
10	A. I wouldn't be surprised if they did.	10:19:59
11	Q. You wouldn't be surprised if you did?	10:20:02
12	A. If they did, yes.	10:20:04
13	Q. Well, you say "they," but you're a	10:20:05
14	co-founder of the company; right?	10:20:08
15	A. If I wear my Elsie hat, then we.	10:20:10
16	Q. Right. You have a lot of hats?	10:20:13
17	A. Correct.	10:20:15
18	Q. As -- withdrawn.	10:20:21
19	MR. EDWARDS: Sorry. We didn't catch what	10:20:25
20	you just said, Dan.	10:20:26
21	MR. SHORES: I just withdrew the question.	10:20:28
22	It was withdrawn.	10:20:29
23	MR. EDWARDS: Gotcha.	10:20:31
24	BY MR. SHORES:	10:20:33
25	Q. So as Elsie develops its oligonucleotide	10:20:33

1 technology, Elsie is seeking patent protection on 10:20:37
2 some of its innovations I would imagine; correct? 10:20:41

3 A. Yes. 10:20:45

4 Q. And is it the intention of Elsie to 10:20:46
5 potentially license that technology to third 10:20:52
6 parties? 10:20:54

7 A. Potentially, yes. 10:20:56

8 Q. Has Elsie ever in its program used a 10:21:01
9 guanosine phosphoramidite as claimed in the '885 10:21:07
10 patent? 10:21:12

11 MR. EDWARDS: Object to form and scope. 10:21:15

12 THE WITNESS: I don't recall. 10:21:17

13 BY MR. SHORES: 10:21:21

14 Q. So you don't recall whether Elsie uses any 10:21:22
15 of the phosphoramidites at issue in this case; 10:21:24
16 right? 10:21:28

17 A. They certainly might. 10:21:28

18 MR. EDWARDS: Repeating my scope objection. 10:21:31

19 MR. SHORES: Counsel, this goes to bias. 10:21:36

20 THE WITNESS: There is another company, 10:21:43
21 Counsel, that's not on the CV that also is 10:21:44
22 oligonucleotide based. 10:21:47

23 BY MR. SHORES: 10:21:50

24 Q. There is an additional company that you 10:21:50
25 didn't previously disclose. Is that what you're 10:21:52

1	saying?	10:21:54
2	A. That's correct, because it was fully formed	10:21:54
3	and codified after this affidavit.	10:21:56
4	Q. Who is that company? What is that company?	10:22:02
5	A. That company is called PolyARNA, and	10:22:04
6	they're located in Cambridge.	10:22:07
7	Q. Dr. Baran, we actually are aware of that.	10:22:11
8	I think that was listed in your affidavit.	10:22:13
9	A. Sorry. I didn't remember.	10:22:15
10	Q. Does Elsie utilize phosphoramidites when	10:22:26
11	manufacturing chimeric oligonucleotides?	10:22:30
12	A. When you say "manufacturing," it implies a	10:22:37
13	scale regime that Elsie does not operate on yet.	10:22:40
14	Q. Okay. Fair. When Elsie synthesizes	10:22:44
15	oligonucleotides -- does Elsie synthesize chimeric	10:22:49
16	oligonucleotides?	10:23:04
17	A. Yes.	10:23:05
18	Q. And in Elsie's synthesis of chimeric	10:23:06
19	oligonucleotides, does Elsie utilize guanosine	10:23:12
20	phosphoramidites with fluoro at the 2 prime	10:23:17
21	position?	10:23:21
22	A. Now you're sort of teetering on the edge of	10:23:23
23	things that are in confidential land. And even if I	10:23:26
24	knew the precise answer to that, I would be worried	10:23:31
25	about violating my confidentiality contract with the	10:23:35

1	company.	10:23:39
2	Q. There is a standard protective order in	10:23:44
3	place in this -- that can be invoked in this	10:23:48
4	proceeding.	10:23:52
5	MR. EDWARDS: To be clear, it's not in	10:23:53
6	place.	10:23:56
7	MR. SHORES: It's not in place. That's	10:23:58
8	correct. Like there hasn't been an occasion for it	10:23:59
9	to be in place.	10:24:02
10	BY MR. SHORES:	10:24:08
11	Q. So, Dr. Baran, are you refusing to answer	10:24:08
12	on that basis?	10:24:11
13	A. I don't want to get myself in trouble	10:24:15
14	outside of this room.	10:24:17
15	MR. SHORES: We reserve all rights to	10:24:29
16	re-call Dr. Baran on any of the questions that he	10:24:31
17	doesn't answer, but we can move on.	10:24:33
18	BY MR. SHORES:	10:24:38
19	Q. With respect to your other affiliations,	10:24:38
20	what is your affiliation with the Nutcracker?	10:24:50
21	A. I'm on their scientific advisory board and	10:24:52
22	I serve as a consultant.	10:24:55
23	Q. And Nutcracker utilizes oligonucleotides --	10:24:59
24	A. Correct.	10:25:03
25	Q. -- in its therapeutic candidates; is that	10:25:03

1	right?	10:25:14
2	A. Correct.	10:25:15
3	Q. What is Nutcracker's pipeline?	10:25:20
4	A. You can look at their website, but I can't	10:25:24
5	say anything that's confidential. All of their --	10:25:27
6	their pipeline, which is mRNA based, is on the	10:25:30
7	website.	10:25:34
8	Q. Does Nutcracker sell oligonucleotides to	10:25:39
9	pharmaceutical companies?	10:25:41
10	A. Their focus is on developing their own	10:25:45
11	pipeline. And in a similar vein to Elsie, they may	10:25:50
12	partner on occasion with pharma to sell candidates	10:25:56
13	or technologies. But all I'm at liberty to say	10:26:01
14	about them is what you can find on the website.	10:26:05
15	Q. Well, but you have personal knowledge,	10:26:13
16	though; right?	10:26:15
17	A. Of course.	10:26:16
18	Q. And are -- so does your personal knowledge	10:26:18
19	extend beyond what's posted on the website?	10:26:21
20	A. Yes.	10:26:27
21	Q. So you do have knowledge, but you're just	10:26:27
22	refusing to answer on the basis of confidentiality;	10:26:29
23	is that correct?	10:26:31
24	A. I'm just complying with the law.	10:26:33
25	Q. But you're refusing to answer the question	10:26:36

1	on the basis of confidentiality; right?	10:26:39
2	A. Yeah. I mean, it's either -- neither here	10:26:44
3	nor there. They may sell things to companies or	10:26:47
4	they may not, but it doesn't sort of affect the	10:26:49
5	conclusion of the topic, which is that Nutcracker is	10:26:54
6	an oligonucleotide-focused company and I helped them	10:26:58
7	a lot on the chemistry side.	10:27:01
8	Q. And does Nutcracker use phosphoramidites in	10:27:05
9	its program?	10:27:08
10	A. Yes.	10:27:10
11	Q. Does Nutcracker purchase phosphoramidites	10:27:11
12	from Hongene?	10:27:13
13	A. I don't know.	10:27:15
14	Q. You don't know or you know but you --	10:27:17
15	A. I legitimately do not know.	10:27:25
16	Q. I'm just trying to understand. So you	10:27:27
17	don't know?	10:27:29
18	A. Correct.	10:27:30
19	Q. You talked earlier about PolyARNA?	10:27:42
20	A. Yes.	10:27:45
21	Q. You testified earlier about PolyARNA.	10:27:46
22	Excuse me. PolyARNA is listed in your declaration.	10:27:49
23	A. Good.	10:27:52
24	Q. So please -- role at PolyARNA.	10:27:52
25	A. Please what?	10:27:57

1	Q. Explain your role at PolyARNA.	10:27:58
2	A. I'm a co-founder and consultant of that	10:28:00
3	company.	10:28:03
4	Q. And PolyARNA utilizes oligonucleotides in	10:28:08
5	its therapeutic candidates; is that right?	10:28:12
6	A. Correct.	10:28:16
7	Q. What is PolyARNA's pipeline?	10:28:17
8	A. PolyARNA's pipeline is only now being -- is	10:28:21
9	crystallizing now and being developed. It's a very	10:28:24
10	new company, so we're in the midst of hiring people.	10:28:26
11	The C-suite has not been finalized. So it's at the	10:28:30
12	very beginning stages.	10:28:37
13	Q. And does PolyARNA intend to sell	10:28:39
14	therapeutics ultimately?	10:28:43
15	A. Correct.	10:28:44
16	Q. Does PolyARNA intend to sell	10:28:48
17	oligonucleotides to the pharmaceutical industry?	10:28:50
18	A. It's the same answer I gave you for Elsie.	10:28:52
19	Q. Well, I'd like an answer with respect to	10:28:56
20	PolyARNA.	10:28:58
21	A. So the intention is to become a successful	10:28:59
22	company by eradicating disease. And that may take	10:29:03
23	the form of developing their own medicine and	10:29:07
24	selling it directly from the company or through	10:29:10
25	partnership with pharma.	10:29:13

1	Q.	Does PolyARNA intend to manufacture	10:29:18
2		oligonucleotides and sell it to pharmaceutical	10:29:20
3		companies?	10:29:23
4	A.	It's too early to know whether they will do	10:29:26
5		the manufacturing in-house or they will team up with	10:29:28
6		a CRO or another big pharma. It's too early to	10:29:30
7		know.	10:29:35
8	Q.	PolyARNA uses some phosphoramidites in its	10:29:38
9		program, though; right?	10:29:39
10	A.	Some of it, yes.	10:29:42
11	Q.	Does PolyARNA use 2 prime -- deoxy 2 prime	10:29:45
12		fluoroguanosine in the oligonucleotides it's	10:29:47
13		developed?	10:29:52
14	A.	They may, but at this point -- I have to	10:29:57
15		remember the last chemistry update. I don't recall	10:30:04
16		if we used that exact phosphoramidite yet, but it is	10:30:05
17		very likely something planned in the future. It is	10:30:13
18		a common analog.	10:30:15
19		(Reporter clarification with counsel.)	10:30:18
20	MR. EDWARDS:	Dan?	10:30:40
21	MR. SHORES:	I can't really hear.	10:30:41
22	MR. EDWARDS:	Your voice is cutting in and	10:30:43
23		out. I don't know how close you are to a	10:30:45
24		microphone, but we're getting intermittent cutting	10:30:47
25		in and out.	10:30:50

1	MR. SHORES: I'm very close to a microphone	10:30:52
2	here, so...	10:30:54
3	MR. EDWARDS: Okay.	10:30:55
4	MR. SHORES: I'll speak a little louder if	10:30:58
5	you want. I can.	10:31:00
6	So if the court reporter can please repeat	10:31:01
7	back the previous question and answer sequence.	10:31:04
8	(Record read.)	10:32:00
9	BY MR. SHORES:	10:32:02
10	Q. Let's kind of reframe it here.	10:32:03
11	So my question -- my prior question,	10:32:06
12	Dr. Baran, was: Does PolyARNA use 2 prime deoxy,	10:32:10
13	2 prime fluoroguanosine in its oligonucleotides?	10:32:17
14	A. They may.	10:32:26
15	Q. And when you said "They may," are you	10:32:34
16	saying you just don't recall, you don't have	10:32:37
17	knowledge, or are you not answering because of	10:32:39
18	confidentiality?	10:32:44
19	A. Well, they may because they have now a	10:32:46
20	number of chemistry employees and they may be doing	10:32:49
21	things independently that I'm not completely aware	10:32:54
22	of. They are in Cambridge. They are not local. So	10:32:57
23	they may be.	10:33:02
24	But I'm certain it will be planned in the	10:33:02
25	future because it is a common analog. And it's	10:33:05

1 certainly one we would want to interrogate. 10:33:07

2 Q. And because it has advantages? 10:33:14

3 A. It may have advantages. That's the whole 10:33:21

4 reason that medicinal chemists working in the 10:33:23

5 oligonucleotide space use that building block often 10:33:27

6 because you can't predict what the exact effect will 10:33:30

7 be until you incorporate it into your own 10:33:34

8 oligonucleotide. That's why medicinal chemists make 10:33:37

9 analogs. 10:33:42

10 Q. So you anticipate that PolyARNA will use 10:33:49

11 2 prime deoxy 2 prime fluoroguanosine in its 10:33:51

12 oligonucleotides if it hasn't already; correct? 10:33:56

13 A. That would be my guess, yeah. 10:34:00

14 Q. Is there an advantage of using 10:34:08

15 phosphoramidites that have fluoro at its 2 prime 10:34:09

16 position? 10:34:14

17 A. The word advantage doesn't make sense in 10:34:18

18 that context. 10:34:20

19 Q. Why would you use a phosphoramidite? Why 10:34:24

20 would you use a 2 prime deoxy 2 prime 10:34:27

21 fluoroguanosine, for example? 10:34:30

22 A. Simply because you would like that analog 10:34:34

23 of G and you want to incorporate it into the growing 10:34:37

24 oligonucleotide chain. And you want to then explore 10:34:41

25 the resulting properties from the oligo containing 10:34:44

1	that monomeric unit.	10:34:47
2	Q. And would you use those in connection with,	10:34:50
3	for example, chimeric oligonucleotides? That	10:34:53
4	building block, the 2 prime deoxy 2 prime	10:34:56
5	fluoroguanosine, would you use that as a building	10:34:59
6	block in a chimeric oligonucleotide?	10:35:02
7	A. You could. Sure.	10:35:06
8	Q. With respect to PolyARNA, is it possible	10:35:24
9	that PolyARNA could -- that PolyARNA could	10:35:26
10	manufacture the oligonucleotides and supply them to	10:35:32
11	the pharmaceutical industry?	10:35:35
12	A. I don't have a crystal ball. The answer is	10:35:41
13	sure, it's possible.	10:35:45
14	Q. If we can go to -- go to Exhibit 1001,	10:36:09
15	which is the '885 patent. I want to clarify some	10:36:23
16	more things relating to these claims. You've	10:36:31
17	testified to some of this, but let's, you know, firm	10:36:39
18	up some of the testimony here.	10:36:42
19	You testified that claims 1 and 2 are	10:36:46
20	directed to nucleoside phosphoramidites; right?	10:36:47
21	A. That's what's written.	10:36:53
22	Q. And that claims 3 through 5 are directed to	10:36:57
23	nucleosides, succinates, and solid supports; right?	10:37:09
24	A. Yes. That is what is written on the page.	10:37:15
25	Q. These claims are not, though, directed to	10:37:18

1	oligonucleotides; correct?	10:37:23
2	A. The claims as written are not -- there is	10:37:30
3	no mention of oligonucleotide here. That's in the	10:37:37
4	written description.	10:37:39
5	Q. Right. These are claims to building	10:37:41
6	blocks. The claims themselves are claims to	10:37:43
7	building blocks that can be used in	10:37:45
8	oligonucleotides; right?	10:37:47
9	A. Yes. Or other things too.	10:37:49
10	Q. Or other things. What other things?	10:37:55
11	A. Well, these building blocks could be used	10:37:57
12	in principal for making dinucleotides or smaller	10:38:00
13	fragments, analogs thereof.	10:38:06
14	Q. Analogs; right?	10:38:09
15	A. Yeah.	10:38:10
16	Q. Okay.	10:38:10
17	A. So a POSA would be able to use such	10:38:11
18	building blocks for other things too, but the	10:38:14
19	motivation would clearly be for oligonucleotide	10:38:16
20	synthesis.	10:38:21
21	Q. Right. Let's go to -- back to	10:38:21
22	Exhibit 1003, which is Dr. Baran's declaration. And	10:38:28
23	if we can go to paragraph 24.	10:38:34
24	You see paragraph 24?	10:39:13
25	A. Yes.	10:39:15

1	Q. Here you say -- you use the term medicinal	10:39:17
2	chemistry. What do you mean when you say medicinal	10:39:23
3	chemistry?	10:39:29
4	A. Medicinal chemistry is generally defined as	10:39:30
5	chemistry where the end goal is to generate some	10:39:33
6	sort of bioactive material.	10:39:36
7	Q. Okay. What would that bioactive	10:39:40
8	material -- if you can expand a little bit on that.	10:39:50
9	In terms of medicinal chemistry, if you can expand	10:39:56
10	on your answer a little bit, I'd appreciate it.	10:40:00
11	A. Sure. Well, in general a medicinal chemist	10:40:02
12	aspires to invent a medicine. And as part of that,	10:40:06
13	one needs to have compounds that are bioactive. One	10:40:09
14	needs to be able to explore how to make analogs of a	10:40:14
15	target compound and have some working knowledge of	10:40:20
16	the steps involved to optimize the compound that	10:40:24
17	could be useful in a veterinarian or human context.	10:40:28
18	Q. But the medicinal chemist would not be	10:40:36
19	involved like -- let's talk about in the context of	10:40:38
20	this case. You know, we've looked at the claims of	10:40:41
21	the '885 patent. They're directed to building	10:40:45
22	blocks for oligonucleotides; right?	10:40:48
23	A. Yes.	10:40:52
24	Q. Would a medicinal chemist be intimately	10:40:53
25	familiar with how those building blocks are	10:40:58

1	synthesized?	10:41:00
2	A. In general, I would believe they would be.	10:41:03
3	Q. So a medicinal chemist would -- if you were	10:41:10
4	to ask a medicinal chemist, you know, can you	10:41:15
5	synthesize this building block, a medicinal chemist	10:41:20
6	would be able to just do that; right?	10:41:23
7	A. Well, it's a very broad question. The	10:41:26
8	medicinal chemist would be able to know where to	10:41:29
9	look and what literature to identify if they had not	10:41:32
10	already done that, if it was not already part of	10:41:36
11	their experience, but...	10:41:38
12	Q. I'm just trying to understand the term	10:41:42
13	medicinal chemist.	10:41:45
14	So is it fair to say that a medicinal	10:41:46
15	chemist really is focused on using the synthesized	10:41:51
16	molecule, for example, oligonucleotide, and applying	10:42:00
17	that to some type of a biological or therapeutic	10:42:07
18	area?	10:42:12
19	A. It really depends on the program and the	10:42:13
20	context. I mean, if you have a -- I mean, one -- it	10:42:16
21	really -- yeah, there is a spectrum. So if what the	10:42:24
22	medicinal chemist is asked to do is to make some	10:42:31
23	very rudimentary and well-known construct that they	10:42:34
24	can purchase building blocks in order to make, they	10:42:38
25	may purchase those building blocks, but they would,	10:42:45

1 of course, know how those building blocks are made 10:42:47
2 because they're not ignorant. And they would also 10:42:50
3 have to be well-versed in the ways that people 10:42:53
4 handle and subsequently manipulate and use those 10:42:57
5 building blocks. 10:43:01

6 Q. But you'd agree that -- you know, if you 10:43:02
7 were forming a team, so if you had a team where 10:43:04
8 you're developing a therapeutic and the medicinal 10:43:08
9 chemist wouldn't be responsible for synthesizing 10:43:14
10 the -- for example, synthesizing a novel molecule; 10:43:17
11 right? 10:43:22

12 A. No. That totally mischaracterizes what 10:43:22
13 medicinal chemists do. It is the exact opposite of 10:43:25
14 what you just said. 10:43:30

15 Q. I'm just trying to -- I am trying to 10:43:30
16 understand what you mean by medicinal chemistry and 10:43:31
17 how it fits in the context of this case. So, 10:43:33
18 please, you know, explain, you know, more about what 10:43:35
19 your view on what a medicinal chemist does. 10:43:42

20 MR. EDWARDS: Object to form. 10:43:45

21 Ask a question. 10:43:47

22 THE WITNESS: I mean -- 10:43:50

23 MR. EDWARDS: Hold on. Hold on. There is 10:43:51
24 no question pending. 10:43:52

25 MR. SHORES: You don't have to get upset, 10:44:16

1	Jeremy.	10:44:16
2	MR. EDWARDS: You're talking over me, so	10:44:16
3	I'm trying to make sure you don't.	10:44:17
4	MR. SHORES: You're talking over me too.	10:44:17
5	Come on.	10:44:17
6	MR. EDWARDS: Well, maybe there is a delay.	10:44:17
7	I'm not doing it on purpose. I hope you aren't	10:44:17
8	either.	10:44:18
9	MR. SHORES: Well, I'm just trying to	10:44:18
10	understand --	10:44:18
11	MR. EDWARDS: The current situation -- hold	10:44:18
12	on a second, Dan. The current situation is there is	10:44:18
13	no question pending. Ask a question and then he'll	10:44:18
14	try to answer. That's the way this works.	10:44:20
15	MR. SHORES: Okay. Oh, no. The way this	10:44:22
16	works is you don't continue with speaking	10:44:25
17	objections. That's how this works.	10:44:26
18	MR. EDWARDS: There is no question pending.	10:44:28
19	I'm not objecting.	10:44:30
20	MR. SHORES: I will ask a question as I've	10:44:31
21	said several times before you have taken part in	10:44:33
22	speeches. So I will ask a question.	10:44:40
23	MR. EDWARDS: Go for it.	10:44:45
24	BY MR. SHORES:	10:44:46
25	Q. Yes. So, Dr. Baran, what I'm trying to	10:44:46

1 understand is your -- what you mean by medicinal
2 chemistry in the context of this case. So I asked
3 you what you meant by that and you've given some
4 responses. And so my -- I'm trying to draw some
5 context here.

6 So my question is: If you were to build a
7 team -- if you were to build a team that was going
8 to develop a therapeutic, you would have a medicinal
9 chemist on that team; right?

10 A. Yes. I've built such a team --

11 Q. Yes. Okay.

12 A. Yes.

13 MR. EDWARDS: Don't interrupt the witness.

14 MR. SHORES: Dan, it's a yes-or-no
15 question.

16 MR. EDWARDS: He can answer your questions
17 the way he sees fit.

18 MR. SHORES: You're interrupting me. We
19 can call the PTAB, Jeremy. You're interrupting.

20 MR. EDWARDS: Do not interrupt the witness
21 when he's answering your question.

22 MR. SHORES: He answered the question yes.

23 MR. EDWARDS: He was not finished. You
24 interrupted him. Please do not do that.

25 THE WITNESS: I was just going to say, yes,

10:44:53

10:45:03

10:45:06

10:45:09

10:45:13

10:45:14

10:45:17

10:45:22

10:45:30

10:45:32

10:45:35

10:45:35

10:45:36

10:45:37

10:45:38

10:45:40

10:45:41

10:45:43

10:45:45

10:45:48

10:45:50

10:45:51

10:45:52

10:45:54

10:45:58

1	I've done this many times, built teams to do exactly	10:46:00
2	that.	10:46:03
3	BY MR. SHORES:	10:46:04
4	Q. Okay. Thank you.	10:46:04
5	And by the way, my intention is not to cut	10:46:07
6	you off or to speak over you. It was a simple	10:46:09
7	yes-or-no question, and you answered yes and so	10:46:13
8	that's why I went to my next question. So --	10:46:16
9	A. No offense taken.	10:46:21
10	Q. Excuse me?	10:46:23
11	A. No offense taken.	10:46:23
12	Q. Okay. So if the therapeutic were a novel	10:46:25
13	oligonucleotide, for example, or that utilized a	10:46:36
14	novel oligonucleotide, would the medicinal chemist	10:46:40
15	on that team be responsible for designing and	10:46:49
16	synthesizing the novel oligonucleotide?	10:46:53
17	A. Yes.	10:46:56
18	Q. What about the building blocks that	10:47:02
19	comprised the oligonucleotide?	10:47:04
20	A. Yes as well.	10:47:09
21	Q. Even if they're novel building blocks?	10:47:11
22	A. Of course.	10:47:15
23	Q. So your testimony is that a medicinal	10:47:17
24	chemist would have the expertise to synthesize a	10:47:19
25	novel building block for an oligonucleotide?	10:47:26

1	A. That's reality. Yes.	10:47:28
2	Q. And you wouldn't have anybody else on your	10:47:30
3	team that would have -- that would -- on this	10:47:32
4	hypothetical team, you wouldn't have someone that	10:47:35
5	specializes in the area of phosphoramidite	10:47:41
6	synthesis, for example?	10:47:48
7	A. Again, it's a very vague and	10:47:51
8	context-dependent question. If you're asking about	10:47:54
9	the vagaries of setting up a team that does	10:47:57
10	medicinal chemistry focused on making	10:48:04
11	oligonucleotide therapeutic, you could not have a	10:48:07
12	functional team with medicinal chemists that don't	10:48:12
13	know how to make building blocks and need to ask	10:48:17
14	someone else to do that for them.	10:48:19
15	Now, that said, it is commonplace in pharma	10:48:20
16	companies that work on oligonucleotides to have what	10:48:25
17	they call associate-level chemists who are more	10:48:27
18	focused on making building blocks, for example. And	10:48:31
19	they are almost always, if not always, mentored by	10:48:35
20	the medicinal chemistry lead.	10:48:39
21	Q. So is there -- so your testimony is there	10:48:47
22	are specialists that you're referring to as	10:48:51
23	associate members of this hypothetical team, there	10:48:57
24	are specialists that focus on synthesizing	10:48:59
25	phosphoramidites, for example, or other building	10:49:06

1	blocks; is that right?	10:49:08
2	A. I didn't -- again, it's all a vague	10:49:10
3	hypothetical you're asking for. I'm happy to engage	10:49:14
4	you in a hypothetical. And one hypothetical	10:49:16
5	scenario is that the medicinal chemist has, let's	10:49:20
6	say, a bachelor's degree trained chemist who is	10:49:23
7	instructed and directed by the medicinal chemistry	10:49:26
8	mentor or leader to follow a procedure and make a	10:49:30
9	particular phosphoramidite. That is one scenario	10:49:33
10	that exists in the real world.	10:49:37
11	Similarly, there are scenarios where the	10:49:39
12	company doesn't have enough money to hire such	10:49:41
13	people and the medicinal chemist needs to do	10:49:44
14	everything by themselves.	10:49:46
15	Q. So the medicinal chemist -- your testimony	10:50:02
16	is a medicinal chemist has within his or her skill	10:50:04
17	set the ability to synthesize novel phosphoramidites	10:50:09
18	in other building blocks; right?	10:50:18
19	A. Certainly.	10:50:20
20	Q. Certainly?	10:50:23
21	A. Yes.	10:50:23
22	Q. Do you consider yourself to be a medicinal	10:50:39
23	chemist?	10:50:41
24	A. I mean, I consider myself to be a professor	10:50:43
25	of organic chemistry.	10:50:46

1	Q. But not a medicinal chemist?	10:50:50
2	A. Well, I've consulted in medicinal chemistry	10:50:52
3	for over 20 years now. Founded companies that have	10:50:57
4	gone on to be billion dollar companies in the field	10:51:01
5	of medicinal chemistry. So I would consider myself	10:51:04
6	an expert of medicinal chemistry. I'm even on the	10:51:12
7	editorial board of ACS med chem lab, so yeah.	10:51:15
8	Q. Well, you've received -- you know, you've	10:51:20
9	received recognition for your career; right? I	10:51:24
10	mean, you've received awards; right?	10:51:26
11	A. Yes.	10:51:32
12	Q. You received the Pfizer award for	10:51:33
13	creativity in organic synthesis?	10:51:37
14	A. Yes.	10:51:41
15	Q. Right?	10:51:42
16	And you've been referred to as the sultan	10:51:45
17	of synthesis in some publications; is that correct?	10:51:48
18	A. I guess, if you Googled it. I don't know.	10:51:53
19	Q. Do you consider yourself to be a person of	10:52:01
20	extraordinary creativity with respect to organic	10:52:03
21	synthesis?	10:52:07
22	A. I'm a humble person by nature, so I would	10:52:10
23	consider myself to be an educator.	10:52:13
24	THE TECHNICIAN: Counsel Shores, would you	10:52:36
25	like for me to keep the document up?	10:52:36

1	MR. SHORES: You can take it down.	10:52:49
2	BY MR. SHORES:	10:52:54
3	Q. And in your testimony -- you don't have to	10:52:55
4	look at -- we can pull the declaration up again if	10:52:58
5	we need to, but your testimony was that during SPOS,	10:53:03
6	or solid phase oligonucleotide synthesis, that	10:53:10
7	oligonucleotide sequences with higher yields and	10:53:14
8	greater purity is important; right? Is that fair?	10:53:21
9	A. That's fair.	10:53:25
10	Q. Okay. And by yield -- we talked about this	10:53:27
11	a little bit earlier. By yield you're referring to	10:53:30
12	the -- again, we're talking about for SPOS. It's	10:53:33
13	the number of oligonucleotide molecules obtained as	10:53:38
14	compared to the number of reagents put into the	10:53:46
15	process; right? Like you put a certain number of	10:53:48
16	phosphoramidites reagents into the process and then	10:53:51
17	you get a certain number of molecules on the oligos.	10:53:54
18	Is that what you mean by yield?	10:53:59
19	A. Yield is -- let's not conflate efficiency	10:54:04
20	and yield, because I think yield is -- let's imagine	10:54:06
21	you start with your monomer loaded on the	10:54:12
22	polystyrene solid support. And at the end of a	10:54:17
23	sequence, there is a hypothetical quantity you	10:54:22
24	should get if every coupling went with 100 percent	10:54:26
25	efficiency and every deprotection went with	10:54:29

1 100 percent efficiency. That -- 10:54:33

2 Q. Right. 10:54:35

3 A. -- quantity is the 100 percent yield. The 10:54:35

4 observed amount is what you get and then calculate 10:54:40

5 by division times 100 the percent yield. 10:54:45

6 Q. And when you -- we're talking about purity. 10:54:50

7 What do you mean by purity? 10:54:52

8 A. So a compound that is 100 percent pure 10:54:56

9 would be a compound for which the weight of the 10:55:01

10 material corresponds to only the expected compound 10:55:03

11 and nothing else. 10:55:08

12 So, for example, if you had 100 milligrams 10:55:10

13 of product and you're holding in your hand and you 10:55:14

14 checked HPLC or NMR or some analytical 10:55:19

15 characterization and you found that of the 10:55:23

16 100 milligrams only 99 milligrams were the actual 10:55:26

17 compound and there was 1 milligram of other stuff, 10:55:30

18 you would refer to that as 99 percent pure. 10:55:34

19 Q. Those are key goals; right? I mean, when 10:55:42

20 you're synthesizing oligo, you want to have as high 10:55:44

21 a yield as possible; right? 10:55:49

22 A. Not always. 10:55:51

23 Q. Not always? Well, what circumstances don't 10:55:52

24 you want that? 10:55:54

25 A. That's a great question. So when you're a 10:55:54

1	medicinal chemist, often all that matters is getting	10:55:57
2	enough to test a hypothesis. So yield is very	10:56:01
3	important when you're doing manufacturing or you	10:56:06
4	need to prepare, let's say, a much larger quantity	10:56:12
5	for a toxicology batch and you really care about how	10:56:14
6	much you get. In the case of oligonucleotides,	10:56:17
7	often a very small amount of product is enough to	10:56:19
8	test a biological hypothesis and run an assay.	10:56:23
9	So, for example, a medicinal chemist	10:56:28
10	treasures their time more than anything else. So if	10:56:31
11	they can do something fast and quick and get	10:56:33
12	5 percent yield of highly pure -- it needs to be	10:56:36
13	pure, of course. If they can get 5 percent yield of	10:56:40
14	highly pure material, that's far preferable to	10:56:43
15	something which takes much longer that gives them	10:56:46
16	10 percent yield.	10:56:51
17	Q. Okay. You think other experts in the field	10:57:06
18	would agree with that statement?	10:57:23
19	A. I think so. Sure.	10:57:26
20	Q. Isn't it right that you don't want to have	10:57:38
21	any defects in the oligonucleotide; right?	10:57:41
22	A. That's why you purify it at the end.	10:57:43
23	Q. Adding defects is -- that's problematic;	10:57:47
24	right?	10:57:55
25	A. If you can purify the so-called defect away	10:57:56

1 and you're at an early stage of discovery -- again, 10:57:59
2 it's all context dependent. So you can find, you 10:58:02
3 know, different opinions for different scenarios. 10:58:09
4 But if the scenario is early discovery and the 10:58:12
5 medicinal chemist is told find the best sequence for 10:58:17
6 an oligonucleotide and do it quick, please, they're 10:58:20
7 going to find the fastest -- doesn't matter what the 10:58:23
8 yield is as long as they get enough for the assay. 10:58:26

9 But implicit in that opinion is that, of 10:58:29
10 course, they must purify it, because you can't 10:58:32
11 expose an impure oligonucleotide to your assay or 10:58:34
12 you might get erroneous results. The purification 10:58:38
13 step can be done automated with an HPLC. 10:58:43

14 Q. But if you -- for example, we talked about 10:58:47
15 the SPOS process before. You synthesize your 10:58:49
16 oligonucleotide, but if in your deprotection step 10:58:54
17 you damage the oligonucleotide molecule, that's not 10:58:59
18 a -- that's not a desirous result; correct? 10:59:04

19 A. No one would desire the result. However, 10:59:08
20 the result is still usable if you didn't destroy all 10:59:11
21 of it. So if there is enough -- after the HPLC to 10:59:14
22 get enough material to answer the hypothesis, for a 10:59:18
23 medicinal chemist at an early stage of a drug 10:59:21
24 discovery program, that's fine. 10:59:24

25 When you get to higher scales, yield 10:59:26

1 becomes much more important. And then what you 10:59:31
2 referred to, absolutely, it's not tolerated as much. 10:59:33

3 Q. On the building block level, synthesizing a 10:59:39
4 phosphoramidite, for example, if in a scheme there 10:59:43
5 is -- you know, for example, in a deprotection step 10:59:48
6 and synthesizing a building block like a 10:59:56
7 phosphoramidite, if that deprotection step damages 10:59:59
8 the molecule, that's not a desirable result, is it? 11:00:06

9 A. I think the answer to all these questions 11:00:12
10 is the desirable result in organic synthesis is 11:00:14
11 100 percent yield of product with 100 percent 11:00:19
12 purity. Anything below that is undesirable. 11:00:21

13 Now, the other question is, is it 11:00:24
14 overcomable? The stark reality of organic chemistry 11:00:26
15 is that almost no reactions occur with 100 percent 11:00:30
16 yield in 100 percent purity with minimal 11:00:35
17 purification. And so the reality is that organic 11:00:38
18 chemists deal with lower yields and lower purity, 11:00:43
19 and that's why there is purification. 11:00:46

20 Q. There is a lot of innovation -- you cited 11:00:59
21 to a number of papers in your report, you know, for 11:01:02
22 example, the Beaucage reference. You can pull that 11:01:12
23 up. That's Exhibit 1007. 11:01:18

24 Can you see this exhibit? 11:01:48

25 A. Yes, sir. 11:01:50

1	MR. EDWARDS: You cut out there, Dan.	11:01:56
2	THE WITNESS: He said can you see this	11:01:58
3	exhibit.	11:01:58
4	BY MR. SHORES:	11:01:59
5	Q. This exhibit is dated 1991; correct?	11:02:00
6	A. The publication came out --	11:02:04
7	Q. Yes -- go ahead.	11:02:07
8	A. -- in 1992.	11:02:08
9	Q. Right. And this is titled "Advances in the	11:02:12
10	Synthesis of Oligonucleotides by the Phosphoramidite	11:02:14
11	Approach"; right?	11:02:17
12	A. Correct.	11:02:18
13	Q. And would you agree that there are a lot of	11:02:25
14	building blocks disclosed in this reference?	11:02:29
15	A. Yes.	11:02:33
16	Q. And you would agree that there are a number	11:02:35
17	of different configurations of those building blocks	11:02:38
18	that are disclosed?	11:02:42
19	A. Yes.	11:02:43
20	Q. And you'd agree that there is a tremendous	11:02:48
21	amount of innovation that has gone into solid phase	11:02:50
22	oligonucleotide synthesis over the decades?	11:02:56
23	A. Yes.	11:02:59
24	Q. And you would agree that there is a	11:03:02
25	tremendous amount of innovation that has gone into	11:03:04

1	nucleoside synthesis over the decades?	11:03:08
2	A. Yes.	11:03:11
3	Q. And phosphoramidite synthesis over the	11:03:12
4	decades?	11:03:16
5	A. Yes.	11:03:17
6	MR. SHORES: Counsel, I'm at a good	11:03:42
7	stopping point right now. I don't know if that	11:03:43
8	would work for you guys in terms of taking a break.	11:03:45
9	MR. EDWARDS: Yeah. Let's take a break.	11:03:48
10	THE VIDEOGRAPHER: Off the record at	11:03:53
11	11:03 a.m.	11:03:53
12	(Recess, 11:03 a.m. to 11:23 a.m.)	11:03:59
13	THE VIDEOGRAPHER: Back on the record at	11:23:29
14	11:23 a.m.	11:23:34
15	BY MR. SHORES:	11:23:35
16	Q. Dr. Baran, we're coming back from the	11:23:36
17	break. If we could just go back to exhibits -- go	11:23:37
18	back to Exhibit 2001.	11:23:44
19	We talked before, Dr. Baran -- if you can	11:24:03
20	scroll to the top just so the witness has a	11:24:06
21	reference point. He probably knows what this	11:24:08
22	document is, but...	11:24:09
23	Here you -- you testified earlier that this	11:24:13
24	paper does disclose aspects of oligonucleotide	11:24:21
25	synthesis. Is that fair?	11:24:32

1	A. Yes.	11:24:33
2	Q. Isn't this based on P(V) chemistry, though?	11:24:35
3	A. Well, as you can read, the whole point is	11:24:39
4	to show the context in which P(V) can be	11:24:43
5	advantageous over P(III). So as --	11:24:47
6	Q. Right.	11:24:50
7	A. Yeah. So as part of that, there is a lot	11:24:51
8	of P(III) chemistry in here that is used as a	11:24:54
9	benchmark to substantiate those claims.	11:24:57
10	Q. But there are no synthesis schemes	11:25:02
11	disclosed in here that relate to P(III) chemistry;	11:25:05
12	right?	11:25:07
13	A. No. That's not the case at all. If you	11:25:11
14	look at figure 2 on the third page, right there in	11:25:16
15	panel B of figure 2 is P(III) chemistry. Don't have	11:25:25
16	to look far.	11:25:32
17	Q. That shows P(III) chemistry, but it doesn't	11:25:45
18	show P(III) chemistry in the context of synthesizing	11:25:46
19	a nucleoside, though, does it?	11:25:49
20	A. Well, a nucleoside doesn't have	11:25:54
21	phosphorous, so did you mean oligonucleotide?	11:25:57
22	Q. Sorry. A phosphoramidite.	11:25:59
23	A. Yeah, it does. It's right there. Do you	11:26:00
24	want me to point you to it? It is figure 2b, and	11:26:01
25	you can look on the right-hand side and the	11:26:07

1 left-hand side. They both have P(III) chemistry
2 side by side with P(V). Figure 2, not figure 1.
3 Right there.

4 Q. But the focus of this paper is on P(V)?

5 A. The focus of this paper is awakening people
6 to the difference between P(V) and P(III). So there
7 is a lot of P(III) chemistry in here as well as the
8 2018 disclosure also appearing in Science.

9 Q. Thank you.

10 Let's move on to Exhibit 1017.

11 THE TECHNICIAN: That's 1007?

12 MR. SHORES: 1017.

13 THE TECHNICIAN: Apologies, Counsel.

14 BY MR. SHORES:

15 Q. Dr. Baran -- or Dr. Baran. That's how you
16 pronounce it; right?

17 A. Sure. Either way is fine.

18 Q. Okay. Do you recognize this document?

19 A. Yes, sir.

20 Q. And this is the '031 patent that you cited
21 to in your declaration; is that correct?

22 A. Correct.

23 Q. Okay. You testified that the '031 patent
24 discloses several nucleoside amidites that the
25 inventor synthesized and used as reagents to

1	synthesize RNA oligonucleotides, which the inventors	11:28:46
2	indicated have useful properties; correct?	11:28:50
3	A. That's correct. As part of that	11:28:54
4	disclosure, I should add they also enabled their	11:28:56
5	synthesis.	11:28:58
6	Q. Looking here at this '031 patent, you	11:29:03
7	testified that it discloses several nucleoside	11:29:10
8	amidites, but it really discloses a lot more than	11:29:12
9	that, doesn't it?	11:29:18
10	A. There is many, but there are a few that are	11:29:20
11	really highlighted based on the figures.	11:29:25
12	Q. Let's go to column 17.	11:29:47
13	THE TECHNICIAN: Counsel, could you please	11:29:59
14	repeat that.	11:30:01
15	BY MR. SHORES:	11:30:02
16	Q. So, Dr. Baran, you said there are certain	11:30:02
17	that are highlighted based on the figures. What did	11:30:04
18	you mean by that?	11:30:07
19	A. Well, Melody, maybe you can scroll down	11:30:08
20	slowly. Keep going. Keep going.	11:30:15
21	Okay. That was a different patent. This	11:30:25
22	one is highlighting the particular use in the	11:30:27
23	written description, you know, and also the --	11:30:32
24	points out the direct synthesis of particular	11:30:34
25	nucleoside phosphoramidite reagents.	11:30:42

1	Q. Okay. But this '031 patent discloses at	11:30:46
2	least over 25 building blocks; right?	11:30:48
3	A. I haven't counted. I'll take your word for	11:30:57
4	it.	11:30:59
5	Q. Yeah, let's start at column 17, example 1.	11:31:00
6	Is that one? Does that disclose the synthesis --	11:31:18
7	does example 1 disclose the synthesis of a building	11:31:23
8	block?	11:31:27
9	A. Of several building blocks, yes.	11:31:36
10	Q. We can short-circuit this. If you look at	11:31:40
11	examples -- if you can count the building blocks for	11:31:44
12	examples 1 through 5, you know, just estimate the	11:31:50
13	number of building blocks disclosed. We can do that	11:32:00
14	or I can just walk through every one of them and	11:32:03
15	count them up, just for efficiency purposes. I'll	11:32:05
16	leave it to you how you want to do that.	11:32:09
17	A. Whichever you prefer. If it is on the	11:32:11
18	order of 20 to 25, that's fine. However you want to	11:32:13
19	use your time, Counsel.	11:32:16
20	Q. So your testimony is that example 1	11:32:19
21	discloses -- is there a number of building blocks	11:32:22
22	that example 1 discloses that you can ascertain?	11:32:26
23	A. It's unclear.	11:32:38
24	Q. Okay. Does example 1 disclose at least one	11:32:41
25	building block?	11:32:45

1	A. Yes.	11:32:46
2	Q. Does example 2 disclose -- actually does	11:32:47
3	example 2-a disclose at least one building block?	11:32:54
4	A. By building block we just mean a	11:33:05
5	nucleoside.	11:33:08
6	Q. Well, it's under your definition, which is	11:33:10
7	a phosphoramidite or a nucleotide or nucleoside.	11:33:11
8	A. Yes. In this case it doesn't look like	11:33:17
9	this example has the phosphoramidite part appended	11:33:19
10	to it, but it is a building block.	11:33:24
11	Q. But it's a nucleoside?	11:33:27
12	A. Correct.	11:33:29
13	Q. So you said before that nucleoside was also	11:33:31
14	a building block?	11:33:33
15	A. Yes. Yes.	11:33:34
16	Q. So that's another building block.	11:33:36
17	Example 2-c, is that a building block?	11:33:39
18	A. Yes. Looks like it.	11:33:42
19	Q. Example 2-d of the '031 patent, does it	11:33:47
20	disclose a different building block?	11:33:52
21	A. Yes.	11:33:54
22	Q. And then looking through example 2-e, 2-f,	11:33:58
23	2-g, 2-h, do those also disclose building blocks?	11:34:02
24	A. Sure looks like it, yes.	11:34:07
25	Q. And example 3-a, 3-b, 3-c, those disclose	11:34:12

1 building blocks as well? 11:34:17

2 A. Yes. 11:34:18

3 Q. Example 4-a, 4-b -- I'm sorry. 4-a, 4-b, 11:34:21

4 4-c, and 4-d at the middle of column 25, those 11:34:30

5 disclose building blocks as well? 11:34:37

6 A. Yes. 11:34:40

7 Q. Different building blocks as well? 11:34:42

8 A. Yes. 11:34:43

9 Q. And example 5-a, 5-b, 5-c, 5-d, 5-e, 5-f, 11:34:47

10 5-g, 5-h. Did I miss one? 11:35:08

11 A. Yeah. Certainly agree. 11:35:18

12 Q. 5-j on column 37 and 5-k all disclose 11:35:22

13 different building blocks as well; is that correct? 11:35:32

14 A. That's correct. 11:35:35

15 Q. So I counted about 26 different compounds. 11:35:37

16 A. Okay. 11:35:43

17 Q. 26 different building blocks. So is that 11:35:43

18 fair to say -- 11:35:47

19 A. Sure. 11:35:47

20 Q. -- that they're... 11:35:48

21 And the -- looking at example 4-d, 11:36:10

22 column 25, line 63, if you go to the -- scroll to 11:36:15

23 the next -- actually scroll to the next page, 11:36:35

24 please. Thank you. Keep scrolling down. 11:36:38

25 Can you see at the bottom of -- I can't 11:36:47

1	see. The PDF is --	11:36:51
2	A. I can see it.	11:36:53
3	Q. Okay. Can you see it looks like it is	11:36:54
4	step X in example 4-d?	11:37:00
5	A. 4-d.	11:37:03
6	Q. Well, this is step X in --	11:37:05
7	A. Uh-huh. Yes.	11:37:08
8	Q. Is that right?	11:37:11
9	A. Yes.	11:37:12
10	Q. And this is what you refer to -- and this	11:37:12
11	is what you refer to in your report as compound X,	11:37:15
12	right, compound numeral X?	11:37:22
13	A. Yes, sir.	11:37:24
14	Q. The compound that's listed there, could you	11:37:25
15	read that compound into the record?	11:37:26
16	A. N2-isobutyryl-9-(2 prime-deoxy-2	11:37:28
17	prime-fluoro -- I think that's a 5 prime-O	11:37:42
18	[4,4-dimethoxytrityl]-guanosine-3	11:37:50
19	prime-O-N,N-diisopropyl-beta-D-cyanoethyl	11:38:06
20	phosphoramidite.	11:38:26
21	Q. And that's what you refer to as compound X	11:38:32
22	in your expert declaration?	11:38:34
23	A. Yes, sir.	11:38:37
24	Q. And so you say the compound X is a building	11:38:39
25	block; right?	11:38:44

1	A. Yes.	11:38:47
2	Q. That's your testimony, it's a	11:38:48
3	phosphoramidite; correct?	11:38:49
4	A. Yes.	11:38:50
5	Q. It's a building block; correct?	11:38:51
6	A. Yes.	11:38:55
7	Q. So this 10-step synthesis scheme of example	11:38:57
8	4-d does not show the synthesis of an	11:39:06
9	oligonucleotide; correct?	11:39:10
10	A. The text of 4-d is only for the synthesis	11:39:17
11	of the building block. That's correct.	11:39:21
12	Q. Okay. And then later in the '031	11:39:23
13	specification starting at column 39 -- so if you can	11:39:30
14	move to column 39. Thank you very much.	11:39:35
15	Here the -- can you see that, Dr. Baran?	11:39:44
16	A. Yes, sir.	11:39:46
17	Q. Okay. Here you see -- in column 39 you see	11:39:47
18	an example 6; right?	11:39:54
19	A. Yes.	11:39:57
20	Q. Example 6 says oligoribonucleotide	11:39:58
21	synthesis; right?	11:40:04
22	A. Yes.	11:40:05
23	Q. Then in examples 6, 7, 8, 9, 10, 11, 12,	11:40:06
24	13, 14, and 15, and maybe several other examples	11:40:13
25	going forward, the patent discloses the synthesis of	11:40:21

1	oligonucleotides; right?	11:40:25
2	A. Correct.	11:40:26
3	Q. Okay. And in examples -- from example 6	11:40:27
4	through 17, the disclosure of this '031 patent	11:40:39
5	disclosure provides at least 40 different	11:40:47
6	oligonucleotides; right?	11:40:54
7	A. I haven't counted, but that -- I'll take	11:40:55
8	your number. Sure. It could be more. It could be	11:40:58
9	less. That's fine.	11:41:01
10	Q. None of the examples in -- none of	11:41:10
11	examples 6 through 17 that disclose the over	11:41:14
12	40 different oligonucleotides use compound X; right?	11:41:19
13	A. I don't know.	11:41:24
14	Q. Well, can you -- would you mind looking at	11:41:24
15	the examples?	11:41:27
16	A. That will take me a while to study. So if	11:41:31
17	we want to get a printed-out copy, we can take a	11:41:33
18	look, but that's going to take me a while to go	11:41:35
19	through.	11:41:38
20	MR. EDWARDS: I've got one.	11:41:39
21	BY MR. SHORES:	11:41:40
22	Q. This is Exhibit 1017 to your declaration.	11:41:40
23	I assume you guys have a paper copy?	11:41:51
24	MR. EDWARDS: Yeah. I'm just making sure.	11:41:54
25	You want me to hand him one, Dan? Dan?	11:41:55

1	MR. SHORES: Excuse me?	11:42:07
2	MR. EDWARDS: Do you want me to hand him	11:42:08
3	one?	11:42:09
4	MR. SHORES: Yes, please.	11:42:10
5	MR. EDWARDS: Okay.	11:44:57
6	THE WITNESS: Okay. So, Counsel, I found a	11:45:17
7	few examples.	11:45:19
8	BY MR. SHORES:	11:45:22
9	Q. Sorry. I couldn't hear you, Dr. Baran.	11:45:22
10	A. I found a few. Let's go through them.	11:45:24
11	Column 44, line 30.	11:45:28
12	Q. Okay.	11:45:33
13	A. Column 44, line 66.	11:45:34
14	Column 46, line 56.	11:45:41
15	Q. So column 44, line 30?	11:45:49
16	A. That paragraph.	11:45:53
17	Q. Yes. And then column -- maybe you go by	11:45:55
18	example number. So that was example 12 iii?	11:46:01
19	A. No. That was example 13, example 13 with	11:46:07
20	little Roman numeral iii.	11:46:12
21	Q. Okay.	11:46:15
22	A. And then example 14, little roman	11:46:16
23	numeral i. And example 16, Roman numeral vii.	11:46:19
24	Q. Okay. But that doesn't -- that does not	11:46:29
25	disclose -- so if we're looking at example 13,	11:46:34

1	Roman iii.	11:46:41
2	A. Yeah.	11:46:44
3	Q. That example does not disclose compound X;	11:46:44
4	right?	11:46:46
5	A. It's inherently disclosed because that's	11:46:48
6	the only way you can make that compound.	11:46:50
7	Q. That doesn't really answer my question.	11:46:57
8	Compound X is not disclosed in that?	11:47:00
9	A. It is inherently disclosed because you	11:47:02
10	cannot make that example without the use of	11:47:04
11	compound X.	11:47:08
12	Q. Really? Okay. So read the paragraph -- so	11:47:09
13	let's take this example 13 iii.	11:47:15
14	A. Okay.	11:47:20
15	Q. Three. Read that paragraph into the	11:47:22
16	record, please.	11:47:23
17	A. "In the manner of example 8, a chimeric	11:47:24
18	compound having 2 prime fluoro nucleosides in its	11:47:33
19	'wings' segments, 2 prime OH nucleosides in its	11:47:38
20	'gap' segment and phosphorothioate linkages	11:47:44
21	throughout is prepared."	11:47:52
22	Q. Okay. So it says in the manner of	11:47:53
23	example 8, so let's go to example 8.	11:47:57
24	Example 8 doesn't disclose synthesizing	11:48:10
25	oligonucleotide with 2 prime fluoromonomers, does	11:48:14

1	it?	11:48:18
2	A. Of course not.	11:48:19
3	Q. Let's go back to example 13 iii. It says,	11:48:19
4	"In the manner of example 8, a chimeric compound	11:48:27
5	having 2 prime fluoro nucleosides in its 'wings'	11:48:27
6	segments, 2 prime OH nucleosides in its 'gap'	11:48:27
7	segment and phosphorothioate linkages throughout is	11:48:27
8	prepared."	11:48:27
9	Do you see that?	11:48:57
10	A. Yes.	11:48:57
11	Q. That doesn't make any sense, does it?	11:48:57
12	A. To you.	11:49:00
13	Q. I'll take that as a nonanswer.	11:49:03
14	A. Well, the answer is I don't agree. It	11:49:05
15	makes 100 percent sense to anybody who's a person of	11:49:09
16	skill in the art.	11:49:13
17	Q. Okay. So a person of skill in the art, if	11:49:13
18	you look in the manner of example 8, example 8 does	11:49:16
19	not disclose 2 prime fluoromonomers. So the	11:49:18
20	question is: How can you make the compound -- the	11:49:25
21	oligonucleotide in example 13 that has allegedly a	11:49:31
22	2 prime fluoro nucleoside according to -- in the	11:49:36
23	manner according to example 8?	11:49:40
24	A. Very simply. By simply using the building	11:49:43
25	block of compound X in the manner disclosed in	11:49:46

1 example 8. Because example 8 is simply a standard 11:49:49
2 solid phase organic synthesis pathway. 11:49:54

3 So the POSA reading this written 11:49:57
4 description would be very pleased and gratified by 11:50:01
5 this patent because it is so exhaustively enabled 11:50:04
6 allowing one to very clearly know how to make the 11:50:09
7 compounds in this patent. 11:50:13

8 So they would look at example 13, and they 11:50:15
9 would say, oh, I make the 2-fluoro by using the same 11:50:18
10 procedure they used for example 8. And the way I 11:50:22
11 make the 2-fluoro is enabled and described with a 11:50:25
12 nice precise recipe in example 4 X. 11:50:28

13 Q. So your testimony is that a person of 11:50:38
14 ordinary skill in the art would have used example 8 11:50:42
15 that doesn't disclose 2 prime fluoro to achieve the 11:50:46
16 nucleotide or to synthesize the oligonucleotide that 11:50:53
17 has 2 prime fluoro in example 13 iii? 11:50:56

18 A. Of course. That's the way a POSA would use 11:51:00
19 any phosphoramidite building block. They would 11:51:01
20 just think of it as a cassette that could be 11:51:05
21 incorporated into a standard solid phase organic 11:51:07
22 synthesis cycle. 11:51:10

23 Q. But nowhere in example 13 iii or in 11:51:13
24 example 8 is compound X disclosed; correct? 11:51:16

25 A. It's implied. Where do you get the fluoro 11:51:21

1	compound from, Counsel?	11:51:24
2	Q. I'm asking the questions here, with all due	11:51:27
3	respect.	11:51:29
4	A. I can answer it for you then.	11:51:30
5	Q. I'll take that as a nonanswer, because	11:51:32
6	isn't it correct that compound X is not disclosed in	11:51:34
7	example 13 iii, yes or no?	11:51:38
8	MR. EDWARDS: Object to form.	11:51:41
9	THE WITNESS: It doesn't need to be.	11:51:42
10	BY MR. SHORES:	11:51:48
11	Q. So I'll take that as a no?	11:51:48
12	A. You can take it any way you like, Counsel.	11:51:51
13	I have been hired simply to provide to you the	11:51:53
14	scientific expert testimony of what a standard -- I	11:51:58
15	would say even less than ordinary skill in the art	11:52:01
16	person would interpret a document like this. And	11:52:05
17	this is undergraduate level common sense. It's	11:52:09
18	below POSA at this point.	11:52:14
19	Q. And I've been hired to get answers to	11:52:17
20	questions, you know, that relate to this case. And	11:52:20
21	so my question is very simple. It's so simple you	11:52:23
22	should be able to answer.	11:52:27
23	Is compound X disclosed in example 13 iii?	11:52:27
24	I mean, this is below a POSA; right? I mean, is	11:52:31
25	compound X disclosed, written in this document	11:52:35

1	below -- in connection with 13, Roman iii?	11:52:39
2	A. It is inherently written, yes.	11:52:44
3	Q. So your testimony is it is written in	11:52:46
4	there?	11:52:49
5	A. It is inherently written because the only	11:52:49
6	way the POSA would get that 2 prime fluoro building	11:52:51
7	block would be to simply flip a few pages back,	11:52:55
8	so -- I understand what you're doing, but I'm not	11:52:58
9	going to go on the record as being boxed in like	11:53:02
10	this. It's not scientifically accurate. And my job	11:53:06
11	is to be scientifically accurate.	11:53:08
12	Q. Well, my job is to be factually accurate,	11:53:11
13	and I'm asking a very simple question. I mean, the	11:53:13
14	document does speak for itself. Compound X is not	11:53:16
15	disclosed, but you're refusing to acknowledge that.	11:53:19
16	MR. EDWARDS: Let's ask another question	11:53:22
17	and leave the colloquy for another time, Counsel.	11:53:23
18	THE WITNESS: I'm answering --	11:53:29
19	MR. EDWARDS: Hold on. There is no	11:53:29
20	question pending.	11:53:30
21	MR. SHORES: I can answer -- you know, you	11:53:31
22	offered your own colloquy, Counsel. That's fine. I	11:53:34
23	will ask a question.	11:53:37
24	BY MR. SHORES:	11:53:42
25	Q. I'll ask the same question. Is it your	11:53:43

1	testimony that compound X is disclosed in	11:53:45
2	example 13, Roman iii?	11:53:47
3	MR. EDWARDS: Asked and answered.	11:53:51
4	Go ahead.	11:53:52
5	MR. SHORES: It's not been answered.	11:53:53
6	MR. EDWARDS: Definitely has.	11:53:54
7	THE WITNESS: Well, there are two answers	11:53:56
8	to this. The robotic answer is if you read the	11:53:59
9	text, the robot would tell you that information --	11:54:03
10	that word is not there. That's the robotic answer.	11:54:07
11	The common sense answer is of course it is	11:54:11
12	implicitly described because that's the only way you	11:54:15
13	can make such structures is by turning the page	11:54:18
14	back. The POSA doesn't read a patent in a silo	11:54:23
15	where they only look at one example and then they're	11:54:27
16	stuck because they say, oh, in this two sentences, I	11:54:30
17	don't see where the fluoro compound X is described	11:54:33
18	and, therefore, I can't enable -- I can't proceed	11:54:38
19	forward. That's not how a POSA works.	11:54:41
20	BY MR. SHORES:	11:54:46
21	Q. Let's go to example 12, Roman iii.	11:54:46
22	Do you see that, Dr. Baran?	11:54:55
23	A. Yes.	11:54:58
24	Q. And it states, "In the manner of example 8,	11:55:01
25	a chimeric compound having an 'open gap' at its	11:55:02

1	3 prime terminus, 2 prime fluoro nucleosides in its	11:55:05
2	5 prime 'wing' segment" --	11:55:10
3	(Reporter clarification.)	11:55:22
4	Q. In example 12 iii, Roman iii, it states,	11:55:22
5	"In the manner of example 8, a chimeric compound	11:55:26
6	having an 'open gap' at its 3 prime terminus,	11:55:26
7	2 prime fluoro nucleosides in its 5 prime 'wing'	11:55:26
8	segment, 2 prime OH nucleosides in its open 'gap'	11:55:26
9	segment and phosphorothioate linkages throughout is	11:55:44
10	prepared."	11:55:50
11	Did I read that correctly?	11:55:50
12	A. Well, pronunciation issues notwithstanding,	11:55:53
13	then yes.	11:55:57
14	Q. Example 12 iii does not reference	11:56:03
15	compound X; correct?	11:56:06
16	A. It implicitly does.	11:56:07
17	Q. Example 12 iii does not, as you referenced	11:56:11
18	before, robotically recite compound X; correct?	11:56:14
19	A. It doesn't say robotically compound X.	11:56:19
20	It's inferred.	11:56:22
21	Q. I'm sorry. Go ahead.	11:56:24
22	A. It's inferred.	11:56:25
23	Q. It doesn't state the compound, compound X;	11:56:27
24	correct?	11:56:32
25	A. It's not written in this text. It's	11:56:34

1	inferred by the practitioner.	11:56:36
2	Q. It says 2 prime fluoromonomers; right?	11:56:38
3	A. Which are described in example 4.	11:56:41
4	Q. Which several 2 prime fluoromonomers are	11:56:44
5	disclosed in example 4; correct?	11:56:48
6	A. As they should be because you want to make	11:56:50
7	all of them.	11:56:52
8	Q. So it doesn't identify compound X as	11:56:53
9	being -- it doesn't identify compound X in	11:56:55
10	particular; is that correct?	11:56:59
11	A. It doesn't say any specific compound in	11:57:01
12	particular. There is no specific compound listed.	11:57:03
13	It is just a global statement of analog types.	11:57:05
14	There is no specific compound listed there.	11:57:10
15	Q. So if you go to example 13, Roman v, and if	11:57:18
16	you would read that into the record in perfect	11:57:30
17	pronunciation, please.	11:57:35
18	A. "In the manner of example 8, a chimeric	11:57:37
19	compound having 2 prime-O-methoxyethyl nucleosides	11:57:44
20	in its 5 prime 'wing' segment, 2 prime-OH	11:57:50
21	nucleosides in its 'gap' segment, 2 prime fluoro	11:57:56
22	nucleosides in its 3 prime 'wing' segment, and	11:58:03
23	phosphorothioate linkages throughout is prepared."	11:58:09
24	Q. Example 13 v does not reference compound X;	11:58:16
25	correct?	11:58:22

1	A.	It actually references no compound building	11:58:22
2		blocks. That's not the purpose of this paragraph.	11:58:24
3	Q.	Moving on to example 14 i, could you please	11:58:30
4		read that paragraph into the record.	11:58:37
5	A.	"In the manner of example 8 using	11:58:39
6		chemistries of example 6, a chimeric compound having	11:58:42
7		2 prime-O-methyl nucleosides in its 5 prime 'wing'	11:58:46
8		segment, 2 prime-OH nucleosides in its 'gap,'	11:58:52
9		2 prime-O-fluoro nucleosides in its 3 prime 'wing'	11:59:01
10		segment, phosphorothioate linkages in the 'gap'" --	11:59:09
11		that's in quotes -- "segment, and the 3 prime 'wing'	11:59:15
12		segment and methyl phosphonate linkages in the 5	11:59:20
13		prime 'wing' segment is prepared."	11:59:25
14	Q.	Example 14 i does not reference compound X;	11:59:29
15		correct?	11:59:33
16	A.	It references no compounds.	11:59:33
17	Q.	Okay. Moving on to example 16, Roman vii.	11:59:38
18	THE REPORTER:	Counsel, this is the court	11:59:41
19		reporter. I'm going to need a break soon.	11:59:41
20	THE WITNESS:	Do you want me to read it,	11:59:54
21		Counsel?	11:59:55
22	MR. SHORES:	I've got two questions here.	11:59:57
23		I'm not sure the court reporter -- I'm not	12:00:05
24		sure what your name is. I'm sorry.	12:00:24
25	THE REPORTER:	Cindy.	12:00:28

Transcript of Phil S. Baran, Ph.D.
Conducted on September 13, 2023

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1	MR. SHORES: Okay, Cindy. Yeah, just a	12:00:29
2	little bit longer. We'll go for just a little bit	12:00:31
3	if you can, a few minutes, and then we can take a	12:00:35
4	break.	12:00:39
5	THE REPORTER: Just a few minutes.	12:00:41
6	MR. SHORES: Okay. Let's take a break now	12:00:42
7	then. We'll come back to this. Thank you.	12:00:43
8	THE VIDEOGRAPHER: Off the record at	12:00:47
9	12:00 p.m.	12:00:47
10	(Recess, 12:00 p.m. to 12:10 p.m.)	12:03:07
11	THE VIDEOGRAPHER: Back on the record at	12:10:35
12	12:10 p.m.	12:10:35
13	BY MR. SHORES:	12:10:36
14	Q. I believe, Dr. Baran, we were just	12:10:39
15	discussing before the break example 16 vii. Is that	12:10:43
16	your recollection, 16, Roman vii?	12:10:50
17	A. Yes.	12:10:54
18	Q. Okay. Could you please read the paragraph	12:10:54
19	lines 54 through 60 into the record.	12:11:00
20	A. Starting with "In the manner of"?	12:11:05
21	Q. Yes, please.	12:11:08
22	A. "In the manner of example 8, a chimeric	12:11:08
23	compound having 2 prime-O-fluoro-2-thio-5-methyl	12:11:12
24	uridine nucleosides in its 'wing' segments,	12:11:27
25	2 prime-OH nucleosides in its 'gap' segment and	12:11:35

1	phosphorothioate linkages throughout is prepared."	12:11:46
2	Q. Compound X is not described in that	12:11:55
3	paragraph, is it?	12:12:01
4	A. It is not written on the paragraph.	12:12:03
5	Q. So none of the oligonucleotides in	12:12:13
6	examples 6 through 17 describe compound X; correct?	12:12:19
7	A. No. They're all implicitly described --	12:12:28
8	while not in the text, they're implicitly described	12:12:32
9	in the prior examples because that's how you make	12:12:35
10	the oligos. You must use the building blocks to	12:12:39
11	make them.	12:12:43
12	Q. But in these examples that we just covered,	12:12:50
13	12 iii, 13 iii, 13 v, 14 i, 16 vii, they all	12:12:55
14	describe using example 8; right?	12:13:07
15	A. You're conflating things. Example 8 is the	12:13:10
16	solid phase organic synthesis technique that you use	12:13:15
17	to employ all the monomers to make the	12:13:17
18	oligonucleotide. Example 8 is just procedurally how	12:13:22
19	you use the building blocks to make the	12:13:27
20	oligonucleotide desired.	12:13:29
21	Q. So if we go to example 8, your testimony is	12:13:34
22	that example 8 -- well, let's go to example 8.	12:13:47
23	Example 8 discloses a chimeric --	12:13:54
24	(Reporter clarification.)	12:14:07
25	Q. Example 8 discloses a chimeric	12:14:09

1	phosphorothioate oligoribonucleotides with, and it	12:14:10
2	says for example, 2 prime-O-Me/PS 2 prime-OH/PS-2	12:14:15
3	prime-O-Me/PS oligoribonucleotide; correct?	12:14:17
4	A. Correct.	12:14:34
5	Q. And that's in column 40, lines 30 through	12:14:35
6	32?	12:14:42
7	A. Yes.	12:14:44
8	Q. Correct?	12:14:45
9	A. Yes.	12:14:47
10	Q. Example 8 does not disclose the synthesis	12:14:49
11	of an oligonucleotide with a 2 prime fluoromonomer;	12:14:55
12	right?	12:15:00
13	A. The procedure is identical and you know	12:15:03
14	that from the other examples we talked about because	12:15:06
15	it said it was synthesized in a manner similar to	12:15:08
16	that of example 8.	12:15:12
17	So to make things easy for everyone to	12:15:13
18	understand, example 8 is viewed as a general	12:15:17
19	procedure for which you conduct solid phase organic	12:15:20
20	synthesis. The building blocks employed in that	12:15:24
21	general procedure as exemplified in example 8 are	12:15:27
22	described in the prior examples. That's how you	12:15:31
23	make the building blocks.	12:15:33
24	Q. Your testimony is that example 8 is viewed	12:15:50
25	as a general procedure?	12:15:52

1	A. Correct.	12:15:54
2	Q. But example 8 provides a specific procedure	12:15:56
3	to create the cited chimeric oligoribonucleotide;	12:16:00
4	right?	12:16:06
5	MR. EDWARDS: Object to form.	12:16:07
6	THE WITNESS: No. There is no specific	12:16:07
7	compound that's described here. It's clearly a	12:16:09
8	general procedure.	12:16:11
9	BY MR. SHORES:	12:16:15
10	Q. Why is it clearly a general procedure?	12:16:15
11	A. Well, read it for yourself. What specific	12:16:17
12	compound is shown in here?	12:16:20
13	Q. I am reading. Go ahead.	12:16:23
14	A. Okay. Go ahead. Point to me the specific	12:16:24
15	compound that's made. I can't find it. That's why	12:16:28
16	we call it a general procedure.	12:16:38
17	Q. The general procedure that relates to --	12:16:51
18	strike that.	12:16:54
19	Your testimony is that it's a general	12:16:54
20	procedure; right?	12:16:57
21	A. Correct.	12:16:59
22	Q. It is a general procedure that in your --	12:17:03
23	strike that.	12:17:05
24	But this procedure in example 8 refers only	12:17:05
25	to building blocks that have OH at the 2 prime	12:17:15

1	position; correct?	12:17:19
2	A. And as mentioned in the following examples,	12:17:20
3	the procedure outlined here can be used in their own	12:17:23
4	language in a similar manner.	12:17:28
5	Q. But you're just adding that as commentary;	12:17:32
6	correct? There is nothing in the patent that	12:17:34
7	identifies this as a general procedure; correct?	12:17:40
8	A. I'm not adding commentary. I'm telling you	12:17:45
9	facts. Fact number one is that the examples we just	12:17:49
10	talked about, they all say "In the manner of	12:17:53
11	example 8."	12:17:57
12	Fact number two, example 8 is by definition	12:17:58
13	a general procedure because the specific construct	12:18:03
14	is not disclosed in this procedure.	12:18:07
15	Q. So the specific construct of a 2 prime	12:18:36
16	fluoro building block is not disclosed there in	12:18:41
17	example 8; right?	12:18:44
18	A. This specific building block section is	12:18:47
19	prior to this. Example 8 doesn't disclose any	12:18:51
20	building blocks. Example 8, again, is a general	12:18:55
21	procedure for solid phase oligonucleotide synthesis.	12:19:00
22	Q. Example 8 says, "Chimeric	12:19:16
23	oligoribonucleotides having 2 prime-O-alkyl	12:19:17
24	phosphorothioate and 2 prime-hydroxyl	12:19:20
25	phosphorothioate oligonucleotides segments were	12:19:26

1	synthesized using an Applied Biosystems automated	12:19:28
2	DNA synthesizer model 380B, as above"; correct?	12:19:31
3	A. Yes.	12:19:37
4	Q. So that describes a 2 prime hydroxyl group;	12:19:37
5	correct?	12:19:41
6	A. Among other things.	12:19:43
7	Q. Well, for the 2 prime position, it's just	12:19:45
8	the hydroxyl; right?	12:19:48
9	A. No.	12:19:50
10	Q. Okay. Well, what else is on 2 prime?	12:19:50
11	A. 2 prime-O-alkyl.	12:19:53
12	Q. Excuse me -- go ahead. I'm sorry.	12:19:58
13	A. 2 prime-O-alkyl.	12:20:01
14	Q. Okay.	12:20:03
15	A. And as we read in the other examples -- I	12:20:04
16	think this is my third time explaining it to you.	12:20:08
17	In the other examples, they all say, for example,	12:20:09
18	for the ones that contain fluorine, they all say in	12:20:13
19	a manner -- in the manner of example 8, because 8 is	12:20:17
20	a general procedure. And the patent makes it clear	12:20:21
21	that you can use this general procedure whether you	12:20:24
22	have a 2-O-methyl, a 2-OH, or a 2-fluoro.	12:20:28
23	Q. Dr. Baran, I'm looking at example 8, and	12:20:35
24	example 8 says chimeric oligoribonucleotides	12:20:38
25	having --	12:20:41

1	(Reporter clarification.)	12:20:49
2	Q. It is stated in the patent, so these can be	12:20:50
3	corrected later.	12:20:53
4	But my question is this: First, example 8	12:20:54
5	does not disclose fluoro at the 2 prime position in	12:21:00
6	these chimeric oligoribonucleotides; correct?	12:21:09
7	A. That's irrelevant.	12:21:15
8	Q. It's not irrelevant. It's very relevant.	12:21:16
9	And I'd like an answer to my question, please.	12:21:18
10	A. Well, the answer is one that has -- I'm	12:21:20
11	trying to give you an answer as a scientist, not as	12:21:23
12	a lawyer.	12:21:25
13	Q. Yes or no.	12:21:27
14	A. These are scientific arguments I was hired	12:21:27
15	to evaluate. And my expert testimony is that a	12:21:30
16	practitioner of -- in this field does not read a	12:21:33
17	patent the way you're reading it. They look at the	12:21:37
18	patent holistically, and they identify, oh, the	12:21:40
19	fluorine-containing examples were made in the manner	12:21:43
20	described in example 8. They read the paragraph of	12:21:47
21	example 8, and they see, ah, this is a general	12:21:51
22	procedure.	12:21:54
23	So you don't need me to provide testimony	12:21:54
24	of what the document says. You can read it however	12:21:58
25	you want. My job is to give you my opinion as to	12:22:01

1 the state of mind of what a POSA would have when 12:22:04
2 they read this patent. And they most certainly 12:22:08
3 would not compartmentalize the examples in the way 12:22:11
4 you are. 12:22:14

5 MR. SHORES: I move to strike the witness's 12:22:16
6 answer as nonresponsive. 12:22:18

7 BY MR. SHORES: 12:22:27

8 Q. If we can look at the figures. So let's 12:22:27
9 look at figure 1. Let's look at column 8, figure 1, 12:22:30
10 please. The description for -- on column 8, 12:22:35
11 line 17, it states, "Figure 1 schematically depicts 12:22:55
12 certain illustrative chimeric oligomeric compounds 12:23:01
13 of the invention wherein open squares represent 12:23:06
14 2 prime-methoxy modified ribonucleotides, filled 12:23:08
15 circles represent 2 prime-hydroxyl 12:23:08
16 ribonucleotides" -- 12:23:08

17 (Reporter clarification.) 12:23:28

18 MR. SHORES: Fine. You're using some time 12:23:39
19 on the record here, so that's fine. 12:23:45

20 BY MR. SHORES: 12:23:45

21 Q. So, Dr. Baran, looking at column 8, 12:23:45
22 line 18, do you see the description there that 12:23:48
23 relates to figure 1? 12:23:52

24 A. Yes. 12:23:52

25 Q. Does that description provide a description 12:23:58

1	of oligonucleotides with 2 prime fluoro groups?	12:24:04
2	A. The keyword here is certain, so the -- if	12:24:16
3	you read what it says, it says, "Figure 1	12:24:24
4	schematically depicts certain illustrative chimeric	12:24:28
5	oligomeric compounds of the invention wherein open	12:24:34
6	squares represent 2 prime-methoxy modified	12:24:36
7	ribonucleotides, filled circles represent	12:24:36
8	2 prime-hydroxyl ribonucleotides and	12:24:36
9	phosphorothioate linkages are utilized throughout	12:24:36
10	the compounds shown in this figure."	12:24:50
11	So in this text the word fluoro or fluorine	12:24:54
12	is not depicted, but I wouldn't expect it to be	12:24:59
13	because it says it schematically depicts certain	12:25:03
14	illustrative examples, not all of them.	12:25:08
15	Q. So the answer to the question is no;	12:25:14
16	correct?	12:25:16
17	A. You don't need me for that. The answer to	12:25:17
18	the question is right on the screen. There is no	12:25:19
19	word fluoro or fluorine, sure.	12:25:21
20	MR. SHORES: Counsel, if I can -- Counsel,	12:25:23
21	this is a very obstructionist approach that's being	12:25:25
22	taken here. And I'm asking a very simple question	12:25:30
23	on a document, and things are going to move along	12:25:34
24	much more smoothly if I can just get direct answers	12:25:40
25	to my questions. So I'm expressing that concern on	12:25:43

1 the record.

12:25:46

2 MR. EDWARDS: I disagree. Your question
3 was, does that description provide a description of
4 oligonucleotides with 2 prime fluoro groups. You
5 have an answer to that question which directly
6 addresses your question.

12:25:47

12:25:49

12:25:56

12:25:59

12:26:01

7 I imagine you don't like the answer, but
8 it's not a problem with the manner in which the
9 witness is answering. I think you have a way to ask
10 more specific questions if you desire more specific
11 answers.

12:26:02

12:26:05

12:26:09

12:26:11

12:26:14

12 BY MR. SHORES:

12:26:17

13 Q. Is 2 prime fluoro -- a question to the
14 witness, which I'll just repeat it.

12:26:17

12:26:20

15 Is 2 prime fluoro stated in that paragraph?

12:26:21

16 A. That word is not appearing in that
17 paragraph.

12:26:26

12:26:30

18 Q. If you turn to figure 1 -- so if we go to
19 figure 1 of the patent.

12:26:30

12:26:35

20 A. I'm there.

12:26:48

21 Q. I can't see it on the screen here.

12:26:51

22 THE TECHNICIAN: Counsel, where is
23 figure 1 in the patent?

12:26:57

12:26:58

24 MR. SHORES: The second page of the PDF.

12:27:00

25 ///

1	BY MR. SHORES:	12:27:09
2	Q. Figure 1 shows 6 oligos; correct?	12:27:09
3	A. Correct.	12:27:13
4	Q. None of this data relates to 2 prime	12:27:14
5	fluoromonomers; correct?	12:27:17
6	A. The data on this figure, I don't see it	12:27:20
7	explicitly shown with the fluorine.	12:27:23
8	Q. It shows 2 prime methoxy; right?	12:27:25
9	A. Correct.	12:27:30
10	Q. If we go to figure 2.	12:27:31
11	Figure 2 also says 2 prime methoxy; right?	12:27:36
12	A. Yes.	12:27:40
13	Q. Figure 2 does not include data relating to	12:27:42
14	2 prime fluoromonomers; correct?	12:27:44
15	A. I'm not sure if the bottom has data for the	12:27:49
16	2 prime fluoro. I don't know.	12:27:52
17	Q. Can you see it now?	12:28:02
18	A. Yeah. I don't know if there is fluorine in	12:28:03
19	that or not.	12:28:05
20	Q. It says 2 prime -- figure 2b says full	12:28:11
21	2 prime methoxy; right?	12:28:14
22	A. Yeah. I'm talking about figure 2d.	12:28:17
23	Q. Okay. Looking at figure 2d, you can't tell	12:28:19
24	one way or the other whether that includes 2 prime	12:28:25
25	fluoro; right?	12:28:28

1	A. No.	12:28:29
2	MR. SHORES: Okay. So I think now we can	12:28:29
3	take a break if you guys want.	12:28:35
4	MR. EDWARDS: Sure.	12:28:38
5	THE VIDEOGRAPHER: Off the record at	12:28:39
6	12:28 p.m.	12:28:40
7	(Lunch recess, 12:28 p.m.)	
8		
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SAN DIEGO, CALIFORNIA

WEDNESDAY, SEPTEMBER 13, 2023, 1:04 P.M.

THE VIDEOGRAPHER: Back on the record at
1:04 p.m.

BY MR. SHORES:

Q. Dr. Baran, welcome back.

01:04:59

A. Thanks.

01:05:01

Q. If we can put up Exhibit 1018, please.

01:05:03

Can you see that?

01:05:24

A. Yes, sir.

01:05:26

Q. Okay. And you recognize this document?

01:05:26

A. Yes, I do.

01:05:30

Q. And this is the Pitsch reference that you
refer to in your expert declaration; correct?

01:05:32

01:05:35

A. One of the two.

01:05:39

Q. Okay. And if we can go to scheme 1. Just
want to confirm some things here. So in scheme 1 in
compound 20, do you see -- do you know what I'm
referring to when I say compound 20?

01:05:40

01:05:50

01:05:59

01:06:01

A. Yes, I do.

01:06:03

Q. Okay. Compound 20 has an acetyl protecting
group at the N2 position of guanine; right?

01:06:03

01:06:10

A. Correct.

01:06:15

Q. It does not have an isobutyryl group;

01:06:16

1	right?	01:06:19
2	A. Correct.	01:06:20
3	Q. Pitsch -- this entire reference of Pitsch,	01:06:26
4	it doesn't disclose building blocks having fluoro at	01:06:28
5	the 2 prime position; right?	01:06:37
6	A. Correct.	01:06:41
7	Q. Instead, the focus of Pitsch is to use tom	01:06:45
8	to protect the reactive hydroxyl group at the	01:06:51
9	2 prime position; right?	01:06:55
10	A. I wouldn't call that the focus because	01:06:57
11	there is a large amount of the paper that's actually	01:07:01
12	focused on the overall way to employ such	01:07:07
13	structures. And a considerable amount of the paper	01:07:10
14	is directed to the at the time inventive finding	01:07:13
15	that the acetyl protective group is superior for a	01:07:20
16	number of reasons to the isobutyryl for making RNA.	01:07:24
17	Q. But it discloses using tom to protect the	01:07:29
18	OH group at the 2 prime position; right?	01:07:34
19	A. Correct.	01:07:36
20	Q. And it also discloses using the	01:07:40
21	tom-protected phosphoramidites to make	01:07:43
22	oligoribonucleotides; right?	01:07:50
23	A. Correct.	01:07:53
24	Q. There is no scheme or data in Pitsch in	01:07:53
25	this reference, Exhibit 1018, that compares the	01:07:58

1	deprotection rates between isobutyryl and acetyl;	01:08:04
2	right?	01:08:08
3	A. That I would have to check again.	01:08:09
4	Q. Okay.	01:08:16
5	A. If I can have the paper copy, that would be	01:08:18
6	good, just to make sure my answer is accurate.	01:08:19
7	MR. EDWARDS: Dan, would you like me to	01:08:22
8	hand him the paper copy of Exhibit 1018?	01:08:22
9	MR. SHORES: Yes. And feel free to do so	01:08:28
10	going forward with all of the exhibits.	01:08:31
11	MR. EDWARDS: Okay. Thanks. I didn't want	01:08:35
12	to presume. It's your examination.	01:08:36
13	While he's reading, for the reporter's	01:09:10
14	sake, do you want the spelling of acetyl? I have a	01:09:13
15	feeling it is about to be said a lot.	01:09:16
16	THE WITNESS: I don't see a discussion of	01:10:16
17	isobutyryl. I think the reference that does the	01:10:19
18	head-to-head comparison is Fan 2004.	01:10:22
19	BY MR. SHORES:	01:10:26
20	Q. Okay. Is it also correct that Pitsch does	01:10:26
21	not disclose isobutyryl being used as a protected	01:10:31
22	group -- as a nucleobase protected group?	01:10:35
23	A. I don't see it.	01:10:38
24	Q. Okay. And you testified that Pitsch -- you	01:10:40
25	testified that Pitsch explains acetyl was used for	01:10:49

1	its, quote, fast deprotection speed; right?	01:10:52
2	A. Among other reasons, yes.	01:10:55
3	Q. But Pitsch doesn't use the term fast, does	01:10:57
4	it?	01:11:00
5	A. They're more scientifically accurate than	01:11:33
6	fast. So they use actual numbers that show relative	01:11:35
7	rate is very rapid.	01:11:44
8	Q. But it doesn't, to your knowledge,	01:11:52
9	disclose -- use the term fast; right?	01:11:53
10	A. They use a superior language, which is to	01:11:57
11	give the actual numbers. Rather than using	01:11:59
12	subjective analysis, they just objectively say what	01:12:03
13	the rate is, which is preferable.	01:12:08
14	Q. So is that a no?	01:12:15
15	MR. EDWARDS: Object to form.	01:12:19
16	THE WITNESS: I mean, if you're asking for	01:12:19
17	me to do a word search on the word fast, I don't see	01:12:20
18	the word fast. I see a more scientifically accurate	01:12:23
19	description than fast.	01:12:28
20	BY MR. SHORES:	01:12:29
21	Q. To your knowledge, the term fast is not	01:12:29
22	used in the document; right?	01:12:33
23	A. The only referral to speed is actual rate,	01:12:38
24	which looks to be very quick.	01:12:41
25	Q. Okay. So that's nonresponsive to a	01:12:45

1	yes-or-no question. That is nonresponsive. We will	01:12:50
2	let the document speak for itself.	01:12:55
3	A. Okay.	01:13:00
4	Q. Now, if we go to page 3778 of Exhibit 1018,	01:13:03
5	which is on the upper right-hand corner. Here in	01:13:08
6	this document on page 3778 of Exhibit 1018, there is	01:13:25
7	a sentence that says, "Prior to the synthesis of	01:13:35
8	oligonucleotides, we established the conditions	01:13:39
9	required for the removal of the base-protecting	01:13:40
10	acetyl groups with MeNH ₂ . By UV measurements and	01:13:46
11	reversed-phase HPLC, we determined half-lives of	01:13:53
12	less than two minutes for the	01:13:58
13	2 prime-O-tom-protected N4-acetyl-cytidine and	01:14:00
14	N6-acetyladenosine derivatives, and a half-life of	01:14:08
15	four minutes for the 2 prime-O-tom-protected	01:14:14
16	N2-acetylguanosine, respectively"; right?	01:14:19
17	A. Yes.	01:14:23
18	Q. And those rates relate to the deprotection	01:14:29
19	of the nucleobase of a tom-protected nucleoside;	01:14:36
20	correct?	01:14:40
21	A. Correct.	01:14:41
22	Q. There is nothing in Pitsch regarding the	01:14:45
23	effects of using acetyl in guanosine	01:14:48
24	phosphoramidites having 2 prime fluoro groups;	01:14:56
25	right?	01:15:01

1	A. That's correct.	01:15:01
2	Q. And so if we move down to table, which is	01:15:05
3	just table, and that's on page 3782 of this exhibit,	01:15:12
4	in table there are certain rates disclosed,	01:15:27
5	deprotection rates disclosed as well; correct?	01:15:29
6	A. Correct.	01:15:33
7	Q. And those rates disclosed in table relate	01:15:36
8	to deprotection rates for tom-protected	01:15:39
9	oligonucleotides; right?	01:15:44
10	A. Yes.	01:15:47
11	Q. But not oligonucleotides containing 2 prime	01:15:47
12	4 monomers; right?	01:15:53
13	A. Correct.	01:15:56
14	Q. If we can go back to Exhibit 1017, please.	01:15:59
15	And exhibit -- I'm sorry. Example 8.	01:16:10
16	And you recall example 8 from testimony	01:16:34
17	from earlier today?	01:16:36
18	A. Yes.	01:16:39
19	Q. Example 8 does not teach deprotection rates	01:16:42
20	of acetyl; right?	01:16:46
21	A. That's correct.	01:16:57
22	Q. And example 8 does not teach deprotection	01:17:00
23	rates of isobutyryl; right?	01:17:04
24	A. It does not teach rates.	01:17:10
25	Q. Right. Example 8 says the treatment in	01:17:13

1	methanolic ammonia for 24 hours at room temperature	01:17:16
2	was then done to deprotect all bases and sample was	01:17:16
3	again lyophilized to dryness; right?	01:17:16
4	A. Yes.	01:17:31
5	Q. But the 24-hour deprotection period	01:17:31
6	disclosed in example 8 of the '031 patent is not a	01:17:36
7	rate of deprotection; right?	01:17:41
8	A. I mean, that is the length of time it took	01:17:44
9	them before they isolated and purified. So in an	01:17:46
10	absolute sense, it is the time they took, but what	01:17:55
11	we don't know is what the absolute rate was. Maybe	01:17:57
12	they only needed seven hours. Maybe they needed	01:18:00
13	19.2. We don't know that.	01:18:04
14	Q. And nowhere in the '031 patent in this	01:18:10
15	Exhibit 1017 does -- are deprotection rates for	01:18:22
16	acetyl or isobutyryl disclosed; correct?	01:18:30
17	A. Just overall reaction time.	01:18:32
18	Q. Right. We're talking about the example 8.	01:18:36
19	I'm just being -- clarifying. Nothing in the	01:18:38
20	'031 patent discloses deprotection rates for acetyl	01:18:44
21	or isobutyryl; right?	01:18:50
22	A. Not relative to each other. So not in a	01:18:58
23	competition format. Is that what your question is?	01:19:00
24	Q. Well, no. Just in general. I mean,	01:19:03
25	nothing in the '031 patent discloses a rate, a	01:19:06

1	deprotection rate of acetyl; right?	01:19:09
2	A. They don't, right, in the same way that	01:19:14
3	Pitsch does with kinetics and half-life and	01:19:18
4	sampling, correct.	01:19:21
5	Q. And nothing in the '031 patent discloses a	01:19:25
6	deprotection rate of isobutyryl; right?	01:19:28
7	A. Well, we just need to be careful on the	01:19:31
8	language. Because if you interpret the question of	01:19:34
9	rate being equivalent to reaction time, then they do	01:19:39
10	say it was left for 24 hours, but if you're looking	01:19:43
11	for a rigorous assessment like Pitsch or Fan did,	01:19:47
12	that's not included.	01:19:51
13	Q. Right. When you talk about the assessment	01:19:55
14	in Pitsch, you're referring to the assessment	01:19:57
15	relating to the deprotection of acetyl?	01:20:01
16	A. Correct.	01:20:03
17	Q. Pitsch doesn't disclose the deprotection	01:20:05
18	rate of isobutyryl; right?	01:20:07
19	A. That's Fan.	01:20:09
20	Q. Right. But Pitsch doesn't disclose the	01:20:10
21	deprotection rate of isobutyryl; right?	01:20:13
22	A. Correct.	01:20:15
23	Q. So let's look at Fan, so Exhibit 1019.	01:20:17
24	Then if we can look at compound 6a, which	01:20:37
25	is on the next page. Which is on -- excuse me --	01:20:40

1	page 2556 of Exhibit 1019; right?	01:20:46
2	A. Yes.	01:21:02
3	Q. You see the table -- scheme 2? Excuse me.	01:21:03
4	A. Yes, sir.	01:21:09
5	Q. Can you see compound 6a?	01:21:14
6	A. Yes.	01:21:16
7	Q. So compound 6a is not a phosphoramidite;	01:21:19
8	right?	01:21:29
9	A. Correct.	01:21:29
10	Q. Is it fair to say that compound 6a is a	01:21:30
11	nucleoside derivative?	01:21:31
12	A. Yes. Certainly.	01:21:34
13	Q. And compound 6a has TBS as a protecting	01:21:37
14	group at the 2 prime position; right?	01:21:45
15	A. Correct.	01:21:47
16	Q. Compound 6a does not have fluoro at the	01:21:50
17	2 prime position; right?	01:21:59
18	A. That's correct.	01:22:01
19	Q. And then compound 6a uses 3 prime, 5 prime,	01:22:02
20	O-di-tert-butylsilylene to protect the hydroxyl	01:22:05
21	groups at the 3 prime and 5 prime positions; right?	01:22:12
22	A. Correct.	01:22:16
23	Q. And Fan is the only reference that you rely	01:22:18
24	on that provides a comparison of deprotection rates	01:22:20
25	between isobutyryl and acetyl; right?	01:22:27

1	A. Yes.	01:22:29
2	Q. Okay. And looking at this reference at	01:22:33
3	Fan, Exhibit 1019, table 1 -- so let's go to table 1	01:22:37
4	which is at the bottom of page 2556.	01:22:44
5	A. Okay. I'm there.	01:22:51
6	Q. Do you see that?	01:22:54
7	A. Yes.	01:22:54
8	Q. And the reference discloses -- and you can	01:22:58
9	see above the language that's there; right? It says	01:23:02
10	to compare deprotection rates. Do you see that	01:23:05
11	language?	01:23:08
12	A. Yes.	01:23:08
13	Q. Okay. So Pitsch uses -- going back to	01:23:08
14	Pitsch -- I'm sorry. Looking at this table, it	01:23:17
15	discloses using 1.3 percent methylamine, 2.6 percent	01:23:23
16	ethanol, and 96 percent methylene chloride by weight	01:23:30
17	as its deprotection conditions; right?	01:23:36
18	A. Yes.	01:23:38
19	Q. And those deprotection conditions are very	01:23:40
20	different than the deprotection conditions that were	01:23:43
21	used in Pitsch; right?	01:23:45
22	A. Correct.	01:23:46
23	Q. Because Pitsch uses methylamine, ethanol,	01:23:49
24	and water; right?	01:23:54
25	A. With, I believe, 12 molar of the amines, so	01:23:56

1	a lot.	01:23:59
2	Q. Let's go to Pitsch. Let's just go back to	01:24:04
3	Pitsch, which is Exhibit 1018. I think if we go up	01:24:07
4	to --	01:24:20
5	A. It's on page 3778 in the third paragraph.	01:24:25
6	It says in parentheses the conditions, 10 molar and	01:24:30
7	water ethanol 1 to 1, 25 degrees. Is that what	01:24:34
8	you're referring to?	01:24:38
9	Q. Yes. Thank you.	01:24:38
10	A. Sure.	01:24:39
11	Q. You're saying that was a lot?	01:24:43
12	A. 10 molar is a lot. It's what people do in	01:24:44
13	solid phase organic synthesis of oligos. They use a	01:24:49
14	large quantity of methylamine.	01:24:52
15	Q. Okay. So I just wanted to clarify that.	01:25:02
16	We now have the -- in the record exactly what we're	01:25:03
17	referring to on Exhibit 1018. So let's go back to	01:25:09
18	Exhibit 1019.	01:25:13
19	A. Okay.	01:25:14
20	Q. Methylene chloride and methylamine are	01:25:19
21	different; right? They're completely different?	01:25:24
22	A. Sorry. Methylamine is the same in both	01:25:30
23	papers. The solvent is different in 1019 for a very	01:25:33
24	specific reason.	01:25:37
25	Q. I guess my question is: Methylene chloride	01:25:40

1	and methylamine are totally different?	01:25:42
2	A. Relative to what? Those are two different	01:25:46
3	chemical compounds? Is that your question?	01:25:49
4	Q. Yeah. Because we were talking about Fan	01:25:50
5	discloses using 96 percent methylene chloride,	01:25:54
6	right, and Pitsch discloses using methylamine	01:25:57
7	10 molar?	01:26:07
8	A. No. They both use methylamine. You're	01:26:08
9	just talking about the solvent.	01:26:11
10	Q. Right.	01:26:14
11	A. Yeah. Methylene chloride is a solvent for	01:26:15
12	Fan, but the active reagent that does the	01:26:21
13	deprotection, they're both methylamine.	01:26:28
14	Q. Okay. Okay. So methylamine chloride is	01:26:31
15	hydrophobic; right?	01:26:35
16	A. Yes.	01:26:40
17	Q. And then oligonucleotides are polar?	01:26:40
18	A. That's correct.	01:26:44
19	Q. And that means they're soluble in water but	01:26:51
20	not in hydrophobic solvents like methylene chloride;	01:26:55
21	right?	01:27:00
22	A. Correct.	01:27:01
23	Q. And Fan uses methylene chloride in its --	01:27:03
24	as part of its deprotection conditions?	01:27:05
25	A. That is, I would say, mock conditions that	01:27:10

1 are chosen specifically to dramatically attenuate 01:27:13
2 the rate of deprotection, number one. And, number 01:27:18
3 two, this compound is quite hydrophobic, and so they 01:27:20
4 need to pick a solvent that dissolves in really 01:27:25
5 well. So the solvent choice is solely to make the 01:27:29
6 point of the differences in rate. 01:27:35

7 Q. But I mean, the deprotection conditions are 01:27:41
8 quite different between the two? 01:27:44

9 A. But that's not the point of the conclusion. 01:27:46
10 Like whether the conditions -- the solvent they used 01:27:50
11 are different or not is irrelevant to the mechanism 01:27:53
12 of this reaction and the rate thereof. Completely 01:27:56
13 irrelevant. 01:28:01

14 Q. I'm just asking -- you know, I'm looking at 01:28:03
15 the different references, and I'm just asking 01:28:06
16 factual questions. 01:28:07

17 A. And I'm giving you factual answers. 01:28:08

18 Q. You're giving me opinions about it. I'm 01:28:12
19 just asking you, you know, facts. 01:28:14

20 A. I was hired to give you facts and opinions 01:28:18
21 based on 25 years of experience. 01:28:21

22 Q. If you try to deprotect oligonucleotide 01:28:33
23 using the deprotection conditions of Fan, it 01:28:36
24 wouldn't work very well, would it? 01:28:39

25 A. Nobody would do that. That's not the point 01:28:42

1	of the study.	01:28:44
2	Q. Do you have familiarity with what the	01:28:55
3	standard protecting group for guanosine, the NH ₂	01:28:58
4	protecting group for guanosine was in the 2009 time	01:29:08
5	frame?	01:29:11
6	A. In the 2009 time frame, people used either	01:29:14
7	isobutryl. Some people used -- in some cases	01:29:18
8	you'll find phenoxyacetyl. In some cases acetyl was	01:29:22
9	used. Benzoyl was also used.	01:29:30
10	Q. You said acetyl was used for guanosine	01:29:37
11	nucleosides; right?	01:29:50
12	A. Yes.	01:29:51
13	Q. To protect N2 of guanine?	01:29:52
14	A. Yes. Correct.	01:29:54
15	Q. Was it also used to protect guanosine with	01:29:59
16	fluoro at the 2 prime position?	01:30:07
17	A. Perhaps. You know, very likely. When you	01:30:15
18	think of the monomers employed, the 2-fluoro is the	01:30:18
19	easiest RNA monomer to manipulate. It reacts just	01:30:23
20	like DNA. So the cases you see here of O-methoxy,	01:30:26
21	O-tom, O-MOE are much more difficult in coupling	01:30:30
22	than the 2-fluoro. The 2-fluoros are always the	01:30:38
23	easiest. They're like DNA.	01:30:42
24	Q. They're like what?	01:30:44
25	A. They're like DNA.	01:30:45

1	Q. And then you testified that guanosine --	01:30:54
2	that acetyl was used to protect guanosine in the	01:30:56
3	2009 time frame; right?	01:31:03
4	A. I'm sure.	01:31:05
5	Q. Was that -- you're saying that that was a	01:31:06
6	standard protecting group from guanosine, acetyl?	01:31:09
7	A. It was a standard option in the tool kit	01:31:15
8	that a medicinal chemist could choose from.	01:31:17
9	Q. What is that based on?	01:31:23
10	A. It is based on my experience in reading the	01:31:25
11	literature.	01:31:27
12	Q. Is there a particular piece of literature	01:31:29
13	that you're relying on to offer that opinion?	01:31:32
14	A. Well, Pitsch is the most obvious reference	01:31:37
15	to just point to.	01:31:40
16	Q. Pitsch doesn't have fluoro at the 2 prime	01:31:44
17	position.	01:31:48
18	A. And to my point, the fluoro is far easier	01:31:48
19	than the O-tom. So a medicinal chemist or a person	01:31:50
20	of skill in the art looking at Pitsch would say,	01:31:54
21	wow, this works great for O-tom. It's going to be a	01:31:56
22	lot easier with 2-fluoro.	01:31:59
23	So it's really important that the folks in	01:32:02
24	this room understand the logic of how	01:32:05
25	oligonucleotides are made and how people think about	01:32:10

1 the protecting group issue. They don't equate the 01:32:12
2 protecting group on the nitrogen relative to what is 01:32:16
3 on the periphery of the sugar. That is dealt as a 01:32:20
4 secondary consideration or separate from the 01:32:24
5 N-protecting group. 01:32:28

6 Q. So if you can -- the technician can put up 01:32:33
7 Exhibit 2006. 01:32:38

8 And if you can please go to, I guess, the 01:32:53
9 second page of this document. 01:32:59

10 (Exhibit 2006 marked for identification.) 01:33:00

11 MR. EDWARDS: Is this one of the ones you 01:33:05
12 emailed me today? 01:33:07

13 MR. SHORES: Yes, Counsel. 01:33:10

14 MR. EDWARDS: Could you give me a second to 01:33:11
15 try and extract it from my various piles to give to 01:33:13
16 the witness, or do you want to question him just on 01:33:17
17 the screen? 01:33:19

18 MR. SHORES: It's up to the witness. 01:33:22

19 THE WITNESS: Let's see what the question 01:33:23
20 is. Go ahead. 01:33:24

21 MR. EDWARDS: Go ahead. 01:33:25

22 BY MR. SHORES: 01:33:29

23 Q. So do you see this -- let's go to the first 01:33:29
24 page so there is some context for the witness. 01:33:31

25 Okay. Dr. Baran, you see the title of this 01:33:38

1	Exhibit 2006 is "Current Challenges in Nucleic Acid	01:33:41
2	Synthesis"?	01:33:46
3	A. Yes.	01:33:46
4	Q. And it's dated -- I guess if you scroll	01:33:50
5	down -- if the technician can scroll down.	01:33:53
6	It is dated 2013; right?	01:34:00
7	A. Yes.	01:34:02
8	Q. And your understanding is that is after the	01:34:04
9	filing date of the '885 patent; right?	01:34:08
10	A. Correct.	01:34:12
11	Q. Okay. So if you go to the page 327 of this	01:34:12
12	document, which is page 2 of the PDF.	01:34:16
13	Keep scrolling down, please. You can stop.	01:34:18
14	Could you read the paragraph that -- into	01:34:26
15	the record that starts with Khorana, et al.	01:34:33
16	A. "Khorana, et al., also developed the	01:34:37
17	oligonucleotide protection/deprotection scheme that	01:34:40
18	is still used today more or less intact. The	01:34:43
19	4,4 prime dimethoxytrityl, or DMT, protecting group	01:34:47
20	for the protection of the 5 prime hydroxyl group is	01:34:54
21	ubiquitous in oligonucleotide chemistry. Khorana,	01:34:57
22	et al., introduced protecting groups for the	01:35:00
23	nucleosidyl exocyclic amines that are known today as	01:35:05
24	standard protecting groups: isobutyryl for guanosine	01:35:05
25	and benzoyl for adenosine and cytidine. Although	01:35:18

1 others exist, these groups are the most commonly 01:35:25
2 used, with the possible exception of 01:35:28
3 acetyl-protected cytidine, which is more readily and 01:35:32
4 cleanly removed compared with benzoyl (figure 1).\" 01:35:35
5 Q. So in this article it states as of 2013 01:35:43
6 that the standard protecting group for isobutyryl 01:35:51
7 was -- for guanosine was isobutyryl; right? 01:35:54
8 A. Yes. 01:35:59
9 Q. And while it cites to acetyl as another 01:36:04
10 standard group, it refers to acetyl as standard in 01:36:06
11 some cases for cytidine; right? 01:36:11
12 A. Yes. 01:36:14
13 Q. Okay. So is it fair to say that the 01:36:14
14 standard protecting group for guanosine in the 2013 01:36:18
15 time frame was isobutyryl? 01:36:24
16 A. For most applications, isobutyryl is fine. 01:36:28
17 Q. Okay. And going back to, you know -- if 01:36:36
18 you look at claim 2, you know, claim 2 of the '885 01:36:40
19 patent, that claim is being challenged by petitioner 01:36:44
20 on the grounds of obviousness; right? 01:36:52
21 A. Yes. 01:36:54
22 Q. That means that there is no reference -- 01:36:55
23 out of the thousands of potential building blocks 01:36:58
24 available in the prior art, there was no reference 01:37:03
25 that disclosed all of the -- that disclosed the 01:37:06

1	precise configuration of the molecule, particularly	01:37:12
2	the guanosine molecule claimed in claim 2; right?	01:37:16
3	A. Then it would be anticipated.	01:37:21
4	Q. But it wasn't anticipated; right?	01:37:24
5	A. That's why the affidavit points to the	01:37:26
6	obviousness of it.	01:37:29
7	Q. Let's go to example 4-d of the '031 patent,	01:38:09
8	which is Exhibit 1017.	01:38:12
9	THE TECHNICIAN: Counsel, could I have that	01:38:22
10	example number again?	01:38:24
11	MR. SHORES: Yes. I'm sorry. Example 4-d.	01:38:25
12	THE TECHNICIAN: Thank you, Counsel.	01:38:29
13	BY MR. SHORES:	01:39:19
14	Q. And your testimony is that in step 2 of	01:39:19
15	example 4-d, a person of ordinary skill in the art	01:39:26
16	would have simply substituted acetic anhydride for	01:39:33
17	isobutyric anhydride and synthesized it, the claimed	01:39:41
18	molecule, right, the molecule claimed in claim 2?	01:39:49
19	That's your testimony?	01:39:53
20	A. In order to synthesize the compound of	01:39:55
21	claim 2, they would use a very similar procedure	01:39:57
22	with acetic anhydride, but they would have to be	01:40:00
23	motivated to do that.	01:40:04
24	Q. So if you look at paragraph 122 of your	01:40:19
25	declaration, which is Exhibit 1003.	01:40:24

1	A. 122. Okay.	01:40:39
2	Q. Okay. There you say "a POSA would have	01:40:41
3	simply substituted acetic anhydride (for isobutyric	01:40:49
4	anhydride) in step 2 and thereafter performed the	01:40:55
5	remaining steps 3 through 10 -- or Roman iii through	01:40:58
6	x of example 4-d in the '031 patent to make the	01:41:04
7	molecule claimed in claim 2 of the '885 patent where	01:41:09
8	B is guanine-N-acetyl and Z is ribo fluoro"; right?	01:41:13
9	A. Correct.	01:41:21
10	Q. So I'm just confirming your testimony.	01:41:22
11	Your testimony is that -- if we go back to the	01:41:23
12	'031 patent, which is Exhibit 1017.	01:41:30
13	A. I see it.	01:41:38
14	Q. Yes. In step 2 of example 4-d, you're	01:41:39
15	saying just simply swap out -- you know, take the	01:41:43
16	set of isobutyric anhydride, put acetic anhydride	01:41:50
17	in, and follow through with the remaining steps 3	01:41:57
18	through 10, and then the molecule in claim 2 of the	01:42:01
19	'885 patent would have been synthesized; right?	01:42:08
20	A. That's what a POSA would have done.	01:42:11
21	Q. Okay. So that's your testimony?	01:42:14
22	A. Yes.	01:42:18
23	Q. Okay. You didn't provide any experimental	01:42:18
24	results, though, right, to support your testimony?	01:43:03
25	A. I was not asked to do experiments in the	01:43:08

1	laboratory for this -- for this endeavor.	01:43:10
2	Q. Okay. Sorry.	01:43:16
3	A. Yeah. Counsel didn't ask me to go to the	01:43:19
4	lab and do something with my hands.	01:43:22
5	Q. Okay. So you didn't form any experiments	01:43:25
6	to, you know, substitute acetic anhydride for	01:43:36
7	isobutyric anhydride and follow all the steps here	01:43:42
8	in example 4-d; right?	01:43:46
9	A. There was no need. The literature is	01:43:48
10	replete with examples of how to put an acetyl group	01:43:49
11	on guanosine or any other amino heterocycle.	01:43:53
12	Q. Yeah. I'm just trying to, you know,	01:44:01
13	confirm that you didn't conduct this steps 1 through	01:44:05
14	10 or steps 2 through 10 using acetic anhydride	01:44:10
15	instead of isobutyric anhydride; right?	01:44:17
16	A. If I were to go to the lab and do it, I	01:44:19
17	would use this literature and Pitsch. Even today,	01:44:22
18	'885 enables me to do nothing, unfortunately. So	01:44:26
19	there is no procedure in there that I would even be	01:44:30
20	able -- if I had '885, it would be useless to me.	01:44:31
21	So I'd have to go to this patent, and I'd have to	01:44:35
22	use Pitsch to help me because those are the only	01:44:37
23	things that have anything enabling in them.	01:44:40
24	Q. But my question is whether you -- did you	01:44:44
25	conduct experiments to prove your theory or not?	01:44:46

1	A. I already answered that.	01:44:50
2	Q. Is it okay if I ask again?	01:44:52
3	A. I didn't do any wet chemistry in the	01:44:55
4	laboratory for any of this endeavor.	01:44:57
5	Q. Did you -- did anyone that you supervised	01:45:03
6	do any wet chemistry to -- for this experiment?	01:45:07
7	A. For this litigation?	01:45:11
8	Q. That was a bad question. I withdraw it.	01:45:14
9	So you personally did not perform any	01:45:17
10	experiments to -- perform any experiments to follow	01:45:24
11	through the steps 1 through 10 in the example 4-d of	01:45:31
12	the '031 patent; right?	01:45:35
13	A. No. I wasn't asked to.	01:45:39
14	Q. I'm not asking if you were asked to. I'm	01:45:40
15	just asking if you did conduct any experiments	01:45:43
16	relating to example 4-d of the '885 patent.	01:45:46
17	A. Again, the answer is no. And I wasn't	01:45:51
18	asked to.	01:45:53
19	Q. Okay. I mean, whether you were asked to,	01:45:54
20	that -- thank you for that testimony. That's not	01:45:57
21	really what I was asking.	01:45:59
22	I mean, sometimes, you know, somebody can	01:46:00
23	do something and not be asked to do it. So I'm just	01:46:03
24	wondering if you conducted these tests, you know,	01:46:07
25	because your testimony is that a POSA would have	01:46:10

1 simply substituted acetic anhydride for isobutyric
2 anhydride in step 2 and thereafter performed the
3 remaining steps 2 through 10 of example 4-d of the
4 '031 patent to make the molecule claimed in claim 2
5 of the '885 patent where Z is ribo-fluoro.

6 So that was your testimony. And my
7 question was whether you went into the lab to prove
8 that theory.

9 A. No, because this is undergraduate level
10 chemistry, so there would be no need to even
11 contemplate doing something like that. So the
12 answer is no.

13 Q. Because it would have -- so you're
14 100 percent certain that if you substituted -- if
15 you used acetic anhydride in step 2 instead of
16 isobutyric anhydride in step 2, you're absolutely
17 certain the molecule claimed in claim 2 would have
18 resulted; right?

19 A. I mean, in organic chemistry there is no --
20 it would be scientifically inaccurate for me to say
21 with 100 percent certainty. Nothing is 100 percent
22 certain. But with a huge amount of confidence, yes.

23 Q. Okay. And do you have any knowledge of
24 whether anyone else, not you, but whether anyone
25 else conducted experiments to synthesize the

01:46:13

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01:47:06

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01:47:47

1	compound claimed in claim 2 of the '885 patent using	01:47:55
2	example 4-d -- using the methods disclosed in steps	01:48:00
3	1 through 10 of example 4-d?	01:48:06
4	A. There may be. For example, Fan, in their	01:48:09
5	reference, talks about for some reason the	01:48:14
6	procedural difficulty they had in putting the acetyl	01:48:17
7	group on guanosine, and that's why the paper	01:48:21
8	discloses an improved route. However, Pitsch has no	01:48:24
9	problem making an acetyl guanosine just by using DMF	01:48:28
10	impurity.	01:48:32
11	So it's unclear to me -- you know, it looks	01:48:32
12	like a simple reaction based on Pitsch. And then	01:48:35
13	you have the 2004 Fan paper that gives you an even	01:48:38
14	better procedure to make the same compound.	01:48:42
15	So the bottom line is you could easily make	01:48:44
16	acetylated guanosine by either trying the patent	01:48:47
17	procedure shown here, trying Pitsch's protocol, or	01:48:51
18	trying Fan's protocol.	01:48:54
19	Q. Right. And so I should have been more	01:48:57
20	specific in my question in that for purposes of this	01:49:00
21	case, you're not aware of others -- not yourself,	01:49:03
22	but you're not aware of others that ran this	01:49:07
23	synthesis to simply substitute acetic anhydride for	01:49:11
24	isobutyric anhydride in step 2 and thereafter	01:49:19
25	performed the remaining steps 3 through 10 of	01:49:21

1	example 4-d of the '885 -- of the '031 patent to	01:49:24
2	make the molecule claimed in claim 2 of the '885	01:49:29
3	patent where B is guanine-N-acetyl and Z is	01:49:33
4	ribo-fluoro; right?	01:49:35
5	A. If there was such literature to that end,	01:49:41
6	this would be an anticipation discussion rather than	01:49:42
7	an obvious one.	01:49:45
8	Q. But in connection with this case -- it	01:49:46
9	wasn't you, but was there anyone else in connection	01:49:50
10	with this case that you have knowledge of that	01:49:52
11	performed that experiment?	01:49:55
12	A. I have no idea. Perhaps Hongene did it. I	01:50:01
13	have no idea. No clue.	01:50:04
14	Q. You just don't know one way or the other?	01:50:06
15	A. I don't know.	01:50:07
16	Q. Okay. That's all I was asking.	01:50:08
17	A. Okay.	01:50:11
18	Q. Yeah. You testified that you didn't, and	01:50:12
19	now I'm confirming that your knowledge of whether	01:50:16
20	another party involved in the case did or did not.	01:50:19
21	And your testimony was that you don't know.	01:50:24
22	So you testified that to your knowledge	01:50:31
23	these experiments have not been done, so you don't	01:50:39
24	know firsthand whether or not that would actually	01:50:45
25	work, substituting acetic anhydride for isobutyric	01:50:47

1 anhydride in step 2 and thereafter performing the 01:50:52
2 remaining steps 3 through 10 of example 4-d to make 01:50:57
3 the molecule claimed in claim 2 of the '885 patent 01:51:02
4 where B is guanine-N-acetyl and Z is ribo-fluoro 01:51:07
5 would actually work; right? 01:51:08

6 MR. EDWARDS: Object to form. 01:51:12

7 Go ahead. 01:51:13

8 THE WITNESS: Well, as a general matter, I 01:51:13
9 should say that I can't guarantee with 100 percent 01:51:16
10 accuracy whether any known -- no matter how simple 01:51:20
11 the procedure is, any known procedure can be 01:51:23
12 replicated every single time. There could be 01:51:26
13 experimental error. There could be reagents that 01:51:28
14 are not properly dried. There could be a variety of 01:51:31
15 reasons. 01:51:33

16 But what I can tell you in my scientific 01:51:33
17 opinion, which would be the same in a consulting 01:51:36
18 session that a company hires me to do, is say I'm 01:51:38
19 very, very confident that it would work. That's all 01:51:41
20 I can do as a scientist. I can't -- chemistry, you 01:51:44
21 can't 100 percent guarantee really anything. 01:51:48

22 BY MR. SHORES: 01:51:55

23 Q. Okay. Let's go to paragraph 123 of your 01:51:55
24 report. Here you testified that, as another 01:52:39
25 example, a POSA could have also synthesized the 01:52:52

1	molecule in claim 2 of the '885 patent by starting	01:52:55
2	with -- I'm sorry -- where B is guanine-N-acetyl and	01:53:00
3	Z is ribo-fluoro by starting with 2 prime fluoro 2	01:53:01
4	prime deoxyguanosine either acquired from a	01:53:09
5	commercial source or synthesized according to	01:53:12
6	Sivets; right?	01:53:15
7	A. Yes.	01:53:17
8	Q. Then let's look at Sivets, which is	01:53:24
9	Exhibit 1028. Okay.	01:53:30
10	Exhibit 1028, Technician.	01:53:42
11	You recognize this document?	01:53:45
12	A. Yes, sir.	01:53:51
13	Q. And if you go back to your report -- sorry	01:53:57
14	about that -- 123.	01:54:00
15	A. Yes.	01:54:01
16	Q. Which is Exhibit 1003. You cite to	01:54:06
17	compound 17 in Sivets; right?	01:54:09
18	A. Yes.	01:54:14
19	Q. Let's go back to 1028. Scroll down. Stop	01:54:14
20	there. Keep scrolling. Somewhere there is -- it	01:54:44
21	discloses compound 17. Here we go, compound 17.	01:54:53
22	Scheme 2.	01:55:00
23	Compound 17 has an N7 linked guanine;	01:55:06
24	right?	01:55:17
25	A. Correct.	01:55:17

1	Q. Okay. And if we look at Exhibit 1001,	01:55:18
2	claim 2 -- well, actually if we go to your report	01:55:27
3	and look at the structure of what you described	01:55:46
4	claim 2 as, if we go to page 41 of your report, so	01:55:54
5	paragraph 100. Looking for the structure, but my --	01:56:11
6	I can find it.	01:56:37
7	Actually go to page 48, paragraph 117.	01:56:39
8	Compound claimed in claim 2. Do you see the -- on	01:56:53
9	page 48, do you see the -- on your report you have	01:56:58
10	the compound X as compared to claim 2?	01:57:01
11	A. Uh-huh. Yes.	01:57:06
12	Q. Do you see that?	01:57:07
13	A. Yes.	01:57:09
14	Q. The compound in claim 2 is anilines; right?	01:57:11
15	A. Yes. In that reference, so that's --	01:57:17
16	they're all made -- so I guess instead of compound	01:57:18
17	17, one should say compound 15, but they're all made	01:57:22
18	on that paper.	01:57:27
19	Q. So your citation was to compound 17, but	01:57:29
20	you were referring to compound 15?	01:57:34
21	A. Yes.	01:57:36
22	Q. Okay. And then later in your -- if you go	01:57:36
23	back to paragraph 124 of your report.	01:57:48
24	A. Yes.	01:57:52
25	Q. Paragraph 124 of your report.	01:57:54

1	Paragraph 124 -- actually 123. Excuse me. You	01:57:55
2	testified that a POSA would have reasonably expected	01:58:23
3	a 2 prime fluoro 2 prime deoxyguanosine would react	01:58:26
4	similar to a regular 2 prime deoxyguanosine. That	01:58:30
5	is one with the 2 prime H instead of a 2 prime F	01:58:34
6	substitution; right?	01:58:40
7	A. Correct.	01:58:41
8	Q. What is your basis for that statement?	01:58:41
9	A. Tons of experience in the area and doing	01:58:46
10	this chemistry through supervision and seeing it	01:58:49
11	over the years. The 2-fluoro -- you can find this	01:58:54
12	in the literature. The 2-fluoro reacts very	01:58:57
13	similarly to the DNA as I mentioned before. It's a	01:59:01
14	very, very small atom. It doesn't require any	01:59:02
15	protected group chemistry and is minimally	01:59:08
16	disruptive to the remaining -- to the other parts of	01:59:11
17	the molecule.	01:59:14
18	So a POSA in this time period would be very	01:59:21
19	happy to work with the 2-fluoro derivative because	01:59:25
20	they would know I don't have to protect anything,	01:59:27
21	and the reactivity should be very similar to DNA.	01:59:30
22	Q. But the 2 prime fluoro 2 prime	01:59:39
23	deoxyguanosine is a different molecule, right, than	01:59:44
24	the 2 prime deoxyguanosine?	01:59:48
25	A. Of course.	01:59:53

1	Q.	They have different molecular weights?	01:59:55
2	A.	Yes.	02:00:01
3	Q.	Different electronic properties?	02:00:01
4	A.	They do.	02:00:05
5	Q.	Different three-dimensional structures?	02:00:07
6	A.	Very slightly, yeah.	02:00:11
7	Q.	They synthesize differently?	02:00:15
8	A.	Yes.	02:00:17
9	Q.	I'm sorry?	02:00:20
10	A.	Yes.	02:00:20
11	Q.	And they have different multi-step reaction	02:00:23
12		schemes; right?	02:00:26
13	A.	Yes.	02:00:27
14	Q.	And they'll exhibit different reactivities;	02:00:30
15		right?	02:00:33
16	A.	Well, my point is that their reactivity is	02:00:33
17		very similar.	02:00:39
18	Q.	And they require completely different --	02:00:45
19		they require completely different SPOS protocols;	02:00:47
20		right? S-P-O-S.	02:00:56
21	A.	Not to my knowledge. They just require the	02:00:58
22		use of the 2-fluoro building block during the solid	02:01:01
23		phase synthesis scheme. The building blocks are	02:01:04
24		different, of course.	02:01:08
25	Q.	Let's go back to Exhibit 1018 and then	02:01:12

1	scheme 1.	02:01:19
2	A. Okay.	02:01:27
3	Q. Let's go to scheme 1. So these molecules	02:01:27
4	here in scheme 1, they have OH at the 2 prime	02:01:42
5	position; right?	02:01:47
6	A. Correct.	02:01:48
7	Q. But the molecules in scheme 1 as disclosed	02:01:50
8	in Pitsch do not have regular 2 prime deoxyguanosine	02:01:55
9	as you refer to it; right?	02:02:02
10	A. Correct.	02:02:04
11	Q. So Pitsch doesn't disclose regular 2 prime	02:02:06
12	deoxyguanosine?	02:02:09
13	A. Correct. That's because he's making RNA,	02:02:11
14	not DNA.	02:02:19
15	Q. Let's go to paragraph 125 of your report.	02:02:40
16	You testified that -- let's look at that.	02:02:59
17	Let's go to paragraph 127 of your report.	02:03:03
18	You testified that the only difference between the	02:03:10
19	phosphoramidite claimed in claim 2 of the '885	02:03:14
20	patent where B is guanine-N-acetyl and Z is	02:03:18
21	ribo-fluoro in compound 5 in the '991 patent is that	02:03:25
22	one has guanine and the other has cytosine; right?	02:03:29
23	A. Correct.	02:03:33
24	Q. And if you scroll up to paragraph 126.	02:03:38
25	These are the -- this figure compares the molecules	02:03:49

1	in claim 2 in the '885 patent with, I guess we can	02:03:52
2	call this compound number 5 in the '991 patent?	02:03:58
3	A. Yes.	02:04:01
4	Q. So compound 5 has cytosine as its	02:04:02
5	nucleobase; right?	02:04:12
6	A. Yes.	02:04:14
7	Q. And compound -- and the compound claim in	02:04:16
8	claim 2 has guanosine?	02:04:19
9	A. Yes.	02:04:25
10	Q. Right?	02:04:26
11	Guanine has its nucleobase, excuse me;	02:04:28
12	right?	02:04:30
13	A. Yes.	02:04:31
14	Q. Wouldn't you consider that to be -- these	02:04:36
15	to be fundamentally different molecules?	02:04:39
16	A. I would call them different molecules, but	02:04:44
17	I wouldn't -- fundamentally different molecules	02:04:46
18	would be, for example, if we were trying to compare	02:04:48
19	a steroid to a nucleoside, so I wouldn't use the	02:04:52
20	adjective of fundamentally.	02:04:57
21	Q. Would you say that they're substantially	02:05:02
22	identical?	02:05:03
23	A. I wouldn't use any of that language. I	02:05:04
24	would say they're both just 2-fluoro nucleoside	02:05:05
25	derivatives.	02:05:12

1 Q. And then compound 5, that's an L
2 configuration of cytosine; right?

3 A. Well, the stereochemistry is unclear from
4 the depiction because it is drawn flat. So if you
5 flip compound 5, you end up with the same enantiomer
6 because it is drawn flat. But if you recall from
7 basic organic chemistry, the reactivities of
8 enantiomers do not differ.

9 Q. So you're testifying that these are
10 enantiomers?

11 A. No. My testimony is what I just said.
12 It's --

13 Q. Okay.

14 A. It's unclear because the depiction in
15 compound 5 that is copied right out of the patent is
16 drawn flat. There is no stereochemistry shown here.
17 It is flat. So if I flip it -- if you can draw a
18 pretend mirror between the two molecules and flip
19 it, it's still the same stereochemistry as the '885
20 patent, claim 2.

21 Now, I'm aware that the '991 patent talks
22 about L and D sugars as part of their invention.
23 And my point to you is that the stereochemistry in
24 an absolute sense, whether they use the D or the L
25 sugar is irrelevant to a person of the skill in the

1	art who wishes to make the natural enantiomer of the	02:06:42
2	guanosine derivative because enantiomers react the	02:06:49
3	same.	02:06:53
4	Q. So is your testimony then that the '991	02:06:59
5	patent does not disclose the L configured cytosine?	02:07:02
6	A. I don't recall if they do the -- for	02:07:07
7	compound 5 use L or D or both. To me, it's	02:07:09
8	irrelevant.	02:07:17
9	Q. These molecules are not substantially	02:07:37
10	identical, though; right? I mean --	02:07:40
11	A. I've never heard that terminology before.	02:07:41
12	I don't know what it means.	02:07:43
13	Q. Are they identical?	02:07:46
14	A. They're not identical.	02:07:47
15	Q. They have different nucleobases?	02:07:49
16	A. They have different nucleobases.	02:07:52
17	Q. Claim 2 is deconfigured; right?	02:07:55
18	A. Correct.	02:08:00
19	Q. And this depiction which is in your report	02:08:02
20	that comes from the '991 patent is L configured;	02:08:06
21	right?	02:08:09
22	A. No.	02:08:09
23	Q. It's not L configured?	02:08:13
24	A. There is no stereochemistry. It's flat. I	02:08:15
25	can't assign R and S to those carbons because there	02:08:18

1	is no stereochemistry given. You can flip the	02:08:22
2	structure and it's the same enantiomer. You know	02:08:27
3	what I mean?	02:08:32
4	Q. So what -- why didn't you draw it as a D	02:08:33
5	enantiomer? Are you saying the '991 patent	02:08:40
6	discloses a deconfigured cytosine molecules that's a	02:08:44
7	flipped compound 5?	02:08:52
8	MR. EDWARDS: Object to form. Compound.	02:08:54
9	THE WITNESS: I didn't want to manipulate	02:08:57
10	any of the images from the patent, so I just put	02:08:58
11	what was in the patent here. It can be	02:09:01
12	interpreted -- if I were to show that to any organic	02:09:03
13	chemist and say, assign a stereochemistry, they	02:09:06
14	wouldn't be able to because there is no	02:09:09
15	stereochemistry. It's flat.	02:09:11
16	Now, if the question whether it is D or L,	02:09:12
17	again I'll tell you, it is irrelevant what the	02:09:16
18	stereochemistry is of that sugar because enantiomers	02:09:19
19	have identical reactivity towards achiral reagents.	02:09:24
20	MR. SHORES: The '991 patent, I guess we	02:09:56
21	can put that up, which is --	02:09:58
22	MR. EDWARDS: Exhibit 1020.	02:10:13
23	MR. SHORES: Exhibit 1020, yeah. Thank	02:10:27
24	you.	02:10:29
25	///	

1	BY MR. SHORES:	02:10:34
2	Q. This is a fairly large disclosure. But the	02:10:34
3	'991 patent doesn't disclose guanosine, does it?	02:10:44
4	A. I don't recall.	02:10:52
5	Q. Okay. You don't know one way or the other?	02:10:54
6	We will let the document speak for itself?	02:10:57
7	A. Yeah. I would let the document speak for	02:10:59
8	itself.	02:11:01
9	Q. Okay. And the '991 patent does not	02:11:01
10	disclose the synthesis of compound 5 at all; right?	02:11:08
11	A. The synthesis of compound 5 is depicted in	02:11:21
12	figure 16.	02:11:23
13	Q. Okay. So let's go to figure 16. So your	02:11:25
14	testimony is that this depicts the synthesis -- this	02:11:54
15	figure 16 depicts the synthesis of compound 5?	02:11:56
16	A. Of course.	02:12:01
17	Q. And then where in the description -- so	02:12:04
18	let's go to figure 16, I guess. To your knowledge,	02:12:07
19	is there an example that describes the synthesis of	02:12:39
20	compound 5 in the '991 patent?	02:12:44
21	A. As far as I'm aware, there is a set of	02:12:48
22	reagents and conditions somewhere where reagents	02:12:51
23	used that correspond to A, B, C, D, E, F. I just	02:12:54
24	need time to find it.	02:13:02
25	Q. Okay.	02:13:03

1	A.	Okay. On column 45.	02:13:59
2	Q.	Okay.	02:14:01
3	A.	Starting with example 6, it says on	02:14:03
4		line 54, "The references according to figure 15	02:14:06
5		mean" -- and here we go. On column 46, line 8, "The	02:14:11
6		references to figure 16 mean," and then it defines	02:14:17
7		what A, B, C, D, E, F mean.	02:14:23
8	Q.	That's not a detailed scheme; right?	02:14:32
9	A.	It's far more detailed than you'll get from	02:14:37
10		'885 for which we have nothing.	02:14:40
11	Q.	That wasn't my question.	02:14:45
12	A.	It is detailed enough for a POSA to know	02:14:47
13		exactly what to do.	02:14:49
14	Q.	Okay. You testified -- you can take this	02:15:04
15		down.	02:15:07
16		You testified earlier that -- you testified	02:15:07
17		in your declaration that acetyl has a smaller	02:15:09
18		physical size in lower molecular weight than	02:15:15
19		isobutyryl; right?	02:15:22
20	A.	Correct.	02:15:23
21	Q.	So isobutyryl is a larger molecule; right?	02:15:28
22	A.	It's a larger functional group.	02:15:31
23	Q.	Okay. It is larger than acetyl; correct?	02:15:35
24	A.	Correct.	02:15:40
25	Q.	And isobutyryl is more hydrophobic --	02:15:45

1	isobutyryl group is more hydrophobic than an acetyl	02:15:49
2	group; right?	02:15:53
3	A. I would expect that to be the case, yes.	02:15:54
4	Q. So an acetyl group is more polar than an	02:16:00
5	isobutyryl group?	02:16:03
6	A. That would be my expectation, yes.	02:16:04
7	Q. And you agree that the larger size of	02:16:09
8	isobutyryl would render it more apt to act as a	02:16:16
9	steric shield than acetyl?	02:16:23
10	A. It would be -- when you talk about a steric	02:16:30
11	shield, it always needs to be in reference to	02:16:35
12	something. So in this case it would be a steric	02:16:36
13	shield in reference to the carbonyl group that is	02:16:40
14	attached to the amine of the nucleobase.	02:16:44
15	Q. What if it was attached to the N2 position	02:16:50
16	in guanosine, would isobutyryl tend to, you know,	02:16:55
17	act more as a steric shield than acetyl?	02:17:06
18	A. Relative to the carbonyl group that's	02:17:10
19	attached to the heterocycle, yes.	02:17:12
20	Q. Are you familiar with -- for guanosine, are	02:17:26
21	you familiar with any solubility issues with	02:17:31
22	guanosine in organic solvents?	02:17:38
23	A. Yeah. Many nucleosides often have	02:17:44
24	solubility issues and there are some bespoke	02:17:48
25	protecting groups out there specifically for that	02:17:52

1	conundrum that sometimes people encounter.	02:17:57
2	Q. Just kind of back to the acetyl versus	02:18:08
3	isobutyryl. You agree that under basic conditions	02:18:10
4	that acetyl would have a greater tendency to cleave	02:18:19
5	off from the N2 position of guanosine -- guanine on	02:18:24
6	a guanosine than isobutyryl would; right?	02:18:32
7	A. Under basic nucleophilic conditions, yes.	02:18:37
8	Q. Nucleophilic; right?	02:18:43
9	A. Yes.	02:18:45
10	Q. You agree that TBAF would create those	02:18:45
11	basic conditions?	02:18:52
12	A. No. That's not the normal way people	02:18:55
13	remove the N2 protecting group for TBAF. It can	02:19:02
14	happen by mistake if your TBAF is wet, because then	02:19:09
15	you have hydroxide, but normally the conditions you	02:19:13
16	use to remove these acetyl type protecting groups is	02:19:16
17	an amine like methylamine or ammonia or ethylene	02:19:22
18	diamine. There is many.	02:19:27
19	Q. What about sodium hydroxide?	02:19:30
20	A. Sodium hydroxide is not as clean generally.	02:19:34
21	Q. But back to TBAF, that TBAF would create	02:19:45
22	basic conditions, though. It could cleave	02:19:49
23	isobutyryl from -- or acetyl from a guanosine at the	02:19:53
24	N2 position of guanine; right?	02:20:00
25	A. If the TBAF is wet, but as you can see from	02:20:03

1	Pitsch, if TBAF was sufficient to remove the acetyl	02:20:07
2	groups, there would be no need for the methylamine	02:20:13
3	step. They would just use TBAF for all of that, but	02:20:16
4	they don't do that.	02:20:20
5	Q. And in your practice, do you use TBAF for	02:20:26
6	selective deprotection?	02:20:33
7	A. We have used TBAF over the course of my	02:20:36
8	career dating back to undergraduate days, yes. It	02:20:39
9	is a common reagent.	02:20:42
10	Q. For selective deprotection?	02:20:45
11	A. Well, the word selective has a context	02:20:46
12	associated with it. So generally you use TBAF as a	02:20:50
13	reagent to remove silyl-based protecting groups.	02:20:54
14	Q. I'm sorry. To remove silyl?	02:21:00
15	A. Silyl-based protecting groups.	02:21:02
16	Q. Okay.	02:21:04
17	THE REPORTER: I'm going to ask for a break	02:21:19
18	when you get to a point, Counsel, please.	02:21:20
19	MR. SHORES: Yeah. We can take a break.	02:21:22
20	How much time is left, by the way?	02:21:23
21	THE VIDEOGRAPHER: Off the record at	02:21:26
22	2:21 p.m.	02:21:26
23	(Recess, 2:21 p.m. to 2:33 p.m.)	02:24:07
24	THE VIDEOGRAPHER: Back on the record at	02:33:17
25	2:33 p.m.	02:33:18

1	BY MR. SHORES:	02:33:19
2	Q. Dr. Baran, if we go back to the '991 patent	02:33:23
3	which is Exhibit 1020.	02:33:32
4	A. Okay.	02:33:36
5	Q. Stay here. We have -- Exhibit 1020 we have	02:33:47
6	figure 16 and on the far right we see compound	02:33:52
7	number 5; right?	02:33:55
8	A. Uh-huh. Yes.	02:33:56
9	Q. And my question was whether this was an	02:33:57
10	L configuration of cytosine; right?	02:34:06
11	A. Yes.	02:34:08
12	Q. And I just want to confirm your testimony.	02:34:11
13	Are you saying that this is not an L configuration	02:34:14
14	of cytosine?	02:34:17
15	A. I am saying, based on this graphic, it's	02:34:18
16	impossible to tell.	02:34:21
17	Q. Okay. So if we go to column 16 of the	02:34:23
18	'991 patent. I guess this is sideways now.	02:34:31
19	A. Okay. I'm there.	02:34:43
20	Q. Okay. If we can get the exhibit oriented	02:34:44
21	properly.	02:34:55
22	So if we go to column 16 of the	02:34:55
23	'991 patent.	02:35:06
24	A. Yes.	02:35:07
25	Q. And this is for -- you're there. I want	02:35:09

1	the technician to get there as well.	02:35:11
2	So it should be pretty deep in the PDF	02:35:15
3	here. Let's scroll down. You'll see in the top	02:35:18
4	there column numbers. 16, right. Exactly.	02:35:22
5	And then if -- Dr. Baran, if you look down	02:35:40
6	on line 38.	02:35:43
7	A. Yes.	02:35:45
8	Q. You see a description for figure 16?	02:35:47
9	A. Yes.	02:35:50
10	Q. Could you read that into the record?	02:35:51
11	A. "Figure 16 shows the illustration of	02:35:53
12	2 prime-fluoro-L-cytidine phosphoramidite based on	02:35:57
13	2 prime-fluoro-L-uridine."	02:36:02
14	Q. Right. So does that clarify for you that	02:36:06
15	figure 16 shows L configured cytosine?	02:36:10
16	A. Yes.	02:36:21
17	Q. You said yes?	02:36:21
18	A. Yes.	02:36:22
19	Q. Okay. Thank you.	02:36:22
20	We talked earlier about -- you can take	02:36:28
21	this exhibit down.	02:36:31
22	We talked earlier about the use of TBAF and	02:36:32
23	sodium hydroxide; right? Do you remember that?	02:36:42
24	A. Yes.	02:36:48
25	Q. So with respect to sodium hydroxide, would	02:36:49

1	sodium hydroxide cleave an acetyl attached to the N2	02:36:54
2	position of guanine on a guanosine phosphoramidite?	02:37:18
3	A. You would never treat a phosphoramidite	02:37:18
4	with sodium hydroxide because the first thing that	02:37:18
5	would happen would be the phosphoramidite would	02:37:18
6	hydrolyze. That's the first thing that would	02:37:19
7	happen.	02:37:20
8	Q. Okay. What if it was a -- what if you	02:37:22
9	treated -- what if you treated a guanosine that had	02:37:28
10	protecting groups in its 3 prime and 5 prime	02:37:39
11	positions, you treated that with sodium hydroxide	02:37:45
12	and then the -- if there was a protecting group on	02:37:48
13	the guanine -- N2 position of guanine, would the	02:37:52
14	sodium hydroxide cleave the acetyl group?	02:37:59
15	A. It could. There are examples in literature	02:38:02
16	of where such compounds are treated with sodium	02:38:04
17	hydroxide, but if you do it quickly enough with a	02:38:08
18	low enough molarity of hydroxide, it will not take	02:38:10
19	them off. It really depends on the strength and	02:38:15
20	equivalents and the temperature how much hydroxide	02:38:18
21	you add.	02:38:21
22	Q. And earlier you testified that, you know,	02:38:26
23	acetyl may not be cleaved cleanly with respect to	02:38:31
24	using sodium hydroxide in a similar scenario; is	02:38:35
25	that right?	02:38:39

1	A. It depends on the context. People normally	02:38:39
2	don't use sodium hydroxide for that kind of	02:38:42
3	cleavage. They usually use an amine or ammonia or	02:38:46
4	some derivative of an amine.	02:38:50
5	Q. But you testified earlier that it	02:38:54
6	wouldn't -- it wouldn't -- acetyl wouldn't be	02:38:55
7	cleaved cleanly. What did you mean by "cleanly"? I	02:39:00
8	guess I'm confused by that.	02:39:02
9	A. I think in that context I meant acyl,	02:39:03
10	meaning encompassing isobutyryl, benzoyl, acetyl,	02:39:09
11	any acyl protecting group there may not be as	02:39:12
12	cleanly removed because in the case of RNA, there is	02:39:16
13	some basal level of base sensitivity. So that's why	02:39:19
14	people use generally amines to remove those groups	02:39:25
15	rather than a concentrated solution of sodium	02:39:30
16	hydroxide. It's a little bit strong.	02:39:34
17	Q. Okay. But when you say it's not clean,	02:39:39
18	what does that -- in a general sense, like it	02:39:43
19	doesn't always -- it doesn't cleave all the	02:39:47
20	nucleosides?	02:39:51
21	A. Clean really refers to -- can be correlated	02:39:52
22	directly to a term in organic chemistry we call	02:39:55
23	chemo selectivity. And chemo selectivity refers to	02:39:58
24	a phenomenon where you have multiple functional	02:40:02
25	groups in the molecule, you desire to get reaction	02:40:05

1	at a particular site, and you want to choose	02:40:07
2	reagents that are exquisitely selective so as only	02:40:11
3	to touch the desired site. So sodium hydroxide	02:40:15
4	would be a less chemo selective reagent for use on a	02:40:18
5	full oligonucleotide.	02:40:23
6	Q. Okay. You also testified in your	02:40:28
7	declaration relating to some alleged errors that	02:40:35
8	were made in the claims of the '885 patent. Do you	02:40:42
9	recall that?	02:40:48
10	A. Yes.	02:40:48
11	Q. And the, you know, comments in your	02:40:51
12	declaration focused on the two succinyl and ethyl,	02:40:56
13	right, for M in claims 3 through 5?	02:41:07
14	A. Yes.	02:41:12
15	Q. Succinyl and ethyl are not the same	02:41:13
16	molecules; right?	02:41:16
17	A. Succinyl and -- you mean an ethylene spacer	02:41:18
18	versus a succinyl group? No, they're not the same.	02:41:23
19	Q. They're just different molecules?	02:41:26
20	A. Well, it would be good if you showed me the	02:41:29
21	exact examples because I don't want to be taken out	02:41:33
22	of context.	02:41:35
23	Q. Okay. If we go to your -- I just go to	02:41:36
24	your report.	02:41:39
25	A. Great.	02:41:41

1	Q.	Let's go to Exhibit 1003, paragraph 137, I	02:41:42
2		guess we can start there.	02:41:49
3	A.	Okay.	02:41:50
4	Q.	131, please. So that paragraph there.	02:41:50
5		So here in paragraph 131 you're saying that	02:42:12
6		a POSA would have readily recognized in the context	02:42:15
7		of the claimed invention use Z rather than M that	02:42:18
8		should have been defined as a succinyl group. And	02:42:24
9		then if we scroll down -- it's okay. But here do	02:42:26
10		you recall your testimony, essentially you're saying	02:42:37
11		that acetyl -- I'm sorry -- succinyl should have	02:42:43
12		been ethyl; right?	02:42:49
13	A.	In this context it could be either ethyl or	02:42:50
14		ethylene. Ethylene or ethyl, then people would know	02:42:53
15		that the M is equal to CH ₂ CH ₂ .	02:42:57
16	Q.	Okay. But that's not succinyl?	02:43:01
17	A.	If M is equal to CH ₂ CH ₂ , then that group	02:43:06
18		is a succinyl group.	02:43:12
19	Q.	Okay. I guess I'm -- we're talking about	02:43:22
20		the substitute. You're talking about -- why don't	02:43:25
21		you explain when you -- your testimony or, you know,	02:43:27
22		what are you -- what's the alleged error in?	02:43:33
23	A.	Well, it's not alleged. It's as clear as	02:43:37
24		day. It makes no sense what was written. It is	02:43:40
25		what it is. If we just go to paragraph 130 of my	02:43:42

1	report --	02:43:48
2	Q. Yes.	02:43:51
3	A. -- and you look at where it says Z is equal	02:43:52
4	to C(O)-M-C(O), where M is selected from the group,	02:43:54
5	you can't have succinyl equal to M because then you	02:44:01
6	get a structure which is nonsensical. And I draw	02:44:06
7	that out in the following paragraphs.	02:44:09
8	If it's oxalyl, you then have four carbonyl	02:44:10
9	groups in a row; also nonsense. And hydroquinolynyl	02:44:15
10	would probably be unstable as well.	02:44:21
11	It is a mistake that I think the POSA would	02:44:23
12	recognize that, you know, what was meant here is --	02:44:25
13	this would have been also correct if they just would	02:44:29
14	have said Z is M-NH. And then it would have been	02:44:32
15	fine because people would have understood, oh,	02:44:37
16	succinyl, oxalyl. When you put the carbonyls group	02:44:39
17	in there, you put the carbonyl groups, now	02:44:44
18	everything is doubled up.	02:44:46
19	So from a factual standpoint, this is	02:44:47
20	100 percent wrong.	02:44:53
21	Q. In order to fix that, you would have --	02:44:56
22	what would you do to this claim? I guess you would	02:45:00
23	say where M is selected from the group consisting of	02:45:02
24	succinyl, oxalyl, and hydroquinolynyl, how would you	02:45:05
25	correct this claim?	02:45:11

1	A.	You can -- that's one way to correct it	02:45:13
2		would just be to keep that as it is and then when	02:45:14
3		you see the column above that says Z is --	02:45:18
4	Q.	Yes.	02:45:21
5	A.	-- I would remove -- if I was the patent	02:45:22
6		attorney writing this, I would remove the C(O) on	02:45:24
7		the one side and the C(O) on the other side. That's	02:45:27
8		one way to fix it.	02:45:36
9		Another way to fix it would be to define M	02:45:37
10		as what it is. So in the case of succinyl, it could	02:45:39
11		be CH ₂ CH ₂ . It could be ethylenol. It could be	02:45:43
12		ethyl. In the case of oxalyl, M is equal to	02:45:48
13		nothing. In the case of hydroquinolynyl, it is	02:45:52
14		equal to a different type of aromatic unit that you	02:45:57
15		would have to define, but you can't have both be	02:46:01
16		true at the same time.	02:46:04
17		So there is a few ways to fix this to make	02:46:05
18		it make sense. Otherwise, you're just relying on	02:46:09
19		the POSA knowing -- you know, hopefully knowing what	02:46:13
20		you mean.	02:46:15
21	Q.	So when you look at paragraph 138 of your	02:46:35
22		declaration -- we're talking about claim 3, so if we	02:46:38
23		go to paragraph 138, your testimony is that a POSA	02:46:45
24		would have understood that claim 3 of the '885	02:46:53
25		patent where B is guanine-N-acetyl, W is	02:46:55

1 ribo-fluoro, and Z is a succinyl group bound to NH,
2 such that M is ethyl claims the following molecule.
3 So are you substituting ethyl for succinyl in that
4 claim?

5 A. Am I substituting ethyl for succinyl? I'm
6 substituting the word ethyl in what you've written
7 to make it make sense.

8 MR. SHORES: And, Counsel, I may be coming
9 to the end of my, you know, questions. I need to
10 take a break.

11 MR. EDWARDS: Okay. Go ahead.

12 THE VIDEOGRAPHER: Off the record at
13 2:48 p.m.

14 (Recess, 2:48 p.m. to 3:01 p.m.)

15 THE VIDEOGRAPHER: Back on the record at
16 3:01 p.m.

17 MR. SHORES: Okay. I have no further
18 questions at this time.

19 MR. EDWARDS: No redirect. I think that
20 closes it.

21 THE WITNESS: Thank you, sir.

22 THE VIDEOGRAPHER: All right. This
23 concludes today's deposition. Time off the record
24 is 3:02 p.m.

25 (Deposition adjourned at 3:02 p.m.)

1 CERTIFICATE OF CERTIFIED SHORTHAND REPORTER

2
3 I, Cynthia J Vega, certified shorthand
4 reporter for the State of California, do hereby
5 certify:

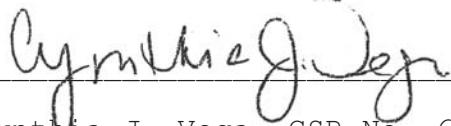
6 That Phil S. Baran, Ph.D., the witness whose
7 deposition is hereinbefore set forth, was duly sworn
8 by me before the commencement of such deposition and
9 that such deposition was taken before me and is a
10 true record of the testimony given by such witness.

11 I further certify that the adverse party,
12 Shanghai Hongene Biotech Corporation, was
13 represented by counsel at the deposition.

14 I further certify that the deposition of
15 Phil S. Baran, PhD, occurred at the offices of
16 Procopio, Cory, Hargreaves & Savitch, 12544 High
17 Bluff Drive, Suite 300, San Diego, California, on
18 Wednesday, September 13, 2023, commencing at
19 8:04 a.m. to 3:02 p.m.

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

1 IN WITNESS WHEREOF, I have hereunto set my
2 hand this 18th day of September, 2023.

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8 Cynthia J. Vega, CSR No. 6640
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ERRATA SHEET

No. 505051

Re: Deposition of **Phil S. Baran, Ph.D.**

Date: 9/13/2023

Case: Shanghai Hongene Biotech Corporation -v- Chemgenes Corporation (PTAB)

Return to: transcripts@planetdepos.com

Reason codes:

1. To clarify the record.
2. To conform the facts.
3. To correct transcription errors.

Page No.	Line No.	Reason	Change
43	2-7	3	Change “nucleotides” to “nucleotide”
75	19	3	Change “entry” to “entrant”
114	16-20	3	Replace entire answer with “N2-Isobutyryl-9-(2'-deoxy-2'-fluoro-5'-O-[4,4-Dimethoxytrityl]-guanosine-3'-O-N,N-diisopropyl-β-D-cyanoethyl phosphoramidite.”
162	10	3	Change “impurity” to “acetic anhydride”
172	17	3	Change “deconfigured” to “D-configured”
173	6	3	Change “deconfigured” to “D-configured”
100	7	3	Change “lab” to “lett”



SIGNATURE

10/3/2023

DATE