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Transcript of Patrick J. Hrdlicka, Ph.D.

Date: December 20, 2023

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

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

Transcript of Patrick J. Hrdlicka, Ph.D.
Conducted on December 20, 2023

1 (1 to 4)

1 UNITED STATES PATENT AND TRADEMARK OFFICE 2 ----- 3 BEFORE THE PATENT TRIAL AND APPEAL BOARD 4 ----- 5 SHANGHAI HONGENE BIOTECH CORPORATION, 6 Petitioner, 7 V. 8 CHEMGENES CORPORATION, 9 Patent Owner. 10 ----- 11 IPR2023-00490 12 U.S. Patent No. 9,884,885 B2 13 14 Videotaped Deposition of PATRICK J. HRDLICKA, PH.D. 15 Washington, D.C. 16 Wednesday, December 20, 2023 17 9:44 a.m. 18 19 20 Job No. 518522 21 Pages 1 - 197 22 Reported by: Karen Young	3 1 A P P E A R A N C E S 2 ON BEHALF OF SHANGHAI HONGENE BIOTECH 3 CORPORATION: 4 STEVEN MADDOX, ESQUIRE 5 BRETT GARRISON, ESQUIRE 6 PROCOPIO, CORY, HARGREAVES & SAVITCH, LLP 7 1901 L Street, NW 8 Suite 620 9 Washington, D.C. 20036 10 (202) 830-0238 11 12 ON BEHALF OF CHEMGENES CORPORATION: 13 DANIEL L. SHORES, ESQUIRE 14 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 15 One Boston Place 16 Suite 2600 17 Boston, Massachusetts 02108 18 (617) 312-3101 19 20 21 22
2 1 Videotaped Deposition of PATRICK J. HRDLICKA, 2 PH.D., held at the offices of: 3 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 4 901 New York Avenue, Northwest 5 Suite 900 East 6 Washington, D.C. 20001 7 (202) 783-6040 8 9 10 11 12 Pursuant to notice, before Karen Young, 13 Notary Public of the District of Columbia. 14 15 16 17 18 19 20 21 22	4 1 AYDIN H. HARSTON, PH.D., ESQUIRE 2 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 3 901 New York Avenue, NW 4 Suite 900 East 5 Washington, D.C. 20001 6 (202) 783-6040 7 8 ALSO PRESENT: 9 Chris Melton, Videographer 10 Jeremy Little, Ph.D., ChemGenes (remote) 11 Yann Tillier, ChemGenes (remote) 12 Anuj Mohan Srivastava, ChemGenes (remote) 13 Kevin O'Connor, Esquire, ChemGenes (remote) 14 Phil Baran, Ph.D. (remote) 15 16 17 18 19 20 21 22

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2 (5 to 8)

5	7
1 C O N T E N T S	1 P R O C E E D I N G S
2 EXAMINATION OF PATRICK J. HRDLICKA, PH.D. PAGE	2 (Exhibits were previously marked.)
3 By Mr. Maddox..... 8	3 THE VIDEOGRAPHER: Here begins Media
4	4 Number 1 in the videotaped deposition of Patrick
5	5 Hrdlicka in the matter of Shanghai Hongene Biotech
6 EXHIBITS REFERRED TO	6 Corporation versus ChemGenes Corporation in the
7 (Exhibits retained by counsel.)	7 United States Patent Trial and Appeal Board, Case
8 Exhibit 1001 U.S. Patent No. 9,884,885 B2.... 9	8 Number IPR2023-00490. Today's date is December
9 Exhibit 1003 Declaration of Phil S. Baran,	9 20th, 2023. The time on the video monitor is 9:44
10 Ph.D..... 153	10 a.m. The videographer today is Chris Melton,
11 Exhibit 1007 Tetrahedron Report Number 309... 27	11 representing Planet Depos. This video deposition
12 Exhibit 1018 Paper by Pitsch et al..... 34	12 is taking place at 901 New York Avenue, Northwest,
13 Exhibit 1019 Paper by Fan et al..... 132	13 Washington, D.C. 20001. Would counsel please
14 Exhibit 1020 U.S. Patent No. 7,879,991 B2.... 177	14 voice-identify themselves and state whom they
15 Exhibit 1029 Paper by Donga et al..... 147	15 represent.
16 Exhibit 2008 Declaration of Patrick J.	16 MR. MADDOX: This is Steven Maddox and
17 Hrdlicka, Ph.D..... 9	17 Brett Garrison of the Procopio firm. We represent
18 Exhibit 2012 Paper by Shaller et al..... 140	18 the petitioner, Hongene. Also present is Dr. Phil
19 Exhibit 2013 Paper by Schulhof et al..... 117	19 Baran. He's on the telephone remotely.
20 Exhibit 2014 Paper by Guschlbauer and	20 MR. SHORES: And for patent owner, Dan
21 Jankowski..... 183	21 Shores from the law firm Rothwell Figg. Here with
22 Exhibit 2015 Paper by Ober et al..... 163	22 me is my colleague, Aydin Harston, and joining via
6	8
1 Exhibit 2016 Paper by Radhakrishnan P. Iyer.. 123	1 Zoom is Kevin O'Connor from ChemGenes Corporation,
2 Exhibit 2018 Paper by Sinha et al..... 130	2 Anuj Mohan, also from ChemGenes Corporation, as
3 Exhibit 2024 "Analysis of Oligonucleotides	3 well as Jeremy Little and Yann Thillier,
4 and their Related Substances"..... 129	4 T-H-I-L-L-I-E-R, also from -- and all from
5 Exhibit 2029 ChemGenes Catalog..... 37	5 ChemGenes Corporation.
6	6 THE VIDEOGRAPHER: The court reporter
7	7 today is Karen Young, representing Planet Depos.
8	8 The witness will now be sworn.
9	9 PATRICK J. HRDLICKA, PH.D.,
10	10 having been duly sworn, testified as follows:
11	11 EXAMINATION BY COUNSEL FOR
12	12 SHANGHAI HONGENE BIOTECH CORPORATION
13	13 - - -
14	14 BY MR. MADDOX:
15	15 Q Good morning, Doctor.
16	16 A Good morning.
17	17 Q Have you had your deposition taken
18	18 before?
19	19 A Yes.
20	20 Q Okay. So I won't dwell on it, but you
21	21 know it's a bunch of questions to which you must
22	22 answer unless you're instructed not to, and that

9 1 your attorney may from time to time put in 2 objections, correct? 3 A I understand. 4 Q And that regardless of his objections, 5 unless he instructs you not to answer, you do have 6 to answer to the best of your ability. 7 A I understand. 8 Q Okay. I've put in front of you two 9 exhibits, Exhibit Number -- these are all 10 previously marked exhibits today, Exhibit Number 11 2008, which is your declaration in this matter, and 12 Exhibit Number 1001, which is the '885 patent, 13 about which -- the validity of this patent's at 14 issue in this proceeding. Do you recognize them as 15 such? 16 A I do. 17 Q Okay. Throughout today, please feel free 18 to refer to them or any other exhibit, and if you 19 -- if there's an exhibit that is not in front of 20 you that you would like to refer to, please let me 21 know and I'll get it for you, all right? 22 A Okay, thank you.	11 1 have a lot of experience in P(III) phosphoramidite 2 chemistry, correct? 3 MR. SHORES: Object to form. 4 A I know my testimony, which is as -- which 5 is provided and given that I place an emphasis on 6 phospho(III) chemistry, there are some questions 7 that could be raised there. 8 Q But you don't have an opinion one way or 9 the other as to whether Dr. Baran let's say in 2009 10 met that definition? 11 MR. SHORES: Object to form, lack of 12 foundation. 13 A So according to my definition as I've 14 testified as provided here, as of 2009, I don't 15 believe that Dr. Baran would be a POSA. 16 Q Okay. And is it fair to say that is in 17 large part due to the specific requirements of 18 P(III) chemistry? 19 MR. SHORES: Object to form. 20 BY MR. MADDOX: 21 Q Let me rephrase that. Your -- your 22 opinion that in 2009 he was not a person of
10 1 Q Okay. I'd like to first turn to your 2 definition of the person of ordinary skill. You 3 may find that around paragraph 24 of your -- I beg 4 your pardon, around paragraph 90. 5 A Yeah, I'm there. 6 Q Okay. First question is given how you 7 define the person of ordinary skill in the art, is 8 it your opinion that Dr. Baran is a person of 9 ordinary skill in the art today? 10 A That is not something that I have 11 provided an opinion on. You're asking me whether 12 he is a person of skill in the art today. 13 Q Yes. 14 A As of 2023. 15 Q Right. 16 A I haven't provided an opinion on that. 17 Q Okay, and do you hold an opinion on that? 18 A I could speculate, but I -- I -- 19 according to my definition, I haven't provided an 20 opinion on that, so -- 21 Q Okay. Well, you are -- you are familiar 22 with -- with ChemGenes' contention that he does not	12 1 ordinary skill in the art is based in significant 2 part on his background or lack thereof in P(III) 3 chemistry, phosphoramidite chemistry? 4 A It is based on the fact that I don't 5 think he -- he meets the definition as I have put 6 forth. 7 Q And that definition is focused on 8 phosphoramidite P(III) chemistry, correct? 9 A My definition contains several elements, 10 which as you can see in the red line, my suggestion 11 here, for example, in the first paragraph is that a 12 person of skill in the art would have a Ph.D. in 13 organic chemistry, at least two to three years of 14 postgraduate work experience in the development and 15 synthesis of nucleosides, nucleotides and nucleic 16 acids, including but not limited to the synthesis 17 of oligonucleotides through solid phase 18 oligonucleotide synthesis, which going forward we 19 can define as SPOS, pursuant to phospho(III) 20 chemistry. So there are several elements to that, 21 which includes phospho(III) chemistry. 22 Q Okay. There are other types of

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13 1 chemistry, phosphoramidite chemistry, other than 2 III, correct? 3 A I believe that the technical definition 4 of a phosphoramidite actually is phospho(III). 5 Q Okay. Now, in -- for your person of 6 ordinary skill in the art, literature involving 7 P(III) chemistry would be the most relevant, 8 correct? 9 A Relevant to what? 10 Q To -- to -- to developing something using 11 P(III) chemistry. 12 A I find that question a little bit hard to 13 answer. I mean, literature encompasses nucleosides 14 and phospho(III) chemistry material that -- 15 Q Right. 16 A -- would be relevant for -- for the 17 matter at hand, I think we're talking about 18 nucleoside chemistry, phospho(III) chemistry. 19 Q And to the extent the references we're 20 discussing do not involve phospho(III) chemistry, 21 they would be less relevant than the references 22 that do involve phospho(III) chemistry, yes?	15 1 A -- chemistry, some of the reviews, for 2 example, yeah. 3 Q And what I'm asking is to a person of 4 ordinary skill in the art as you've defined them, a 5 reference discussing phosphodiester chemistry 6 versus a reference discussing phospho(III) 7 chemistry, the phospho(III) chemistry reference 8 would be more relevant, correct? 9 MR. SHORES: Object to form. 10 BY MR. MADDOX: 11 Q Would be of greater interest. 12 A I think that for the matter at -- for the 13 case here before us, I believe that papers 14 discussing nucleoside chemistry and phospho(III) 15 chemistry are of -- of relevance. 16 Q Okay. Now, when you say nucleoside 17 chemistry, that is something other than 18 phospho(III) chemistry? 19 A Well, I mean, you could say slightly 20 different or an extension of. 21 Q But a person of ordinary skill in the art 22 would have to have phospho(III) chemistry
14 1 MR. SHORES: Object to form. 2 A Could you repeat the question please? 3 Q There are a bunch of references being 4 discussed in your declaration and in Dr. Baran's, 5 correct? 6 A There are many references being 7 discussed. 8 Q Right, okay. Some of those are -- 9 concern phospho(III) chemistry, correct? 10 A Some of those concern phospho(III) 11 chemistry. 12 Q And some of those do not, correct? 13 A That's correct, and there -- and some of 14 the references include nucleoside chemistry and 15 phospho(III) chemistry both. 16 Q Okay, and some involve phosphodiester 17 chemistry, correct? 18 A Some of the references that are cited in 19 this case by petitioner or by me, I think mostly by 20 petitioner, involve other types of -- of 21 phosphodiester -- 22 Q Uh-huh.	16 1 experience, correct? 2 A For this -- for the matter at hand. 3 Q For this matter, yes. 4 A Surely it's my opinion that a person of 5 skill in the art would be knowledgeable in 6 nucleoside chemistry and phospho(III) chemistry. 7 Q In reaching that definition, did you 8 consider whether Dr. Baran in your opinion would 9 meet the requirements for a person of ordinary 10 skill in the art in 2009? 11 A Could you repeat? 12 Q In deciding how you would define the 13 person of ordinary skill in the art, did you 14 consider that your definition would exclude 15 Dr. Baran as a person of ordinary skill in the art 16 in 2009? 17 A My -- my definition of a POSA had nothing 18 to do with Dr. Baran. It had to do with what I 19 consider to be -- what I considered a person of the 20 skill of the art being in -- in -- in view of the 21 case before us. 22 Q And you consider yourself a person of

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17 1 ordinary skill in the art as of 2009 under your 2 definition, yes? 3 A Yes. 4 Q Do you consider yourself a person of 5 ordinary skill in any other arts or just 6 phospho(III) chemistry? 7 A Of any other arts. I mean -- so -- 8 Q Well -- 9 A I've -- I can provide an opinion on 10 relative to my definition, which I think is broader 11 than just phospho(III) chemistry, as indicated by 12 the word including but not limited to. I consider 13 myself a person of skill in the art in nucleosides, 14 nucleotides, nucleic acids, including phospho(III) 15 chemistry. 16 Q Okay, so perhaps I've stumbled on a 17 language when you say including but not limited to. 18 In your definition as you have drafted it -- 19 A Uh-huh. 20 Q -- is a -- either a thesis on 21 phospho(III) chemistry or a focus of work 22 experience on phospho(III) chemistry a requirement?	19 1 that to require a focus on phospho(III) chemistry, 2 or is that one of many chemistries that would 3 suffice? 4 MR. SHORES: Object to form, and also to 5 the extent it mischaracterizes the witness' 6 testimony. 7 A A POSA should have work -- experience in 8 development and synthesis of nucleosides, 9 nucleotides and nucleic acids, which would include 10 but not limit the synthesis of oligonucleotides. 11 Q Okay. Let me -- I'm sorry, I don't mean 12 to cut you off. 13 A No, it's okay. 14 Q Would -- if we said which must include, 15 would that still be your definition? I'm having 16 trouble with including but not limited to, whether 17 that's a mandatory -- whether what follows is 18 mandatory. 19 MR. SHORES: Object to form and asked and 20 answered. 21 A So again, I mean, including but not 22 limited to the synthesis of solid -- of
18 1 A As I've provided testimony to a person of 2 the skill in the art would have either a Ph.D. in 3 organic chemistry, and then at least two to three 4 years of postgraduate work in the development and 5 synthesis of nucleosides, nucleotides and nucleic 6 acids including but not limited to the synthesis of 7 oligonucleotides through solid phase synthesis 8 pursuant to phospho(III) chemistry, alternatively, 9 someone with a Ph.D. in organic chemistry who 10 during their Ph.D. focused on the development and 11 synthesis of the subject matter I just referenced 12 would be considered a POSA, or as I've drafted 13 here, somebody who has a bachelor's, a master's 14 degree in organic chemistry and then had at least 15 five years of extensive work experience in those 16 fields relating now back again to nucleosides, 17 nucleotides, nucleic acids and so and so forth, and 18 who had obtained a thorough understanding of 19 syntheses of phospho(III) chemistry would be a 20 POSA. 21 Q And I'm sorry, what I'm unclear on, it's 22 the including but not limited to. Is the effect of	20 1 oligonucleotides by SPOS pursuant to phospho(III), 2 it says including but not limited to. 3 Q Okay. With respect to the law you were 4 given to apply, you refer in your report -- in your 5 declaration many times to something called a lead 6 compound. Do you recall that? 7 A Yes, I recall that. 8 Q And were you instructed that a lead 9 compound analysis must be applied to this case? 10 MR. SHORES: Objection, and calls for 11 attorney work product, so -- 12 MR. MADDOX: No, it asked for what he was 13 instructed to -- to apply. 14 MR. SHORES: It asked for a 15 communication. If there's a particular area in his 16 report you want to point to -- 17 BY MR. MADDOX: 18 Q Were you instructed that the legal 19 standard to apply here is a lead compound analysis? 20 MR. SHORES: Objection. That's attorney 21 work product. 22 MR. MADDOX: Okay. You want to give him

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21 1 an instruction? 2 MR. SHORES: Instruct you not to answer 3 that question. Ask it a different way. I mean, I 4 think it's the subject matter that you're looking 5 for -- 6 BY MR. MADDOX: 7 Q You -- you -- 8 MR. SHORES: -- might be obtained in a 9 more reasonable way. 10 BY MR. MADDOX: 11 Q You applied a lead compound analysis in 12 your opinion, didn't you? 13 A That's correct. 14 Q Okay. And why did you apply a lead 15 compound analysis? 16 A It was my -- it's my understanding that 17 that's the most appropriate way to -- to view the 18 matter before us. 19 Q And what did that understanding come 20 from? 21 A So here I'm in doubt whether I'm allowed 22 to --	23 1 fine, going off the record. 2 THE VIDEOGRAPHER: We are going off the 3 record. The time is 10:01 a.m. 4 (Discussion off the record) 5 THE VIDEOGRAPHER: We are back on the 6 record. The time is 10:04 a.m. 7 BY MR. MADDOX: 8 Q Dr. Hrdlicka, if you could get your 9 Exhibit 2008 -- 10 A Uh-huh. 11 Q -- your declaration, and turn to page 18? 12 A Yeah, I'm there. 13 Q You see in paragraph 47, your first 14 sentence is, "I further understand that in 15 situations involving a new chemical compound, one 16 must employ a lead compound analysis." Okay, and 17 could you tell me how you came to that 18 understanding? 19 A So in -- it was through control with 20 counsel -- through conferral. Through conversation 21 with counsel. 22 Q It was based on -- on your conversations
22 1 MR. SHORES: Yeah, I object to the extent 2 it calls for a legal conclusion. I mean -- 3 THE WITNESS: Or if I'm allowed to 4 disclose conversations that I've -- 5 MR. SHORES: No, you are -- 6 MR. MADDOX: I'm not asking -- 7 MR. SHORES: -- not allowed to do that. 8 BY MR. MADDOX: 9 Q Let's be clear. I'm not asking you to 10 disclose conversations. I'm asking him how he 11 concluded that a lead compound analysis was the 12 most appropriate, in his words. 13 MR. SHORES: And my objection is I object 14 to the extent it calls for a legal conclusion. 15 MR. MADDOX: Do you want to confer with 16 him and see if he can answer in some way that 17 wouldn't object or do you want to instruct, or what 18 would you like to do? 19 MR. SHORES: Yeah, maybe we can take a 20 minute. 21 MR. MADDOX: Okay. 22 MR. SHORES: Yeah, sounds good, Steve,	24 1 with counsel, your understanding. 2 A Yes. 3 Q If we look at the next sentence too, "I 4 understand that a lead compound is defined as a 5 compound in the prior art that would be most 6 promising to modify in order to improve upon its 7 activity and obtain a compound with a better 8 activity." Is that understanding also based on 9 your conversations with counsel as to the law? 10 A Yes. 11 Q Okay. And so that is the analysis, the 12 lead compound analysis is what you applied in doing 13 your -- your declaration. 14 A For certain of those claims, certain 15 claims, disputed claims, yes. 16 Q And so in each case you looked for 17 whether a person of ordinary skill in the art would 18 find something to be the most promising candidate? 19 A Could you repeat the question? 20 Q You looked for what the person of 21 ordinary skill in the art would say is the most 22 promising compound?

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25 1 MR. SHORES: Objection to the extent it 2 mischaracterizes his testimony. 3 A I was charged with analyzing the petition 4 and Dr. Baran's declaration, and I analyzed it in 5 view of a lead compound analysis. 6 Q You recall that you offered some opinions 7 with respect to compound X in the '031 patent? 8 A I do, and I would appreciate if I could 9 -- 10 Q Absolutely. 11 A -- obtain that exhibit. 12 Q Sure. Can I get 1017? Bear with me a 13 sec. And we can get on the same page. This is -- 14 so you've been given Exhibit -- what's previously 15 been marked as Exhibit 1017. It's the '031 patent, 16 discussed in your declaration, among other places, 17 and if you -- you can certainly refer to anything 18 you'd like, but you may want to look at column 27, 19 which is where we'll find compound X. It's -- 20 A Yeah. 21 Q -- found on the bottom of the left-hand 22 column. You see that? And it's your position that	27 1 you an article you cited. May I have 1007? Give 2 you what's been previously marked Exhibit 1007. 3 Take a look if you will. You can review as much as 4 you'd like, but this -- you recognize this as one 5 of the articles you cited for the state of the art? 6 I can maybe help you. 7 A Yeah, no, I've -- so first off, this 8 exhibit was also cited by -- by petitioner and 9 Dr. Baran, but yes, it's correct that on -- in 10 paragraph 66, I -- I describe -- I cite this paper 11 -- 12 Q Right. 13 A -- and describe the tremendous amount of 14 adversity there has been developing in SPOS over 15 the decades. 16 Q Now, was there some adversity discussed 17 in this article that the article said has not been 18 overcome yet? 19 A This -- 20 MR. SHORES: I'm going to object to -- to 21 form. Is there a particular -- 22 BY MR. MADDOX:
26 1 compound X does not meet the lead compound 2 requirements under the standard you were given, 3 correct? 4 A That has been my testimony. 5 Q Okay, and why -- why does it not meet 6 that requirement? 7 A So first, as I provide testimony on in my 8 declaration in paragraph 101, compound X is a 9 compound among hundreds if not thousands of -- of 10 compounds, so in analyzing the petition and 11 Dr. Baran's declaration, I saw no argument for why 12 -- why compound X should have been selected. It's 13 one of many compounds. 14 Q Did you identify a compound which -- 15 which would be the lead compound for a person of 16 ordinary skill in the art in this context? 17 A I did not provide any opinions thereto. 18 Q Now, you recall giving some opinions 19 regarding the state of the art relevant to this 20 case, correct? 21 A Relevant to the -- yeah, yes. 22 Q Relative to the '885. And let me give	28 1 Q Well, it's a big long review article, and 2 you talk about adversity, and my question is have 3 the adversities that are discussed in this article, 4 didn't the article also report how they had been 5 overcome over the course of history? 6 MR. SHORES: Object to form, lack of 7 foundation. 8 A This -- this is a review that describes 9 developments and stepwise improvements moving 10 forward in this field, but chemistry is an 11 ever-evolving science, and it's -- SPOS is not a 12 black box. It's not at a black box level where one 13 can assume that it's going to work. There's a 14 considerable amount of unpredictability still 15 entailed in this field of research -- 16 Q Okay. 17 A -- for certain aspects. 18 Q And did this article describe that -- 19 that unpredictability, those areas of 20 unpredictability? 21 MR. SHORES: Objection, lack of 22 foundation.

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29 1 A Per se, I have not provided a direct 2 opinion on that, but this is a hundred page review, 3 so that in and by itself shows the tremendous 4 amount of work that has gone in over the many -- 5 many decades in order to -- to -- to advance the 6 field of -- of SPOS, of solid phase oligonucleotide 7 synthesis to the level where it's today, but I 8 don't believe that any researcher would say that's 9 it, we're done, dust it and done and can stop 10 working. There are adversities. 11 MR. SHORES: Please let him complete -- 12 THE WITNESS: No, no. 13 MR. SHORES: -- his answer, yeah. Are 14 you -- are you finished -- 15 THE WITNESS: Yeah, I'm done. 16 MR. SHORES: -- with your answer? Thank 17 you. 18 BY MR. MADDOX: 19 Q And this article was approximately 1992, 20 correct? 21 A Correct. 22 Q The early '90s.	31 1 Q Okay. It's the challenges that lie ahead 2 that I'd like to ask you about. What were the 3 challenges it identified as lying ahead? 4 MR. SHORES: Same objections. 5 A I have not cited to specific sections of 6 this article, to the best of my recollection, that 7 speak to the challenges lying ahead, but there are 8 undoubtedly -- in each and every area, there were 9 undoubtedly challenges that still were lying ahead 10 that called for -- for improvement because the 11 chemistry here is -- the advances are hard fought, 12 and chemistry is unpredictable. 13 Q Is that specifically phospho(III) 14 chemistry or all chemistry? 15 A That is -- could you perhaps rephrase the 16 question? 17 Q Well, you've made a statement about the 18 chemistry is X, Y and Z. 19 A Uh-huh. 20 Q And I'm saying is that specific to 21 phospho(III) chemistry or to all chemistry? 22 MR. SHORES: Object to form and to the
30 1 A Yeah, early '90s. 2 Q So I understand you to say that this 3 article describes all the wonderful work that has 4 been done and the hurdles that have been overcome 5 up through 19 -- up through its publication in 6 SPOS, correct? 7 A Correct, for logical matters that cannot 8 speak about the matters that have occurred after 9 1992. 10 Q Right, and so as of 1992, did this 11 article identify areas that were still problematic 12 and unpredictable? 13 MR. SHORES: Object to form, lack of 14 foundation. Object to the extent it 15 mischaracterizes the exhibit. 16 A I have not -- I do not believe I have 17 cited to specific -- a specific page where it said 18 oh, this matter has been resolved, but in those 19 hundred pages, in the course of these hundred 20 pages, this review defines the framework, says what 21 the -- what the -- what progress has been made and 22 what challenges lie ahead.	32 1 extent it mischaracterizes his prior testimony. 2 A I think there are challenges in all 3 aspects of nucleoside chemistry, phospho(III) 4 chemistry that still can be improved upon. 5 Q Uh-huh, and -- 6 A Sorry, no, go ahead, Counsel. 7 Q And the -- the presence of challenges to 8 be improved upon in phospho(III) chemistry, that is 9 true today? 10 MR. SHORES: Object to form, lack of 11 foundation, document speaks for itself. 12 A There are challenges -- nucleoside 13 chemistry, phospho(III) chemistry is still -- is a 14 complex subject matter. 15 Q There are parts of it that are generally 16 regarded as fairly standard now though, right? 17 MR. SHORES: Object to form. 18 A Parts of -- could you -- 19 Q Phospho(III) chemistry. 20 A Parts of phospho(III) chemistry. I'm -- 21 there are parts of phospho(III) chemistry that are 22 considered more -- with certain types of

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33 1 modifications probably are considered more routine 2 than with -- with others, but again, nothing is 3 certain in -- in -- in chemistry, and certainly 4 this branch of chemistry. 5 Q Okay. Because nothing is certain in this 6 branch of chemistry, as you say, does it follow for 7 you that nothing can be reasonably predictable in 8 this branch of chemistry? 9 MR. SHORES: Object to form. 10 A In -- in my opinion, chemists working in 11 this field always have an amount of healthy 12 skepticism and always keep eyes open for potential 13 challenges. 14 Q So when they do their work, they never 15 have a reasonable expectation of success in 16 whatever they're trying? 17 MR. SHORES: Object to form and to the 18 extent it calls for a legal conclusion. 19 A Chemists don't deal in absolutes. It's 20 -- it's -- it's -- you know, some protocols may be 21 more likely to work than -- than others. It's a 22 question of probabilities, but ultimately you don't	35 1 to the development of a reliable chemical synthesis 2 of nucleic acids." Do you agree with that sentence 3 as of the time this was published, 2001? 4 A So first off, I acknowledge that the 5 sentence is present in this paper, "During the last 6 decades, many research groups have successfully 7 contributed to the development of the reliable 8 chemical synthesis of nucleic acids." It's a very 9 broad statement, and it very much boils down to 10 what is the definition of nucleic acids here. 11 Q How so? When you say it boils down to 12 that, how's that? 13 A The term "nucleic acids" encompasses -- 14 can encompass a plethora of different types of 15 species. 16 Q Uh-huh. If we can just look at the next 17 sentence, "As a consequence, the synthesis of DNA 18 oligonucleotides is probably the most evolved 19 chemical process known so far and has almost 20 reached perfection in terms of efficiency and 21 automation." Do you agree with that sentence as of 22 the 2011 date of this article?
34 1 know what the probabilities are. You have a 2 general sense of where something might go, but 3 there's -- there's always an element of uncertainty 4 because the science is challenging and 5 unpredictable, sometimes so unpredictable you 6 didn't predict it, the problems that are happening. 7 Q I've handed you what's been previously 8 marked as Exhibit 1018. Do you recognize this as 9 the Pitsch article -- 10 A I do. 11 Q -- you referred to in your declaration, 12 and Dr. Baran referred to? 13 A I do. 14 Q Okay. Could you look at -- well, first, 15 you can look at any part of the article you want to 16 answer the question, but I have a certain portion 17 I'd like to discuss. 18 A Okay, fair. 19 Q On the first page there, the first 20 paragraph -- I'm sorry, the second paragraph, the 21 introduction starts with, "During the last decades, 22 many research groups have successfully contributed	36 1 MR. SHORES: Objection to the extent -- 2 the document speaks for itself. Objection to the 3 extent that mischaracterizes the document, lack of 4 foundation. 5 BY MR. MADDUX: 6 Q Do you have the question in mind? 7 A No, I'm -- 8 MR. SHORES: There's a pending question? 9 THE WITNESS: Yeah 10 MR. SHORES: Take your time. 11 THE WITNESS: No, no, no. 12 BY MR. MADDUX: 13 Q It was -- it was do you agree with that 14 sentence, and there were objections, which we can 15 take as reasserted or you can say them again if you 16 want. 17 A The sentence is very flowery in my 18 opinion. I don't know how to evaluate the most 19 evolved chemical process known so far and has 20 almost reached perfection, those are very flowery 21 terms that -- I don't necessarily think that that 22 statement, as broad as it is, because it speaks

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37 1 about any chemical processes here, I'm not sure I 2 would agree with that. It's very flowery, it's 3 very broad, it's very complimentary, but I think 4 it's overly broad. 5 Q So -- so you disagree with -- in that 6 sense. 7 A I would not have written the sentence 8 like this, had I been the author. 9 Q Understood. Now I'd like to give you -- 10 bear with me a second. Can I have 2029? The 11 reporter has just handed you what's been previously 12 marked as Exhibit 2029. This is an exhibit to your 13 declaration, ChemGenes' catalog you identified as 14 being from 1999. Do you recognize it? 15 A I don't -- 16 MR. SHORES: I object to lack of 17 foundation, also to the extent it mischaracterizes 18 facts in evidence. 19 BY MR. MADDOX: 20 Q Okay. 21 A Okay, sorry, so your question is? 22 Q Did you cite this ChemGenes catalog in	39 1 Q Uh-huh. 2 MR. SHORES: So page 51 of Exhibit 2029? 3 MR. MADDOX: Yes. 4 MR. SHORES: Okay. 5 BY MR. MADDOX: 6 Q And it says here -- actually, if you go 7 in the first under RNA synthesis -- 8 A Uh-huh. 9 Q And one, two, three, four lines up from 10 the bottom -- 11 A Uh-huh. 12 Q -- it says, "Chemical synthesis of RNA 13 has been perfected to the extent that long 14 sequences, such as biologically active 76-mer tRNA 15 and multi-milligram quantities can be produced 16 efficiently." Would you agree with that sentence 17 as of 2009? 18 MR. SHORES: Objection, lack of 19 foundation and to the extent it mischaracterizes 20 the exhibit. 21 A So first off, this is the first time I'm 22 seeing --
38 1 your declaration? 2 A I -- 3 Q Do you remember? 4 MR. SHORES: Feel free to -- 5 A I'm looking here at my appendix, or 6 exhibits, what's called Exhibit C of my -- 7 Q Sure. 8 A -- declaration, and I don't see that 9 exhibit number cited here, so my assumption is that 10 I have not cited to this -- to this exhibit. 11 Q I see what you mean. Well, let me ask 12 you -- I would like to point to a sentence here, 13 and I can either read it to you or you can read it 14 in here, and I'm going to ask you if you agree with 15 it, okay? You don't need this if you don't want. 16 A I would prefer if you -- 17 Q Sure. 18 A -- lead me to where you are at so I can 19 follow along. 20 Q Page -- page 51, and I'm -- and I'm down 21 here, this -- 22 A Got it.	40 1 Q Right. 2 A -- this segment that you have presented 3 -- 4 Q Right. 5 A -- in front of me, so you are forcing me 6 here to speculate if I agree. I haven't had time 7 to -- to contemplate all of this. 8 Q Well, I'm sorry, don't mean to cut you 9 off. 10 A No, go ahead, Counsel. 11 Q Well, putting aside this exhibit, if I 12 asked you do you think that chemical synthesis of 13 RNA was perfected to the extent that long sequences 14 can be produced -- could be produced efficiently by 15 2009, would you agree with that? 16 MR. SHORES: Object to form, lack of 17 foundation. 18 A I don't have a off-the-cuff speculative 19 statement to that. It's not something that I have 20 considered. 21 Q Okay. Was there any aspect of 22 phospho(III) chemistry synthesis that was -- you

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41 1 regard as perfected by 2009? 2 MR. SHORES: Object to form. 3 A Personally -- 4 Q Yeah. 5 A -- I would never use the term "perfected" 6 in any context that has to do with chemical 7 synthesis, so -- I would not use the word 8 "perfected." 9 Q Well, would you use the word "routine"? 10 Were there any aspects of phospho(III) chemistry 11 synthesis that were routine back in 2009? 12 MR. SHORES: Object to form. 13 A Again, this is not really anything I've 14 -- I -- my testimony is that oligonucleotide 15 chemistry has a high level of -- of -- of 16 uncertainty associated with it. There are certain 17 parts that might be more what you characterize as 18 routine than -- than others, but it's not 19 perfected. It's not black box turnkey, you can 20 always 100 percent expect things to work out. 21 There's always -- there's -- there's -- there's 22 some unpredictability.	43 1 A Yeah. 2 MR. SHORES: Just Counsel, we've been 3 going for about 45 minutes. 4 MR. MADDOX: We can take a break. 5 MR. SHORES: I'm not suggesting that. 6 I'm just saying to the extent the witness -- 7 MR. MADDOX: He seems he'd like a break. 8 THE WITNESS: No, no, I'm fine, but I 9 will probably be on a one hour schedule -- 10 BY MR. MADDOX: 11 Q Sure. 12 A -- ish. 13 Q I'll try to remember, but if I forget, 14 just say -- 15 A Yeah. 16 Q -- time. 17 A Yeah. 18 Q If you look at page 64, it might be -- 19 A Of my report? 20 Q Yeah. 21 A Page 64? 22 Q Yeah. This is title -- section 3, it
42 1 Q Okay, so it was -- none of it was 100 2 percent predictable. 3 A By -- if you by this mean oligonucleotide 4 synthesis and chemistry is never 100 percent, one 5 shouldn't go in assuming that -- that matters are 6 trivial or just -- chemistry. Go on. 7 Q Sure. Is there a percent of successful 8 predictability that you would then regard as 9 reasonable expectation of success? 10 MR. SHORES: Object to form to the extent 11 it calls for a legal conclusion. 12 THE WITNESS: I have not -- 13 MR. SHORES: Lack of foundation. 14 THE WITNESS: I would not know what 15 number I would have to associate with that. 16 BY MR. MADDOX: 17 Q Okay. So with respect to your 18 obviousness analysis, there was a section about the 19 reasonable expectation of success, correct? 20 A Uh-huh, let's go to -- 21 Q Sure, take a moment, and maybe I can help 22 you with that.	44 1 says, "A POSA would not have had a reasonable 2 expectation, successfully synthesizing," and it 3 goes on about what -- 4 A Sure, sure. 5 Q So what -- what I'm asking is when you 6 give an opinion about whether a person of ordinary 7 skill in the art would have had a reasonable 8 expectation of successful synthesis, what percent 9 predictability would have been sufficient for 10 reasonable expectation? 11 MR. SHORES: Object to form, calls for a 12 legal conclusion, to the extent it calls for a 13 legal conclusion. There's a pending question? 14 MR. MADDOX: Yes. 15 MR. SHORES: Do you remember the question 16 that's pending -- 17 THE WITNESS: I do. 18 MR. SHORES: -- Patrick? 19 THE WITNESS: But given that this is I do 20 believe a legal term, I want to make sure that I 21 get the definition correct. 22 MR. SHORES: Could we just read the

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Shanghai Hongene Exhibit 1035
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45 1 question again? 2 MR. MADDOX: If you would like. 3 MR. SHORES: If that -- would you like 4 the question read -- 5 THE WITNESS: Sure. 6 MR. SHORES: -- restated or re -- 7 MR. MADDOX: I'll read it. 8 MR. SHORES: Another question or restate 9 it or -- 10 BY MR. MADDOX: 11 Q What I'm asking is when you give an 12 opinion about whether a person of ordinary skill in 13 the art would have had a reasonable expectation of 14 successful synthesis, what percent predictability 15 would have been sufficient for there to be a 16 reasonable expectation of the successful synthesis? 17 MR. SHORES: Same objections -- 18 MR. MADDOX: Sure. 19 MR. SHORES: -- to the extent -- 20 THE WITNESS: So in paragraph 52, I 21 provide that I understand that the law only 22 requires that a POSA would have had a reasonable	47 1 on what the legal definition is. I'm trying to 2 understand your opinion. 3 A I want to make sure that I'm consistent 4 with my testimony, and I don't recall that I've 5 placed a percentage on what constitutes reasonable 6 expectation of success. 7 Q Okay, but you agree it's something less 8 than a hundred percent. 9 MR. SHORES: Objection. 10 A Reasonable expectation of success can be 11 less than a hundred percent. Not absolute 12 certainty, as we read -- as I read in the paragraph 13 before. 14 Q But you have no -- no view at least ready 15 to express today as to what less than a hundred 16 would be sufficient. 17 A It is difficult for me to put a 18 percentage number on, right? Reasonable 19 expectation of success, I've not opined, I've not 20 given a percentage number saying what -- what 21 reasonable expectation of success constitutes 22 except not 100 -- I mean --
46 1 expectation of success and not certain success in 2 combining or modifying the prior art teachings, as 3 the claimed invention does. 4 BY MR. MADDOX: 5 Q Yes, and you were answering questions 6 leading up to now in terms of you -- let me try 7 again. You were saying that this -- this -- this 8 particular part -- excuse me, that this 9 phospho(III) chemistry, nothing was 100 percent 10 predictable. 11 A Correct. 12 Q And I'm asking if nothing is a hundred 13 percent predictable, was there anything that was 14 predictable enough, whether it be 99 percent or 90 15 percent or 70 percent, such that you would regard 16 that as being a reasonable expectation? 17 MR. SHORES: Object. Sorry, I apologize. 18 I object to the extent that it calls for a legal 19 conclusion, object, lack of foundation, object to 20 the extent it mischaracterizes his testimony. 21 BY MR. MADDOX: 22 Q To be clear, I'm not trying to quiz you	48 1 Q Yeah. 2 A Not 100 percent. We're good. 3 Q Okay. Let me ask you this way. In your 4 lab -- 5 A Uh-huh. 6 Q -- you've run synthesis or attempted 7 synthesis that you did not think were 99 percent 8 certain to succeed? 9 A Sure. 10 Q Sure. Ever run them when you thought 11 maybe there's a 50/50 chance that they'll succeed? 12 A I would -- I'm speculating here a little 13 bit, but I'd say that -- that we would run chemical 14 reactions if we think that the likelihood is more 15 likely than not to -- to -- to proceed 16 successfully. 17 Q Let's talk for a moment about what a 18 successful synthesis is. There is a concept called 19 yield, correct? 20 A That's correct. 21 Q Okay, and in broad terms, what is yield? 22 A In broad terms, yield is how many

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49 1 molecules of your starting material compare -- 2 rather, let me rephrase. 3 Q Sure. 4 A How many molecules of product you 5 obtained relative to the molecules of starting 6 material that you used. 7 Q Right, and is yield sometimes -- 8 A Of the limiting factor. Sorry, I should 9 have been more precise. Of a limiting factor. Go 10 ahead. 11 Q Okay, and when you say -- when -- is 12 there ever any yield amount above zero that is a 13 failure in terms of a synthesis? 14 MR. SHORES: Object to form. 15 A An example from our lab that is going on 16 right now, we have a key reaction that runs in 25 17 percent yield, which some people might consider as 18 being inefficient, unsatisfactory -- not 19 satisfactory. For us, it is satisfactory because 20 alternatives would be lower yielding still. 21 Q Okay, and so -- well, let's take a look 22 at page 64 again in your declaration.	51 1 desired product, might not have yielded the desired 2 product at all. 3 Q Okay, and -- and your opinion is that a 4 person of ordinary skill in the art would have 5 expected that it would not produce the desired 6 product at all. 7 A My -- my -- my testimony is that a POSA 8 would have been concerned that the -- that the 9 reaction would not have yielded the product. 10 Q Okay, and did you have -- or do you have 11 any sense of how likely or unlikely that a POSA 12 would have thought getting the product would have 13 been? 14 MR. SHORES: Object to form. 15 A So here you're asking me to speculate on 16 a -- on a percentage number. Again, I would say -- 17 I would say a POSA would have had considerable 18 concerns in not -- in not synthesizing the molecule 19 at issue here. 20 Q So it's not a question of efficiency. 21 It's a question of whether you'd get the molecule 22 at all.
50 1 A Okay, page 64. 2 Q I beg your pardon. Page 64. 3 A Yeah. 4 Q And you see underneath the subheading 3, 5 there's a subheading, small Roman numeral I? 6 A Yeah. 7 Q Or small I. 8 A Yeah, I understand. 9 Q Sure, and it says a POSA would have 10 expected that using acetic anhydride in step small 11 2 -- 12 A Uh-huh. 13 Q -- of the complex synthesis scheme set 14 forth in Exhibit 4-d of the '031 patent would have 15 failed, and by failed, did you contemplate a 16 certain yield for -- to mean failure? 17 MR. SHORES: Objection to -- to form and 18 also to the extent it mischaracterizes his 19 testimony. 20 A My opinion here is that for this 21 particular example that you're pulling up here is 22 that the reaction might not even have yielded the	52 1 A It can be broader than that. I mean, 2 could be not to get the molecule at all, or it 3 could be to get a molecule in a very low yield in a 4 complicated mixture that's difficult that's -- 5 that's not really acceptable to work with. There 6 are many factors that come into play here. 7 MR. MADDOX: Why don't we take our break. 8 THE VIDEOGRAPHER: We are going off the 9 record. The time is 10:47 a.m. 10 (Recessed at 10:47 a.m.) 11 (Reconvened at 11:03 a.m.) 12 THE VIDEOGRAPHER: We are back on the 13 record. The time is 11:03 a.m. 14 BY MR. MADDOX: 15 Q Now, Doctor, in the -- in the field of 16 synthesizing oligonucleotides using phospho(III) 17 chemistry, are there in the field any established 18 protocols for any of the work? 19 A Yes. 20 Q And in general, what types of things are 21 subject to established protocols? 22 A Counsel, that can be a wide range of --

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53 1 of topics as we're talking now nucleic acid 2 chemistry broadly. There can be a very wide range 3 of -- of -- of topics that are covered. For 4 example, in current protocols of nucleic acid 5 chemistry is a collection of -- of protocols, and 6 there's a vast -- vast diversity of techniques, of 7 syntheses and so on that are covered there. 8 Q And with respect to these established 9 protocols, these are something that a person of 10 ordinary skill in the art would have access to in 11 2009, such as they were in 2009? 12 MR. SHORES: Objection, lack of 13 foundation. 14 MR. MADDOX: Let me start again. 15 MR. SHORES: Yeah. 16 BY MR. MADDOX: 17 Q As of 2009, were there some established 18 protocols in synthesis of oligonucleotides using 19 phospho(III) chemistry? 20 MR. SHORES: Objection, asked and 21 answered. 22 A There is -- for example, one example that	55 1 that experience and -- and troubleshoot and -- 2 Q As of 2009, were there established 3 protocols with respect to protecting groups in 4 phospho(III) chemistry? 5 MR. SHORES: Objection. 6 A So I haven't provided opinion on this, 7 but if I'm here to speculate, draw on my memory, if 8 you will, there are certainly reviews in let's say, 9 for example, current protocols of nucleic acids 10 about nucleobase protecting groups. That was your 11 question I believe. 12 Q Yes. 13 A That was a review. Are there protocols 14 for installation of -- I don't know, but I would 15 assume so. 16 Q Now, back in 2009 -- I'm sorry. 17 A No, I'm thinking. That's -- I want to 18 provide of course -- 19 Q Sure. 20 A -- truthful testimony, and I'm thinking 21 on the -- 22 Q Sure.
54 1 I know of myself, current protocols of nucleic acid 2 chemistry, this -- this kind of subscription-based 3 -- 4 Q Uh-huh. 5 A -- it's not a journal, but -- but 6 collection of protocols that is -- that is -- that 7 might have been available to a POSA, provided they 8 have the proper subscription. 9 Q In your labs, as of 2009, how common was 10 it to have what -- what you considered a failure of 11 a synthesis? 12 A Counsel, so I cannot provide a percentage 13 number of this, but we certainly have chemical 14 reactions that work as we had hoped, and we 15 certainly have chemical reactions that do not work 16 as we had hoped. 17 Q And what do you do with the ones that do 18 not work as you had hoped? 19 A What do we do with the chemical reactions 20 that do not work -- 21 Q Right. 22 A -- as had hoped? We try to learn from	56 1 A -- fly, yeah. 2 Q Back in 2009, if you wanted to make -- or 3 wanted your students to make an oligonucleotide, 4 conceptually, what would be the first step to that? 5 You were given an oligonucleotide you wanted to 6 make. How would you go about it broadly? 7 MR. SHORES: Object to form. 8 A So we're sitting here in the context of 9 the '885 patent of course, so are you asking me to 10 think outside the '885 patent here? 11 Q Yes. Well, let me try again. In making 12 oligonucleotide, wouldn't you first figure out 13 which monomers you needed? 14 A The way that research works in my 15 laboratory is one of us, typically me, gets an idea 16 for a molecule we want to make -- 17 Q Okay. 18 A -- and modification we want to build into 19 a oligo. 20 Q And -- and when you're doing that, how do 21 you select the modifications you want to make? 22 A Those are creative tasks that I have some

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57 1 idea or some reason -- 2 Q Okay. 3 A -- to use. 4 Q And how do you select the protecting 5 groups you use? 6 MR. SHORES: Object to form, objection to 7 foundation and to the extent it mischaracterizes 8 prior testimony. 9 A I will go back to we're here sitting in 10 the context of the '885 patent, and if your 11 question is a leading question as to why somebody 12 would have selected compound X perhaps, this is -- 13 Q It was not intended. 14 MR. SHORES: Please let him answer. 15 A But -- but I mean, there would have been 16 thousands of different phosphoramidites to choose 17 from. 18 Q Okay, but I'm saying in the ordinary 19 course of how a person of ordinary skill in the 20 art, you, in 2009 -- 21 A Uh-huh. 22 Q -- works when you're -- when you conceive	59 1 select the protecting groups you're going to use in 2 the nucleotide? 3 A So I feel this goes beyond my testimony 4 that I've provided, but speculatively saying would 5 depend on the application of -- it would depend on 6 the nature of the oligonucleotide that we're 7 synthesizing. 8 Q And would you -- would you -- would you 9 do an analysis to find a protection -- protective 10 group with the most activity? 11 A I don't know what you mean by most 12 activity in this context here. 13 Q Well, let me ask you this. This lead 14 compound analysis you're applying in your 15 declaration -- 16 A Uh-huh. 17 Q Would you apply it to the selection of a 18 protecting group? 19 MR. SHORES: Object to form, object to 20 the extent it calls for a legal conclusion, lack of 21 foundation. 22 A A phosphoramidite is a key reagent in
58 1 a molecule or want to try and make that molecule, 2 there will be some need for protective groups along 3 the way in the synthesis, right? 4 A Not all -- in the synthesis leading -- 5 Q Yeah. 6 A Often. I don't necessarily say always, 7 but often. 8 Q In the synthesis leading to the 9 oligonucleotide. 10 A There would be protecting groups 11 involved. 12 Q Some for a short time, some for a long 13 time, right? 14 MR. SHORES: Object to form. 15 A Again, this is not something I've opined 16 on, but I can -- protecting groups are sometimes 17 installed at the beginning of a synthetic route and 18 persist to almost the end. Others are more 19 temporary. 20 Q Yes, and my question is in general, as a 21 person of ordinary skill in the art would have back 22 in 2009 for any given oligonucleotide, how do you	60 1 incorporating certain monomers into certain 2 oligonucleotides. It's a molecule, and all the 3 bits and pieces need to fit together to have a 4 successful oligonucleotide synthesis. 5 Q Okay. So in your view, the 6 oligonucleotide is not the lead compound. The 7 protecting group in the phosphoramidite is the lead 8 compound. 9 MR. SHORES: Objection to the extent it 10 mischaracterizes his testimony, object to form. 11 A So as I have testified, depending on the 12 context, sometimes an oligonucleotide can be a lead 13 compound. Other times it's a solid support that 14 can be a certain type of lead compound. Depends on 15 the context, and in this context -- context we're 16 sitting in here, the '885 patent, it depends on the 17 claim that we're talking about. 18 Q Okay. Could you go to page 46 of your 19 declaration? That's Exhibit 2008. 20 A Page 46. 21 Q Forty-six. I'm sorry. If you prefer, I 22 could --

61 1 A Yeah, go by paragraph. 2 Q I'm sorry, in paragraph 105. 3 A Thank you. Yeah, I'm there. 4 Q And -- and you can -- I don't mean to 5 narrow your review to this one paragraph, but if 6 you would look at paragraph 105 for a second -- 7 A Yeah. 8 Q The first sentence -- 9 A Uh-huh. 10 Q And it says, "In my opinion, if a POSA 11 were to select any compound from the '031 patent as 12 a lead compound, a POSA would have selected the 13 chimeric phosphorothioate" -- 14 A Uh-huh. 15 Q -- "oligoribonucleotides of the general 16 structure of this." 17 A Uh-huh. 18 Q And then there's a structure that 19 follows. 20 A Uh-huh. 21 Q How did you come to that conclusion? 22 A Well, I -- I looked at the '031 patent	63 1 A Thank you. 2 Q Little Roman numeral 3 starting around 3 64, line 64, and going on to the top of the next 4 column. 5 A Uh-huh. 6 Q Did you review this compound? 7 A The little numeral 3 on top of column 43 8 that says chimeric methylenecarbonylamino/ 9 phosphorothioate/methylenecarbonylamino 10 oligoribonucleotide? 11 Q No. 12 A Oh. 13 Q I'm sorry. Under example 12 in that 14 column 43, starting around line 64. 15 A Oh, down there. Okay, I understand. Got 16 it. Okay, which reads -- I'm going to read into 17 the record -- 18 Q Sure. 19 A -- just to make sure that we're on the 20 same page. As you can see, that was important from 21 the previous answer. 3 prime-end gapped 22 phosphorothioate chimera, for example, parentheses,
62 1 that we have been -- that I've been given. I 2 analyzed the '031 patent, read what the '031 patent 3 is about, and noted that -- that experimental data 4 were provided in figures 1 through 5 really for one 5 type of -- one general type of oligonucleotide that 6 fits the description provided in paragraph 105. 7 Q And what made that general structure in 8 your view the lead compound as opposed to, for 9 instance, compound X? 10 A Counsel, I didn't see any -- in analyzing 11 '031, I didn't see any mention that compound X was 12 being used for the synthesis of oligos, nor did I 13 see evidence of any -- or at least experimental 14 data of any oligonucleotides that would have ensued 15 from that, from compound X. 16 Q Okay. Let's go to the '031 patent. 17 A I'm there. Oh, that's a broad statement. 18 I have it in front of me. 19 Q That's fine. We're good, we're good, and 20 let's look at example 12, column 43. 21 A Column? 22 Q Forty-three.	64 1 2 prime F, parentheses, and PS dot 2 prime OH, 2 parentheses, and PS oligonucleotide, that one. 3 Q Right. 4 A Uh-huh. 5 Q Did you review -- focus on that one in 6 your review of this patent? 7 A I considered all of the material in -- in 8 this patent. 9 Q Okay. Now, when this one says in the 10 manner of example 8 -- 11 A Uh-huh. 12 Q What did you take that to mean? 13 MR. SHORES: Object to form. 14 BY MR. MADDOX: 15 Q What would a person of ordinary skill in 16 the art take that to mean? 17 A So I didn't provide opinion -- a written 18 opinion on that, but sitting here today, I would 19 speculatively say that I took that to mean that -- 20 looking at example 8, which is on column 40, there 21 is what appears to be a description given for how 22 to make the compound of that oligonucleotide of

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65 1 example 8 which does not include 2 prime fluoro. 2 Q Right, and so back to column 43, the 3 little 3 -- 4 A Uh-huh. 5 Q -- compound there does include a 2 prime 6 fluoro. Would you agree it does if you look at the 7 rest of the sentence, "In the manner of"? 8 MR. SHORES: Object to form. 9 A So the rest of that sentence that is at 10 the end of column 43 reads in the manner of example 11 8, a chimeric compound having an open gap at its 3 12 prime terminus, 2 prime fluoro nucleosides in its 5 13 prime wing state -- segment, 2 prime OH nucleosides 14 in its open gap segment, and phosphorothioate 15 linkages throughout in -- throughout -- 16 Q Uh-huh. 17 A -- is prepared. 18 Q Right. 19 A Yeah, so -- so that would -- I mean, it 20 says 2 prime fluoro nucleosides. 21 Q Right, so if this was in the manner of 22 example 8, do you take that to mean that you	67 1 Q Of course. 2 MR. SHORES: Take your time. 3 A Yeah. Okay, so I've read it. 4 Q Okay. Do you agree that this example 8, 5 a person of ordinary skill in the art looking at 6 example 8, and the instruction here on example 12 7 to in the manner of example 8, would use the 8 general -- the general process laid out in 8 but 9 would use it with a compound that's got 2 fluoro? 10 MR. SHORES: Object to form and to the 11 extent it mischaracterizes the document. 12 A I think a POSA would be very confused 13 about what is going on here from example -- was it 14 12? 15 Q Yes. 16 A Example 12, the reference to example 8, a 17 POSA would arrive at example 8 and be very 18 concerned and confused -- confused and concerned 19 because this -- what's written in example 8 is a -- 20 20 is -- is an outline for how to make the compound of 21 example 8 and does not speak of 2 prime fluoro 22 nucleosides.
66 1 dropped the 2 prime fluoro, or the 2 prime fluoro 2 would come through? 3 MR. SHORES: Object to form, lack of 4 foundation. 5 A In my opinion, that reference to example 6 8 becomes nonsensical because example 8 does not 7 speak about 2 prime fluoro modifications. 8 Q Okay. So in addition to the compound 9 under the title of example 8, you see that? 10 A Uh-huh. 11 Q It's your opinion that this -- this 12 example 8 and the inventors did not intend to 13 provide here a general method for making 14 oligonucleotides using different compounds other 15 than just what was in the title. 16 MR. SHORES: Object to form. 17 A Example 8, as I -- allow me to read 18 internally -- 19 Q Absolutely. 20 A -- example 8 here. 21 Q Anytime. 22 A Just refresh.	68 1 Q Okay. So in your view, example 12 little 2 3 at the bottom of column 43 -- 3 A Uh-huh. 4 Q -- does not by its own terms reflect the 5 making of oligoribonucleotide with a 2 prime 6 fluoro. 7 A Example 12 by itself without the 8 reference to example 8? 9 Q No, with the reference to 8. 10 A With -- in my opinion, it does not. 11 Q Okay, and could you take a look at 12 example in column 44, example 13, small -- small -- 13 A Forty-four? 14 Q I'm sorry, let me start again. 15 A Yeah. 16 Q Column 44. 17 A There. 18 Q Next to the example 12, in the next 19 column over, if you look at the top, there's 20 example 13 -- 21 A Uh-huh. 22 Q -- around line 5. Do you see that?

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69 1 A Uh-huh, yes, I do. 2 Q And there's a -- there are a few small 3 Roman numerals, 1, 2 and 3 -- 4 A Yeah. 5 Q -- and 4 and 5. Could you look at Roman 6 numeral 3? 7 A Yeah. 8 Q Would you agree that the Roman numeral 3, 9 the compound at issue has 2 fluoro nucleosides in 10 its wing segments? 11 A I would say that if you look at the 12 heading of -- of little Roman numeral 3, you would 13 think that's nonsensical, what's written there. 14 Q Okay, so you think the heading in Roman 15 numeral 3 there is nonsensical. 16 A Correct. 17 Q When you look at the sentences below 18 that, it does indicate 2 fluoro nucleoside, right? 19 A The -- 20 MR. SHORES: Object to form. 21 A The -- the sentence below says in the 22 manner of example 8, a chimeric compound having 2	71 1 MR. SHORES: Object to form. 2 A I think a POSA would read this and -- and 3 -- and POSA would think that the patent owner of -- 4 of this patent was probably trying to intent to 5 provide a protocol for how to make something 6 containing 2 prime fluoros, but would, A, be -- 7 find the heading -- the -- the -- the title of 8 heading 3 to be nonsensical because it describes 2 9 prime O dash fluoro, which doesn't make any sense. 10 Then they would get confused that there's 11 a discrepancy between the title and the text that 12 is provided. Then there would be -- be confused 13 that this example is directing them back to example 14 8 that does not provide a -- any -- any -- any 15 guidelines for how to make that compound containing 16 2 prime fluoro. 17 Q Okay. Could you look for yourself for a 18 moment at Roman numeral 5 under 13 and just read it 19 for yourself and -- 20 A Okay. 21 Q Then let me know when you're -- 22 A So example --
70 1 prime fluoro nucleoside in its wing segments, and 2 it continues on. 3 Q Okay. And for the same reason that you 4 think a person of ordinary skill in the art would 5 take example 12 Roman 3 to be incomprehensible or 6 nonsensical I believe you said -- 7 MR. SHORES: Object to the form and to 8 the extent -- 9 BY MR. MADDUX: 10 Q What -- what's -- what's the word you 11 want to -- 12 MR. SHORES: To the extent it -- I need 13 to get my objection in. Object to the extent it 14 mischaracterizes the witness' testimony. 15 MR. MADDUX: Okay. 16 MR. SHORES: Object to form. 17 BY MR. MADDUX: 18 Q Let me ask it this way. Would a person 19 of ordinary skill in the art look at example 13 20 Roman 3 and -- in conjunction with example 8, take 21 that to -- understand that to be an oligonucleotide 22 -- oligoribonucleotide with a 2 prime fluoro?	72 1 Q It's not a -- 2 A Numeral 5. 3 Q Small -- small V, yeah. 4 A Small V, yeah, 2 prime O ethyl something. 5 Q Yes. 6 A Yeah. 7 MR. SHORES: So just for the record, just 8 column and line? So column 44? 9 MR. MADDUX: Sure, happy to do that. 10 MR. SHORES: Yeah. 11 BY MR. MADDUX: 12 Q Column 44, line 42 or so, 43. 13 A Yeah, yeah, I've read that. 14 Q And would your opinion about -- about 15 that, the Roman numeral 5, be the same as your 16 opinion was for Roman numeral small 3? 17 A Slightly different in the sense of here 18 at least the title of Roman numeral 5 is not 19 nonsensical. It's not nonsensical, makes more 20 sense perhaps, but then beyond that, same issues at 21 hand here, what appears to be a -- what patent 22 owner probably attempted to do here is to provide a

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73 1 description for how to make this compound seems to 2 suggest to direct the reader to example 8, and then 3 the reader would get confused because example 8 4 does not describe anything entailing 2 prime fluoro 5 modifications, and potentially even I would have to 6 check that closer, even the second type of 7 modification that's mentioned here, metoxyethyl. I 8 don't believe that's mentioned in here in example 8 9 neither. It's not. 10 Q And finally, the same question with 11 respect to example 14, small Roman numeral 1, if 12 you look at column 44 and you go to around line 63 13 -- 14 A Uh-huh. 15 Q Do you see it? 16 A Yeah. 17 Q Okay. If you take a moment to read it 18 for yourself? 19 A Okay. Okay. 20 Q And would you have the same issue with 21 this one as you had the prior ones regarding their 22 interaction with example 8?	75 1 molecules are being described there. The -- the 2 title of the numeral 1 seems to suggest 2 prime 3 fluoro. The main text speaks of 2 prime O fluoro, 4 which there's an inconsistency there in the 5 chemistry. 6 Q Okay. So what if anything would a person 7 of ordinary skill in the art take from this 8 example? 9 MR. SHORES: Object to form. Are we 10 referring to example -- which example are we 11 referring to? 12 MR. MADDOX: Example -- I think it's -- 13 one second. Example 14, Roman numeral small I at 14 the bottom of column 44. 15 MR. SHORES: Yeah, thank you. 16 THE WITNESS: My first answer would be 17 confusion. A POSA would walk away with confusion 18 because of the aforementioned discrepancy in -- in 19 chemistries. 20 BY MR. MADDOX: 21 Q Uh-huh. Could you turn in the '031 22 patent --
74 1 A So we probably -- I don't want to 2 generalize here, and we probably need to go through 3 it -- 4 Q Sure. 5 A -- more step by step. 6 Q Fine, sure, sure. So would a person of 7 ordinary skill in the art reading example 14 in 8 conjunction with example 8, as it says in the 9 manner of example 8, understand this to be the 10 description of the oligonucleotide with the 2 prime 11 fluoro? 12 A So let's start with the title is -- so my 13 short answer to your question is it's complex. 14 Q Okay. Could you -- could you elaborate a 15 little bit? 16 A Okay, I could. So for example, the title 17 seems to suggest -- the title of example 14, 18 rather, the numeral 1 would seem to suggest that 19 there are 2 prime fluoros in it, but the main text 20 of example 14 continues on and says 2 prime O 21 fluoro nucleosides in the 3 prime wing segment. 22 There's a discrepancy, inconsistency between what	76 1 A '031. 2 Q Oh, I'm sorry. I totally -- I might have 3 been cutting you off. 4 A No, no, you weren't cutting me off. 5 Q Okay. If we could go to column 12, and 6 -- 7 A Okay. 8 Q And before we dive into that question, in 9 2009, in nucleosides and nucleotides, was 2 prime 10 floral -- floral. Excuse me, 2 prime fluoro -- 11 A Fluoro. 12 Q Fluoro, thank you, was that getting any 13 attention as a potentially useful group? 14 MR. SHORES: Object to form, lack of 15 foundation. 16 A So it's not something that I've opined 17 upon. What do you mean by attention? Could you -- 18 Q Well, in -- 19 A -- clarify your question? 20 Q Would a person of ordinary skill in the 21 art have -- have had an understanding that 2 prime 22 fluoro is a potentially useful substituent?

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77 1 A Useful in what context? 2 Q In the context of making 3 oligonucleotides. 4 A A POSA would have -- a POSA would -- so 5 I'm sitting here on -- I haven't provided opinions 6 on this, but sitting here speculating, I would 7 probably say that a POSA would have known that 2 8 prime fluoros can be incorporated into 9 oligonucleotides and increase affinity towards such 10 oligos, increase affinity towards target strands, 11 certain target strands. 12 Q Okay, so could we look at column 12, 13 where we were a minute ago? 14 A Sure. 15 Q And if you could look at the paragraph 16 beginning on line 3 of column 12 -- 17 A Uh-huh. 18 Q It says a further particularly useful 2 19 prime substituent group for increasing the binding 20 affinity is the 2 prime fluoro group. Is that the 21 -- you used the term "affinity" in your answer. 22 Are you referring to this type of affinity or some	79 1 A They are -- for sure, there are 2 oligonucleotide therapeutics. 3 Q Right. Are -- are they actually the 4 therapeutic agents? 5 A The oligonucleotides? 6 Q Yes. 7 A Yeah, oligonucleotides can act as 8 therapeutic agents. 9 Q Are the phosphoramidites the -- the 10 therapeutic agents? 11 A I -- sitting here right now, I -- I don't 12 know if there are phosphoramidites that are being 13 used as therapeutic agents against certain types of 14 diseases. I do have a vague recollection of I 15 think there are some compounds that could be 16 classified as phosphoramidites that are being used 17 as prodrugs in -- in HIV work, but -- but I'm not 18 certain on that aspect. 19 Q That's fine. Could you take a moment and 20 read for yourself the paragraph that I read the 21 first sentence on starting on line 3 -- 22 A Yeah.
78 1 other type of affinity? 2 A The type of affinity here is not 3 described in this segment. I don't know if the 4 previous paragraph clarifies specifically what 5 we're talking about here. 6 Q Okay. In the selection of substituent 7 groups, binding affinity is something to be 8 desired, all else being equal? 9 MR. SHORES: Object to form. 10 A First off, binding affinity to what? 11 Let's establish that. 12 Q Okay, to your targets, right? 13 A What targets? 14 Q Well, the target that you're making the 15 oligonucleotide to deal with, correct? 16 A Could you define at the molecular level 17 what the target is that you're referring to? 18 Q Well, let's back up. Why are we making 19 oligonucleotides at all? What -- what do we use 20 them for? 21 A There are many uses for oligonucleotides. 22 Q They're drug discovery?	80 1 Q -- and it concludes on line 31. 2 A Okay. 3 Q Just take -- take your time -- 4 A Uh-huh. 5 Q -- to -- 6 A Is it okay if I stand like this? 7 Q You can, but we can probably get you a 8 seat with better lighting. 9 A No, no, it's okay if this is accepted. 10 MR. MADDUX: Counsel, I've got no problem 11 taking a break and getting him a seat with better 12 lighting. 13 THE WITNESS: No, no, it's -- 14 MR. SHORES: I'm not sure we can. That's 15 the thing. 16 THE WITNESS: It's okay. It's okay. 17 Just -- 18 MR. MADDUX: Can we go off the record for 19 a sec? 20 THE VIDEOGRAPHER: We are going off the 21 record. The time is 11:39 a.m. 22 (Discussion off the record)

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81 1 THE VIDEOGRAPHER: We are back on the 2 record. The time is 11:40 a.m. 3 THE WITNESS: Okay. 4 BY MR. MADDOX: 5 Q Now, in your opinion, a person of 6 ordinary skill in the art reading this in the 7 patent, would they take this to be an indication of 8 the desirability of using a 2 prime fluoro group in 9 the invention? 10 MR. SHORES: Object to form. 11 A I think a POSA reading this paragraph in 12 isolation first off would be -- be in doubt what 13 really is meant here by binding affinity. At least 14 the term "binding affinity" isn't clearly defined, 15 and there also seems to be a switch in what binding 16 affinity means midway through where it says binding 17 affinity of only about 66 percent of that, of the 18 15-mer phosphodiester oligonucleotide. So -- so 19 there's a little bit of confusion of terms there. 20 However, I would say that a POSA reading 21 this, it probably speaks to, as I testified to 22 earlier here, that probably what is being discussed	83 1 necessarily. 2 So what to do with that, that's an 3 entirely different question. That depends on the 4 application, but factually, a POSA would look to 5 this and say -- assuming that they understood that 6 binding affinity here relates to something about 7 thermal denaturation temperatures, they would 8 observe that in here it's stated that binding 9 affinity -- there's a binding affinity of 1.6 10 degrees Celsius per substitute -- increase in 11 binding affinity of 1.6 degrees Celsius per 12 nucleoside subunit in that one particular 13 construct, and then it goes on and describes a 14 series of experiments as far as I can tell. 15 Q So would a person of ordinary skill in 16 the art apply or give any weight to the phrase 17 particularly useful 2 prime substituent group? 18 Excuse me. Let me start again. A person of 19 ordinary skill in the art would not apply any 20 weight to the inventor's statement that a 21 particularly useful 2 prime substituent group for 22 increasing the binding affinity is the 2 prime
82 1 here are some thermal denaturation experiments in 2 which certain increases in temperature which are 3 being equated to binding affinity are being 4 reported here. 5 Q Okay, so when the inventors wrote a 6 further particularly useful substituent group for 7 increasing the binding affinity is the 2 fluoro 8 group -- 9 A Uh-huh. 10 Q You believe a person of ordinary skill in 11 the art would not have taken that as encouragement 12 to use a 2 prime fluoro? 13 MR. SHORES: Object to form, objection, 14 lack of foundation, and an objection to the extent 15 it mischaracterizes the -- the document. 16 A A POSA would have taken what -- I think 17 what a POSA would have taken away from the first 18 part let's say in reading this is that a 2 prime 19 fluoro resulted in an increase in binding affinity 20 of 1.6 degrees Celsius per substituted nucleoside 21 subunit. Not all applications in oligonucleotide 22 chemistry strive towards higher binding affinity	84 1 fluoro group, it's particularly useful, that would 2 not mean anything to a person of ordinary skill in 3 the art? 4 MR. SHORES: Object to the form of the 5 question and to the -- and also to the extent it 6 calls for a legal conclusion. 7 A I think a POSA is well aware of the fact 8 that -- that -- that -- that scientists and 9 inventors embellish in their language sometimes and 10 would focus not on the adjectives in -- in -- in 11 the writing, but focus on the experimental data. 12 The experimental data here is increase in binding 13 affinity of 1.6 degrees Celsius per substituted 14 nucleoside subunit. 15 Q Now, the '031 patent was issued in 1999. 16 You can see that date on the patent on there. 17 A Yeah, I see that. 18 Q So I'd like to look at column 13 -- 19 A Okay. 20 Q -- and line 45. 21 A Okay. 22 Q And it says, "The oligoribonucleotides

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1 and oligoribonucleosides used in accordance with 2 this invention may be conveniently and routinely 3 made through the well known technique of solid 4 phase synthesis," and then it says, "See, for 5 example." 6 A I see that. 7 Q Would you agree with this statement? 8 MR. SHORES: Object to -- object, lacks 9 foundation. 10 BY MR. MADDOX: 11 Q Well, you reviewed the '031 patent, yes? 12 A Yes, I have. The authors assert -- of 13 this patent or patent inventors are certainly 14 writing the -- the oligoribonucleo -- the 15 oligoribonucleotides and oligoribonucleosides, 16 which is a term that doesn't make sense, used in 17 accordance with this invention may be conveniently 18 and routinely made through the well known technique 19 of solid phase synthesis. That's their opinion. 20 It was certainly well known. 21 Q Okay. 22 A I don't think there's any dispute about	1 Q -- et cetera. Is it true that in 1999, 2 equipment for -- for solid phase synthesis was -- 3 was commercially available? 4 A I was not even a Ph.D. student back in 5 1999, but that seems -- that seems to be 6 reasonable, yes, that it was available. That 7 wouldn't surprise me. 8 Q All right. 9 A That -- that equipment for oligo 10 synthesis was available, oligonucleotide synthesis 11 was available, yes. It wouldn't surprise me. 12 Q And then they wrote, "The actual 13 synthesis of oligonucleotides is well within the 14 talents of those skilled in the art." Do you see 15 that on -- 16 A Yeah, I see that. 17 Q -- column 14? And do you agree that as 18 of 1999, that was the case? 19 A I mean, "oligonucleotides" is a very 20 broad term, and given this paper comes from ISIS 21 Pharmaceuticals, which is a leader of RNA targeting 22 oligonucleotides, I mean, to them, it's certainly
1 that. I think routinely is -- is -- is -- it's a 2 debatable word and depends on what's -- 3 oligoribonucleotides indicates that that's RNA. 4 Q Uh-huh. 5 A 1999, I -- I certainly would not have 6 used the term "routinely." 7 Q Could we go down to the bottom of that -- 8 I'm sorry, did I cut you off? 9 A No, no, no, you didn't. No, you didn't. 10 Q Okay. Can we go to the bottom of column 11 13 then? 12 A Yeah. 13 Q And it says, "Equipment for 14 oligonucleotide and oligonucleoside synthesis is 15 sold by several vendors, including Applied 16 Biosystems." 17 A Uh-huh. 18 Q And it says various amidite reagents are 19 also commercially available, including 2 prime O -- 20 A Correct. 21 Q -- methyl amidites -- 22 A Yeah.	1 -- you know, people who work there, it's certainly 2 well within their talents. 3 Q Now, you -- you -- am I correct that you 4 had a relationship with ISIS Pharmaceuticals of 5 some sort? 6 A Yeah, I haven't -- 7 Q What was that? 8 A I served as a consultant for them on an 9 -- on a one case -- one case? One case ad hoc 10 matter. It was I think one visit to the company. 11 Q Uh-huh, uh-huh. 12 A One or two. 13 Q Okay. 14 A I don't recollect. 15 Q So you were never an employee of the 16 company. 17 A I was -- I was receiving compensation for 18 that -- for -- for those services that I provided. 19 Q Right, right, right. Did -- have you 20 ever been involved in -- in drug discovery with -- 21 with a pharmaceutical company? 22 A I have been -- I've had projects, I've

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89 1 published papers that -- that fall in the category 2 of drug discovery. 3 Q Right. 4 A I have not had a formal relationship with 5 a company that would -- that I think would qualify 6 as saying it's a drug discovery project. I've had 7 involvement with -- with companies on -- on 8 applications and stuff, but I wouldn't categorize 9 it as drug discovery. 10 Q Okay. Give me just a moment. 11 A Yeah. 12 Q I know you're familiar -- you're aware of 13 compound X in the '031 patent. 14 A I am. 15 Q You would agree that it's a 2 prime 16 fluoro guanosine phosphoramidite. 17 A There are other groups attached to it. 18 Q Sure. 19 A But yes. Could you repeat -- 20 Q Sure. 21 A -- one more time your -- 22 Q Sure. 2 prime fluoro guanosine.	91 1 A Then it's further derivatized. 2 Q Yes, yes. So would you agree that to the 3 extent elsewhere in the patent, there's a call for 4 2 prime -- I'm sorry, there's a call for 2 prime 5 fluoro with guanine phosphoramidite, that it would 6 be referring to this? 7 MR. SHORES: Object to form. Objection, 8 lack of foundation, and objection to the extent it 9 mischaracterizes the document. 10 BY MR. MADDOX: 11 Q You know what? Withdraw the question. 12 That's fine. Okay, let's just talk in broader 13 terms for a second. In the context of the '031 14 patent -- well, let's -- in the context of the '885 15 patent, what uses -- well, let me put it this way. 16 2 prime fluoro in a phosphoramidite is not the -- 17 is -- is a substituent group, right? 18 A 2 prime fluoro is what chemists typically 19 would refer to as a substituent. 20 Q Right, and do -- do you know -- would a 21 person of ordinary skill in the art evaluate the 22 extent to which having the 2 prime fluoro as
90 1 A I wouldn't agree with that naming -- 2 Q Oh. 3 A -- of it. 4 Q Okay. Well, let's go to it and make sure 5 we understand it. It's at column 27 at the bottom. 6 As you say, there are many other things involved, 7 but -- 8 A Yeah, yeah. 9 Q Let me ask you this. Are you aware -- 10 other than -- than compound X, are you aware of any 11 other 2 prime fluoro phosphoramidites in the patent 12 with guanine? 13 A Any other phosphoramidites. 14 Q Right. 15 A With guanine. 16 Q Uh-huh, or guanosine. I don't know -- 17 A Yeah, so that -- that was my objection to 18 your question before. Compound X is the only 19 compound in -- in -- in -- in the '031 patent that 20 has a 2 prime fluoro substituent and has a guanine 21 nucleobase. 22 Q Right.	92 1 opposed to some other substituent group -- 2 A Uh-huh. 3 Q -- ultimately affects the usefulness of 4 the oligonucleotide that they're producing? 5 MR. SHORES: Object to form, objection, 6 lack of foundation. 7 A So I need you to repeat the question. 8 Sorry. So I got evaluate 2 prime fluoro switching 9 around, but I want -- 10 Q Well, substituent groups are -- are 11 selected at some point. 12 A Yeah. 13 Q Okay, and are they selected by 14 identifying a lead substituent group? 15 MR. SHORES: Object to form. 16 A Again, one -- there has to be a reasoning 17 why to select a certain substituent, and that 18 depends on the planned applications of the 19 molecules that one is synthesizing. 20 Q And there's going to be only one 21 substituent group that is better than all the 22 others, right?

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93 1 MR. SHORES: Object to form. 2 A That's not something I have opined on. 3 That completely depends on the context, and that 4 could be -- I'm speculating here -- different 5 substituents that could work. I mean, there's no 6 way I can answer this question. 7 Q Well, in your work on this case -- 8 A Yeah. 9 Q -- have you imposed a lead compound 10 framework on the selection of the 2 prime fluoro 11 substituent group? 12 MR. SHORES: Objection to the extent it 13 calls for a legal conclusion. 14 A I have opined, right, I mean, that's what 15 -- what my declaration is -- is reviewing the 16 petition, Dr. Baran's declaration, and imparting my 17 own opinions on -- on -- on this entire case, 18 right, and I noted that -- that there was no 19 rationale provided why 2 prime fluoro was 20 purportedly selected -- was selected as a purported 21 lead compound. 22 Q Okay. Prior to your work on this case,	95 1 a desirable property in selecting a lead compound. 2 Q For ultimate administration to a patient. 3 A There's a very big step from lead 4 compound to ultimate administration to patients. 5 Q I didn't mean to imply otherwise, but 6 that's the ultimate target. 7 A It's a starting -- 8 MR. SHORES: You guys are talking over 9 each other here, so -- 10 BY MR. MADDOX: 11 Q My fault. 12 A No, no, my fault too. Sorry. 13 Q And in your medicinal chemistry class, 14 the lead compound is evaluated for activity that -- 15 what type of activity? 16 A That depends -- 17 MR. SHORES: Object to form. Let me get 18 my -- 19 A Sorry. That depends on the case study 20 we're looking at. 21 Q So if it's an ACE inhibitor, you'd look 22 for activity with respect to the ACE, right?
94 1 had you heard the phrase "lead compound"? 2 A Yes. 3 Q And in what context had you heard it? 4 A That's -- so for example, I teach classes 5 in medicinal chemistry -- 6 Q Okay. 7 A -- where we discuss what is a lead 8 compound. 9 Q Okay. In medicinal chemistry in your 10 class, what -- what is a lead compound? 11 A In -- the way that I teach it in my class 12 is a first compound that has some -- we're 13 typically speaking about this in the context of 14 drugs -- 15 Q Yes. 16 A -- that has some first activity. That's 17 not the final drug. 18 Q And the type of activity we're talking 19 about is potentially therapeutic activity? 20 A It depends on the context, what we're 21 talking -- talking about. There can be different 22 properties that can underlie what would constitute	96 1 A That could be an example. 2 Q Right. 3 A But there are different ways of phrasing 4 that activity. It could be binding affinity. 5 Q Sure. 6 A It could be -- it could be biological -- 7 already some type of biological activity. So there 8 are many different parameters that could be 9 selected. 10 Q In your work with -- with SPOS -- 11 A Uh-huh. 12 Q Putting aside any consultancies on law 13 firms and lawsuits, is "lead compound" a term you 14 commonly use? 15 MR. SHORES: Object to form. Let me just 16 read this. 17 A My opinion is -- I mean, again, this is 18 not something I've opined on. Sitting here on the 19 spot here, I would say that it's a term that -- 20 that can be -- that can be -- can -- could be 21 applied to and is sometimes applied to 22 oligonucleotide -- you said oligonucleotides.

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97 1 Q Yes. 2 A Yeah, I mean, it could certainly be 3 applied to an oligonucleotide, as they can be drug 4 in themselves too. 5 Q Right. Would it surprise you if -- if 6 you didn't use the phrase "lead compound" in any of 7 your oligonucleotide writings? 8 A In my own? 9 Q Yeah. 10 A In my oligonucleotide writings. 11 Q Yes. I'm sorry, and by that, I mean to 12 exclude your medicinal chemistry writings. 13 A That's why I meant if you meant my 14 oligonucleotide writings. 15 Q Uh-huh. 16 A My group doesn't have a -- a very strong 17 medicinal chemistry focus as such. We don't -- 18 we're not target oriented, if that makes sense. 19 You used the case of ACE before. So we're not 20 trying to solve a specific disease. 21 Q Uh-huh. 22 A I certainly, and I hope in each and every	99 1 Q Uh-huh. 2 A And the entire molecule means the entire 3 molecule. 4 Q Right, and at the end of SPOS, doesn't -- 5 does the acetyl group get removed? 6 A We can haggle a little bit about what 7 constitutes the end of SPOS, but as one of the 8 steps late on in SPOS involves removal of 9 protecting groups from the phosphor 5 at this 10 point, phosphor 5 functionalities and the 11 nucleobases, those that carry protecting groups. 12 Q So at the end of the process, the acetyl 13 isn't there. It's been removed. 14 A One would hope if one has carried out a 15 successful SPOS synthesis, that protecting groups 16 have been removed -- 17 Q Right. 18 A -- that oligonucleotide has been cleaved 19 from support and -- 20 Q Right. 21 A -- you have a crude oligonucleotide -- 22 Q Right.
98 1 one of my writings, provide a deep rationale for 2 the -- what was the prior art, to use that term, 3 the state of the art, and formulate a hypothesis, 4 something that -- that has inspired us to branch 5 off and to move further on. So in that respect, 6 while I may not have used the term "lead compound," 7 that's -- you know, you're inspired by something 8 that you are moving to improve upon. 9 Q I understand. Now, in this case, it 10 concerns an acetyl protecting group on the guanine. 11 Would you consider -- I'm sorry, would you consider 12 the acetyl group part of the lead compound in your 13 analysis? 14 MR. SHORES: Object to form and to the 15 extent it mischaracterizes his testimony. 16 THE WITNESS: Again, I -- 17 MR. SHORES: Objection to the extent that 18 it calls for a legal conclusion. 19 THE WITNESS: As I've testified before, 20 the entire molecule is important as to -- as to 21 whether or not it'll be successful in SPOS. 22 BY MR. MADDOX:	100 1 A -- of some sorts that -- 2 Q Right. 3 A Yeah. 4 Q Now, have you ever published -- this may 5 sound like a strange question. Have you ever 6 published on a catastrophic failure in SPOS? 7 MR. SHORES: Object to form. 8 A May I look through my C.V. here? 9 Q Absolutely. 10 A Because it's easier to -- 11 Q Yeah. 12 A I -- 13 Q I don't -- 14 A No, no, no, just give me a moment. 15 Q Sure, absolutely. 16 MR. SHORES: Counsel -- I'm sorry. 17 THE WITNESS: No, go ahead. 18 MR. SHORES: I'm sorry to interrupt. 19 Just we've been going a little -- and I know you 20 had a line of questioning. 21 MR. MADDOX: After we get this answer -- 22 MR. SHORES: Well, I'm not --

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101 1 MR. MADDOX: -- let's -- 2 MR. SHORES: That's fine. I'm not -- 3 just letting you know. 4 THE WITNESS: We have certainly been 5 discussing challenges that we have observed during 6 solid phase oligonucleotides. Sorry, back. We 7 have certainly discussed in some of my papers where 8 it's appropriate, any challenges that we have 9 encountered during solid phase oligonucleotide 10 synthesis of the bespoke oligonucleotides that we 11 make, reporting poor coupling, complete failure. 12 I'm -- I'm very -- I'm quite confident that we 13 reported on -- on an outright failure, so we report 14 what we see. 15 BY MR. MADDOX: 16 Q Okay. In the vast majority of cases in 17 your publications, there -- there is a successful 18 synthesis, yes? 19 A Depending on how we define successful. 20 We end up with enough oligonucleotide that allowed 21 us to carry out the experiments that we wanted to 22 do and that we were not embarrassed about	103 1 medicinal chemistry, right? 2 A It's a dual listed course -- 3 Q Sure. 4 A -- of both undergraduate and graduate 5 listed at the same time, if you will. 6 Q Now, when you're trying to make an 7 oligomer -- 8 A Uh-huh. 9 Q -- you necessarily have to start with 10 monomers, correct, usually? 11 A Oligomer of what? You said oligomer. 12 Q Any kind of oligomer. Oligomer's a long 13 chain of monomers, yes? 14 A Yes, that's correct. You haven't defined 15 a chain of what. You said oligomers. Could be 16 oligomers of amino acids. 17 Q Oh, what we're talking about here. Well, 18 what I'm trying to get at is this. Do you ever 19 assay the activity level of monomers? 20 A Your question is very broad. Activity 21 level, so I don't know what you mean by activity 22 level, and monomers, you need to be a little more
102 1 publishing yields. 2 Q Right. 3 A Many -- many of our papers describe 4 successful -- the successful syntheses, but we also 5 discuss when we have had challenges for sure. 6 MR. MADDOX: Let's take another break. 7 Is that all right? 8 MR. SHORES: Yeah, we can go off the 9 record. 10 MR. MADDOX: Whatever you want. 11 MR. SHORES: Let's go off the record and 12 then -- 13 THE VIDEOGRAPHER: We are going off the 14 record. The time is 12:09 p.m. 15 (Recessed at 12:09 p.m.) 16 (Reconvened at 1:12 p.m.) 17 THE VIDEOGRAPHER: We are back on the 18 record. The time is 1:12 p.m. 19 BY MR. MADDOX: 20 Q Welcome back. 21 A Thank you. 22 Q You teach undergraduate chemistry,	104 1 specific for me here. What monomers do you mean? 2 Q Okay. Well, you've -- you've -- you've 3 designed and developed oligomers, yes? You have. 4 A I've -- my group publishes on 5 oligonucleotides. 6 Q Sure, oligonucleotides, and the finished 7 oligonucleotide, do you sometimes assay for 8 whatever activity you're looking for? 9 A We are per se not looking for an activity 10 in the work that we do. 11 Q Well, in eventually arriving at your 12 oligomer, you at one point are dealing with 13 monomers, yes? Your nucleotide? 14 A We work with nucleotides, we work with 15 oligonucleotides. 16 Q Okay. And I guess what I'm trying to get 17 at is there some series of tests or -- or -- or 18 standards that nucleotides must meet in order to be 19 useful in your -- making your oligonucleotides? 20 A You're asking me here to speculate 21 because I haven't provided opinions about that, but 22 I mean, for the work that we do, and now I'm

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105 1 talking outside the '885. 2 Q Right. 3 A Just -- 4 Q This is -- 5 A -- what we are working on, the key thing 6 that we need is to have our phosphoramidite be able 7 to be incorporated into oligonucleotides and get 8 the product that we desire. 9 Q Okay, okay. Now, could we go back to -- 10 and last time, the '031 patent, which is Exhibit 11 1017 -- 12 A Uh-huh, I have it in front of me. 13 Q Sure, sure. And what I wanted to do is 14 to better understand example 8. 15 A Okay. 16 Q First of all, in the beginning sentences, 17 there's references to automated synthesizer. 18 A In example 8? 19 Q Yes, column 40 -- 20 A Uh-huh. Sure, there, okay, I see it, 21 yeah. 22 Q I'm basically wondering, could you break	107 1 A Okay. 2 Q Yeah. Could you read it? 3 A Yeah, let me read it. 4 Oligoribonucleotides were synthesized using the 5 automated synthesizer and 5 prime dimethoxytrityl 2 6 prime tert-butyldimethylsilyl 3 prime O phosphothi 7 -- phosphoramidite for the RNA portion, and 5 prime 8 dimethoxytrityl 2 prime O-methyl 3 prime 9 O-phosphoramidite for 5 prime and 3 prime wings. 10 Q Uh-huh. 11 A Okay. 12 Q Okay, and that -- and as a result of 13 that, you get the compound that's -- that's named 14 in the title of example 8? 15 A There are more steps before you end up at 16 the compound in the title. 17 Q Okay. 18 A Well, okay, let me see if that's a fair 19 characterization. Was synthesized using the -- I 20 mean, so it depends on how you read I guess the 21 first two sentences. It could be a summary that 22 under synthesized, you could probably have all the
106 1 down for me in conceptual terms only, not -- what 2 -- what steps are being done here in example 8? 3 What -- what process is being laid out? 4 A Okay, I mean, the first sentence says 5 Chimeric oligoribonucleotides having 2 prime O- 6 alkyl phosphorothioate and 2 prime OH 7 phosphorothioate oligonucleotide segments were 8 synthesized using an Applied Biosystems automated 9 DNA synthesizer model 380B, as above. So I mean, 10 what this first sentence suggests is basically what 11 it says, chimeric oligoribonucleotides that have 2 12 prime O-alkyl phosphorothioates or -- and 2 prime 13 OH phosphorothioates oligonucleotides were 14 synthesized on this particular brand of a -- what's 15 colloquially known as a DNA synthesizer. 16 Q Okay, as above, and that refers to 17 example -- do you know what example that refers to 18 or -- 19 A There's no direction as to what example 20 that refers to. The only thing I would surmise 21 from this is one of the preceding examples. 22 Q And then the next sentence --	108 1 work, purification, work-up, purification steps and 2 so and so forth. So it can be read as a summary or 3 it could be read in the sense of the strand has 4 been built, but then there are steps -- 5 Q Okay. 6 A -- before we would end up at the title 7 compound. 8 Q And in the next sentence, it talks about 9 protecting groups -- 10 A Uh-huh. 11 Q -- for FARG, RCA, and those are -- those 12 are the nucleoside bases, right? 13 A The next sentence says the protecting 14 groups on the exocyclic amines were phenoxyacetyl 15 for rA, rG, benzoyl for rC, and 2 prime O-methyl A 16 and 2 prime O-methyl C, and isobutyryl for 2 prime 17 O-methyl G. 18 Q All right. 19 A So the A's and the G's and the C's here 20 refer to what nucleobase is sitting on a particular 21 sugar skeleton. 22 Q Right, with an exocyclic amine.

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Shanghai Hongene Exhibit 1035
Shanghai Hongene v. ChemGenes
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109 1 A Protecting group. 2 Q Right. And then the next sentence says, 3 "The standard synthesis cycle was modified," and it 4 goes on to describe some -- 5 A Uh-huh. 6 Q -- some steps. Do you know what standard 7 synthesis cycle is being referred to there? 8 A Counsel, I'm generally also in a research 9 lab quite allergic to the word "standard" because 10 there's not much that's truly standard in this 11 field. Now -- yeah. 12 Q No, no. 13 A But -- but it doesn't specify what the 14 standard synthesis cycle -- 15 Q Uh-huh. 16 A -- is. 17 Q And your belief, that a person of 18 ordinary skill in the art would not be able to 19 reconcile example 8 with, say, example 12 little 3 20 we discussed earlier? 21 A As I testified before our lunch break, I 22 think I used a term that a POSA would have been	111 1 regarding this in petitioner's -- in the petition. 2 Q Okay, but as a person of -- well, in your 3 knowledge, this wasn't available commercially. 4 A My testimony is that I don't know for 5 sure. If I was to speculate, it might have been, 6 but I don't know for sure. 7 Q Okay. 8 A I think what I can add, I don't think my 9 group bought that compound. 10 Q But your group worked with that compound. 11 A 2 prime dioxyfluoro nucleosides? 12 Q Yes. 13 A To the absolute best of my knowledge, I 14 don't believe we did. 15 Q Okay. Now, let's take a look at the 16 Khorana paper you cite. 17 A The Khorana? 18 Q Yeah. 19 A Could I ask for that exhibit please? 20 Q Yeah, absolutely. That's 1 -- I'm sorry, 21 211, 211; is that right? Yeah, I think so. Okay, 22 first of all, do you recognize that as the Khorana
110 1 confused looking at example 12 Roman numeral 3, 2 seeing the reference to example 8 and then coming 3 back to this and seeing no mention of -- of 2 prime 4 -- 2 prime -- I think we were talking 2 prime 5 fluoro in example 12, right? 6 Q Right. 7 A Not seeing any reference to 2 prime 8 fluoro in here. 9 Q Okay. Now, would you agree that as of 10 2009, 2 prime fluoro nucleosides with guanin, not 11 acetyl, but guanin, were commercially available? 12 A Two -- could you -- could you -- I want 13 to get -- 14 Q Sure. 15 A -- the molecular structure exact. 16 Q The nucleoside. 17 A Yeah. 18 Q 2 prime fluoro. 19 A Yeah. 20 Q Guanin in the base. 21 A I don't know for sure. What I do know 22 for sure was that no evidence was provided	112 1 paper you cited in your declaration? 2 A I -- I cited to at least two papers from 3 Khorana I believe, so I just want to make sure. 4 Q Let's do that. Perhaps I can help -- 5 A 2011, yeah, I -- that is one of the 6 Khorana papers that I have -- 7 Q Right. 8 A -- cited. 9 Q Right, and -- and you may -- if you would 10 like to take a look at your declaration, you might 11 look around paragraphs 107 and 108. 12 A Yeah. 13 Q It's -- it's your opinion that this 14 Khorana article taught a person of ordinary skill, 15 taught away -- let me start again. It's your 16 opinion that the Khorana article taught away from 17 using acetyl protective group? 18 A It is my opinion that -- that Khorana 19 here reports the problems associated within the N2 20 acetyl group, and speaking to the benefits of an 21 isobutyryl group, and that has been a very 22 foundational paper that -- that set the stage for

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113 1 the field using isobutyryl, and therefore, not – 2 not using acetyl as a protecting group. 3 Q Okay. So Khorana was saying don't use 4 acetyl as a protecting group? 5 A I don't know if the words "don't use 6 acetyl group" are stated verbatim in Khorana, but 7 certainly the message that a POSA and that I come 8 away with reading this – this paper is that an 9 acetyl group is -- has undesirable characteristics 10 and set the stage for why people were using an 11 isobutyryl group till this very day. I'm done. 12 Q And in this paper, Khorana was using 13 phosphodiester coupling chemistry? Well, in 1972, 14 he wasn't using phosphoramidite chemistry, right? 15 A That's correct. 16 Q Okay, he was using phosphodiester 17 chemistry? 18 A I'm certain that elements in this paper 19 entail phosphodiester chemistry. 20 Q And differences between phosphodiester 21 chemistry and phosphoramidite chemistry are 22 substantial in your view?	115 1 phosphodiester chemistry required prolonged and 2 harsh deprotection conditions? 3 MR. SHORES: Object to form. 4 A I haven't provided opinions on that, so 5 it would – I would be forced to sit and speculate 6 here. Certainly it's a different chemistry than -- 7 it's different, but protecting groups remain 8 isobutyryl and acetyl that are discussed here in 9 this paper. 10 Q And didn't Pitsch use acetyl protecting 11 group? 12 A The Exhibit 1018 -- 13 Q Yeah. 14 A Pitsch reports using two prime O TOM -- 15 O2 prime TOM-protected ribonucleotide 16 phosphoramidites, and they happen to be using the 17 acetyl protecting group there. It's referenced, 18 yes. 19 Q And Pitsch didn't -- didn't report any 20 problems with that. 21 MR. SHORES: Object to form, lack of 22 foundation.
114 1 A It's a different approach for how to 2 stitch together monomers, if you will, nucleotide 3 units, but once again here, the -- the key 4 take-away here that inspired the field going 5 forward was -- and there are many citations to this 6 paper by the field, is that the isobutyryl group 7 was a superior protecting group relative to the 8 acetyl group. 9 MR. SHORES: I just want to put an 10 objection on to your prior question, object to 11 form, and object, lack of foundation. 12 BY MR. MADDOX: 13 Q Just read his answer back. Khorana 14 stands for the proposition that the isobutyryl 15 group is a superior protecting group relative to 16 acetyl in phosphodiester coupling chemistry, yes? 17 A I don't think that's the take-away to -- 18 to -- I don't believe that's the take-away, not 19 with a phosphodiester limitation that you are -- 20 Q Uh-huh. 21 A -- providing. 22 Q Well, isn't it true that the	116 1 A I haven't -- I haven't testified as to 2 whether or not problems were being reported in -- 3 in -- in Pitsch. I certainly have some concerns 4 about some of the experiments that are described 5 here. 6 Q Uh-huh, but you actually cited that 7 Pitsch paper in one of your papers, didn't you? 8 A This paper here, 1018? 9 Q The Pitsch paper, yeah. 10 MR. SHORES: Object, lack of foundation. 11 BY MR. MADDOX: 12 Q I'm just saying in your research, you -- 13 you found this paper credible enough to cite in 14 your letter to Tetrahedron actually. 15 A Could you refer me -- provide me a copy 16 of this? 17 Q I can get that after the break, yeah, but 18 you have concerns about Pitsch now, sitting here 19 today. 20 A Oh, yeah, yeah, I have some concerns 21 about this paper here. 22 Q Uh-huh.

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117 1 MR. SHORES: Object to form and to the 2 extent it mischaracterizes the witness' testimony. 3 BY MR. MADDOX: 4 Q And where was the Pitsch paper published? 5 A Where? 6 Q What journal? 7 A The journal is Helvetica Chimica Acta. 8 Q Is that a well regarded journal? 9 A It's a peer-reviewed journal. 10 Q It's not considered one of the top five 11 journals in your field? 12 A I don't know how I would precisely 13 quantify top five in my field. It's -- it's a 14 journal that I have knowledge of. I have -- I 15 believe I have -- I don't -- I don't believe I've 16 published myself in it. It's a journal I know. 17 Q Okay. Well, let's look at -- let me give 18 you another exhibit to look at, 2013. I may have 19 given you that already. One second. Bear with me. 20 Our numbering system is off. Actually, this is -- 21 there you go, been previously marked as 2013. It 22 came with your declaration. Could you read the	119 1 journal you're familiar with? 2 A Yes. 3 Q Okay. It's a peer-reviewed journal? 4 A It's a peer-reviewed journal. 5 Q He expresses here in the first paragraph 6 that there are -- he says that the -- excuse me, 7 that the isobutyryl protection group now presents a 8 few shortcomings in his view, correct? 9 A That's what the three authors seem to -- 10 to -- want to convey. 11 Q Right. Now, there's reference in the 12 next paragraph to requiring long and drastic 13 deprotection step. Let's put the words aside for a 14 second. The isobutyryl protecting group did 15 require a long deprotection step, right? 16 A Depends on what you want to characterize 17 as long. So we can't get away from words, but the 18 description there, 17 hours in concentrated ammonia 19 at 60 degrees Celsius doesn't strike me as unusual 20 or surprising. 21 Q For that group. 22 A That -- I mean, I want to be clear here.
118 1 first two paragraphs to yourself? 2 A Of the introduction? 3 Q Yes, please, and then let me know when 4 you're done. 5 A Okay. 6 Q Would you agree that at least in the 7 introduction, he is saying that the isobutyryl 8 protection group used by Khorana has some 9 shortcomings now in light of the scientific 10 progress that has ensued? 11 MR. SHORES: Objection to form and to the 12 extent it mischaracterizes the document. 13 A I don't believe -- while it mentions the 14 work of Khorana, I don't believe this paper is 15 citing to Exhibit 2011 that we're looking at, or at 16 least not on the basis of the first two paragraphs 17 that I read. I looked at references 1 and 2. 18 Q Well, whoever this fellow is, Schulhof -- 19 are you familiar with Dr. Schulhof? 20 A I don't know Dr. -- Dr. Schulhof 21 personally, no. 22 Q Nucleic Acids Research -- is that a	120 1 This is one set of conditions that are listed. 2 Q Right. 3 A So -- 4 Q It's an example. 5 A Yeah. 6 Q And then the authors say well, in this 7 way, the deprotection step has become time 8 consuming. Do you see that? 9 A Yeah, I see that language. 10 Q Would you agree with that, that the 11 deprotection step for isobutyryl is time consuming? 12 MR. SHORES: Objection. 13 A I think -- so I don't believe I've 14 provided testimony about that specifically, but 15 sitting here, you know, I mean, depends on how you 16 -- if one was to assume 17 -- what's listed here, 17 17 hours, which I don't think are in any way, shape 18 or form a set figure, but depends on how you feel 19 about 17 hours. 20 Q Uh-huh. 21 A Whether that's time consuming or not, in 22 my lab, we don't necessarily have problems with

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121 1 that. 2 Q Well -- 3 A Depends on the application. Go ahead. 4 Sorry. 5 Q No, no. 6 A No, no, I had a pause there. 7 Q This article is dated 1987. By 2009, 8 isn't it true that the deprotection step in the 9 type of nucleosides we're talking about here became 10 a time-sensitive issue for efficiency? 11 MR. SHORES: Objection, lacks foundation. 12 A I think it depends on the context. Who 13 -- who are you talking about? For whom is that a 14 problem? 15 Q Well, for the people who want to make 16 oligonucleotides in the quantities that are 17 required. 18 A Was that your question? Sorry. 19 Q By 2009, it was a largely automated 20 process, the making of these oligomers, right? 21 MR. SHORES: Objection, lack of 22 foundation.	123 1 A Okay, I mean, automated DNA synthesis 2 means just as much that instead of a person pushing 3 through manually solutions through solid support, 4 that there is a machine that can suck up reagents 5 from bottles and do that work for a practitioner. 6 That's -- I -- my group actually likes to use the 7 word "machine-assisted." If you notice in many of 8 our publications, we use "machine-assisted" -- 9 Q Okay. 10 A -- rather than "automated," because 11 automated gives the false impression that you push 12 a button and out comes beautiful product in the 13 other end. That's not quite how it is. 14 Q Okay. Can I give you Exhibit 2016? 15 A And yes, you may. 16 Q 2016 came with your declaration to us. 17 It's -- if you look on the bottom, the author is 18 Iyer. 19 A I see that. 20 Q And the title is "Nucleobase Protection 21 of Dioxiribo- and Ribonucleosides." 22 A Correct.
122 1 A Well, I disagree with the broadness of 2 your question. It wasn't -- you said routine or -- 3 Q Automated. 4 A Automated. 5 Q By 2009. 6 A By 2009, I mean -- 7 MR. SHORES: Can we get a clean question? 8 This is -- you guys are talking over each other 9 here. What is the pending question? 10 BY MR. MADDOX: 11 Q By 2009, the synthesis of oligomers was 12 largely automated. 13 A So I think there are a couple of things 14 to break down here, what is meant by automated, and 15 I want to make sure that it's not misconstrued as 16 automated being routine. Those are two different 17 terms. 18 Q Okay. So what -- using your definition 19 of automated, is my question correct? 20 A I would need to define -- I can tell you 21 what I consider automated if that helps. 22 Q Sure, please do.	124 1 Q Okay. Now, if you turn to page 9 using 2 the ChemGenes exhibit, page 9, I would like to 3 understand if you agree with the following 4 sentence. It's the last paragraph on the 5 right-hand side, "The choice of a particular n-ACYL 6 protection group also depends on the type of 7 coupling chemistry that is employed." Would you 8 agree with that as a general proposition? 9 A I'm not sure I have an opinion on that. 10 I certainly haven't provided an opinion before. 11 Q Okay. So would you think that the choice 12 of a particular protecting group doesn't depend on 13 the type of coupling chemistry that's employed? 14 A I think the teachings from -- from -- 15 whether it is phospho -- I'm reading on here, 16 whether it's phosphodiester or phosphotriester or 17 phosphoramidite-based chemistry, the teachings 18 traverse the different types of chemistry that are 19 being used, coupling chemistries that are being 20 used. 21 Q I'm sorry, the teachings traverse the 22 different types of chemistries. Is that what -- do

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125 1 I understand what you said? 2 A I -- 3 MR. SHORES: Objection to the extent it 4 mischaracterizes his testimony. He was answering 5 your question. 6 A I believe what -- what is learned across 7 the different chemistries here, coupling 8 chemistries, applies. So I mean, to the extent you 9 mean to insinuate that the teachings of Khorana did 10 not inform procedures in phosphoramidite chemistry 11 or phospho(III) chemistry, I would say that's -- 12 very much say so that's incorrect. It's a natural 13 progression of chemistry since the teaching from an 14 earlier generation of coupling chemistry was taken 15 note of in subsequent generations of chemistry. 16 Q It was taken note of in several papers, 17 and then basically improvements were proposed, yes? 18 MR. SHORES: Objection. 19 A As I've testified, the field has been 20 using -- the oligonucleotide field has been using 21 isobutyryl as a protecting group for G -- does till 22 this very day, and it based -- on the basis of the	127 1 protecting group. 2 MR. SHORES: Object to form. 3 BY MR. MADDOX: 4 Q No implications. 5 A I don't know how to answer your question 6 in other terms than to say that the teachings of 7 Khorana were taken note of and inspired the field 8 in the subsequent works, the decades that followed. 9 Q In your own published work, you yourself 10 have acetylated guanine in a nucleoside, have you? 11 A I acetylated the N2 position -- 12 Q Yes. 13 A -- of guanine. 14 Q Yes. 15 A I don't think so. 16 Q Okay. If you had done that in 2009, 17 would that be relevant to your opinion here? 18 MR. SHORES: Objection. 19 A I would have to see the -- the paper that 20 you are referring to in which you seem to believe 21 that I or our group acetylated G. 22 Q Uh-huh, okay.
126 1 findings of the Khorana paper we discussed before 2 has been the epitome, the go-to protecting groups, 3 but as I also testified, there was -- there were 4 works, there was research conducted to try 5 alternative protecting groups to isobutyryl, none 6 of which ended up at the acetyl protecting group. 7 Q Well, wouldn't you say that Pitsch ended 8 up at the acetyl protecting group? 9 A The Pitsch paper is very much an outlier 10 in the ocean of literature that pertains to -- to 11 protecting groups for G I would say. The vast 12 majority of papers looked to the isobutyryl group 13 as the protecting group for G, and yes, there was 14 certainly efforts being made to come up with 15 alternative protecting groups, many examples that I 16 cite to that I provide testimony to, but none of 17 them ended up with -- with Pitsch -- with Pitsch -- 18 with Pitsch's acetyl, if you will. 19 Q So the conditions and duration of 20 deprotection in phosphodiester chemistry compared 21 to those in phosphoramidite chemistry had no 22 consequences for the desirability of acetyl as a	128 1 A And by G, if I -- I don't know if I'm 2 allowed to add on. 3 Q Yeah, go ahead. 4 A And by G, if you mean the G nucleoside -- as 5 in guanine in nucleobase. 6 Q Yes. 7 A So -- 8 Q That's what you mean by G, that's fine. 9 That's -- 10 A Well, I mean, we need to be consistent 11 here because -- 12 Q We are. 13 A -- G can be very -- mean very different 14 things, but guanine -- I don't -- sitting here -- 15 Q Right. 16 A -- I don't recall that we acetylated a 17 nucleoside that has a guanine in nucleobase. 18 Q Okay, understood, understood. Just give 19 me one second. Would you agree that by 2009, there 20 was a need for milder deprotection conditions than 21 in phosphodiester chemistry? 22 A Could you point me to what's considered

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129 1 typical deprotection conditions in phosphodiester chemistry? 3 Q Well, let me get you a reference. Maybe 4 that will help. Can I have 2024? Read it all and 5 -- 6 A Thank you. 7 Q And obviously there's a lot there, but I 8 can point you to a page that -- bear with me a 9 second. I got the wrong one. 10 A Do you want it back? 11 Q Yeah. Yeah, sure, let's take it back. 12 You guys can keep it. 13 MR. SHORES: Gee, thanks. 14 BY MR. MADDOX: 15 Q Bear with me a second. I'm sorry. 2018, 16 which I think we already did. 17 A And I realize we just had a break, and I 18 apologize, but at some point, I would like a quick 19 -- 20 Q Let's do it now. 21 A -- five-minute bio break. 22 MR. MADDOX: Sure. No problem.	131 1 deprotection conditions than long exposures to 2 concentrated ammonia? 3 A That it asserts a need for -- 4 Q Yeah, uh-huh. 5 A -- other deprotection conditions? Was -- 6 Q Milder. 7 A Milder. 8 MR. SHORES: Objection. 9 A The last sentence says there is a need 10 for milder deprotection conditions in the case of 11 synthetic RNA methylphosphonate oligonucleotide 12 diesters, or oligonucleotides containing 4- 13 thiothymidine or 6-thioguanosine. So it's in those 14 -- in that context this paper references a need for 15 milder deprotection conditions. 16 Q And the -- 17 A It would seem to suggest. 18 Q Right, and would you understand that to 19 be milder than the phosphodiester deprotection 20 conditions? 21 A I don't have an opinion about that. 22 Q Okay. Now, it's true, isn't it, that
130 1 THE WITNESS: I apologize. 2 MR. MADDOX: No problem. 3 THE VIDEOGRAPHER: We are going off the 4 record. The time is 1:52 p.m. 5 (Recessed at 1:52 p.m.) 6 (Reconvened at 1:56 p.m.) 7 THE VIDEOGRAPHER: We are back on the 8 record. The time is 1:56 p.m. 9 BY MR. MADDOX: 10 Q Let me give you what's been previously 11 marked as Exhibit 2018. 12 A Thank you. 13 Q Do you recognize this as the -- one of 14 the Sinha papers you cited in your declaration? 15 A Yes, yes, I do. 16 Q Could you take a moment and read the 17 first paragraph of the introduction to yourself? 18 A Yeah, the first paragraph? 19 Q Yes, sir. 20 A Yeah, I read it. 21 Q Okay, and would you agree that it 22 concludes by asserting a need for milder	132 1 Khorana stated one reason for his selection of 2 protecting group was the extended nature of the 3 present task was going to take days of processing, 4 yes? 5 MR. SHORES: Objection to the extent it 6 mischaracterizes the document. 7 BY MR. MADDOX: 8 Q Let's go to 2011. You have it there, 9 yes? Page 221. 10 A Yes. 11 Q And I can direct you to a particular -- 12 bear with me a second. I'm sorry. 13 A You're good. 14 Q You know what? Skip that. That's all 15 right. Sorry. So you're familiar with the Fan 16 paper? 17 A If you mean Exhibit 1019, yes, I am, if I 18 could ask for a copy of that. 19 Q Sure. 20 A Thank you, Counsel. 21 Q And the Fan paper published some data 22 about the relative speeds of deprotection for

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133 1 isobutyryl, acetyl and phenoxyacetyl, correct? 2 A The Fan paper reports some time required 3 for deprotection of certain model nucleosides that 4 are -- 5 Q Right. 6 A -- silylated at the 2 prime, 3 prime and 7 5 prime position, all in common that they have 8 guanin in nucleobase that -- 9 Q Rate. 10 A -- carries different protecting groups at 11 the N2 position, but it's very highly specialized 12 nucleosides that they're looking at here. 13 Q And it was designed actually to -- to 14 study the relative speeds of the deprotection, 15 correct? The experiment. 16 MR. SHORES: Objection. 17 A I cannot speak to what the thought 18 process that the authors had behind their 19 experiments. I can look at the data and the 20 nucleosides that they used. 21 Q Okay, okay. Well, would you agree that 22 the data they presented at least for their	135 1 Q No, I'm sorry, the oligonucleosides of 2 the invention. 3 A I have testified to that fact, that a 4 POSA, if presented with this paper, would note that 5 data here are reported for this particular 6 nucleoside that is silylated at the two, three and 7 five prime positions using those very specific 8 nondeprotection conditions that wouldn't be used 9 for an oligonucleotide, yes. 10 Q Which deprotection -- you mentioned that 11 twice, deprotection conditions that would not be 12 used for oligonucleotide. What are those 13 deprotection conditions you're talking about? 14 A So right above table 1, it states to 15 compare deprotection rates of the guanin and 16 isobutyryl, acetyl and phenoxyacetyl groups of 17 compound 6a, 6b and the corresponding isobutyryl 18 derivative were dissolved in, and here come now the 19 deprotection conditions. 1.4 milliliter of a 20 solution provided that they use nine micromole 21 samples, 1.4 milliliter of a solution that was 1.3 22 percent methylamine, 2.6 percent ethanol, and 96
134 1 nucleosides, right, suggested that acetyl required 2 a factor of three times less time for deprotection 3 compared to isobutyryl? 4 A I would say that for the nucleoside that 5 they are studying here, which is of the compound 6 6 family I believe, 6a, 6b, and the corresponding 7 isobutyryl derivative, which they subjected to some 8 very peculiar deprotection conditions that one 9 wouldn't use for oligonucleotide synthesis, I would 10 say that table 1 shows that phenoxyacetyl was -- 11 required roughly five minutes, 4.7 minutes for 50 12 percent deprotection, that an acetyl required four 13 and a half hours, and isobutyryl required -- with 14 an -- those nucleosides with an isobutyryl group 15 required 80 hours for 50 percent deprotection. 16 Q Right, and it's your position that a 17 person of ordinary skill in the art would -- would 18 not attach any significance to this data in terms 19 of the nucleotides we're -- that we're discussing 20 here. 21 MR. SHORES: Objection. 22 A We're discussing nucleosides.	136 1 methylene chloride by weight. 2 Q And so a person of ordinary skill in the 3 art would assume that -- well, first of all, take 4 these conditions you just described. 5 A Uh-huh. 6 Q We do agree that these different times 7 were produced under those conditions. 8 A They're -- I have no reason to doubt -- 9 Q Okay. 10 A -- really that the authors for those 11 particular nucleosides that they studied under 12 those particular deprotection conditions, which I 13 note here lack a temperature, at least as far as I 14 can tell here in that brief description, that they 15 obtained those data. 16 Q So a person of ordinary skill in the art 17 would assume that different deprotection conditions 18 might lead to the reversal, which would mean that 19 acetyl and isobutyryl were either the same, or that 20 isobutyryl was even faster than acetyl. 21 MR. SHORES: Objection. 22 A I mean, Khorana already spoke about the

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137 1 lability of the N acetyl group, so I don't think 2 there's any -- any controversy here that acetyl 3 likely would deprotect faster than isobutyryl 4 group. You can come up with deprotection 5 conditions where they would have de facto similar 6 deprotection conditions. I'm guessing one could 7 design that. That would be extremely harsh 8 conditions, but yeah, no, I mean -- yeah, I'll stop 9 there -- 10 Q Okay. 11 A -- and elaborate. 12 Q Acetyl is more labile than isobutyryl. 13 A I already provided testimony that Khorana 14 in 1972 observed that on the -- on the basic 15 conditions, that acetyl group had a tendency to 16 fall off readily -- too readily, whereas the 17 isobutyryl group was -- provided more stability. 18 Q So with respect to the person of ordinary 19 skill in the art, what -- what if anything can the 20 person of ordinary skill in the art in your opinion 21 take from this article with respect to the 22 desirability of using acetyl?	139 1 I'd like to ask is in your opinion, does the person 2 of ordinary skill in the art take anything from 3 Pitsch in combination with the '031 patent and 4 using -- and acetylating the guanin. 5 MR. SHORES: Object to form. 6 A Okay, did I provide an answer to that 7 question -- 8 Q No. 9 A -- because -- 10 Q Sure. 11 A I thought you were talking about -- 12 Q I understand. 13 A -- Fan. And then if you could repeat it 14 again? Sorry. 15 Q Sure. We're reaching the limit of my 16 computer skills here. One second. Does the person 17 of ordinary skill in the art in your opinion take 18 anything from Pitsch as to why the '031 patent 19 compound X should be acetylated? 20 A I believe I provide very rich testimony 21 to -- to that effect already in my written 22 declaration that a POSA would not have been
138 1 MR. SHORES: Objection. 2 A I've provided testimony that really a 3 POSA would not learn much from this paper as it 4 applies to the '031 patent and the asserted -- you 5 know, converting compound X into the corresponding 6 acetyl version. I don't think that this paper 7 provides much information in that -- or any 8 information in that regard. 9 Q Okay, and does Pitsch provide any 10 information in that regard to the person of 11 ordinary skill? 12 A Perhaps you could point me to a paragraph 13 where you believe that Pitsch -- sorry, yeah, okay. 14 Q Back up. I switched papers. 15 A Oh, you -- 16 Q So let's go back to -- 17 MR. SHORES: Is there a pending question? 18 A Yeah, yeah, okay, perhaps you could -- 19 Q Yeah. 20 A -- repeat the -- yeah, repeat the 21 question. 22 Q Working on it, working on it. So what	140 1 motivated to switch from an -- switch the 2 isobutyryl group of the '031 compound X to an 3 acetyl group for a variety of reasons. I mean, 4 again, here, Pitsch is a -- first off, Pitsch 5 speaks about TOM-protected -- O2 prime 6 TOM-protected nucleosides and oligonucleotides, 7 whereas Fan -- no, whereas the '031 is -- compound 8 X is of course a 2 prime fluoro, so we're talking 9 very different compound classes here to begin with, 10 yeah. 11 Q Okay. And I believe -- well, your 12 testimony's your testimony. One second. Can I 13 have 2012? You've been handed what's been 14 previously marked 2012. 15 A Yeah. 16 Q You recognize it as the Shaller paper 17 you've since cited in your declaration? 18 A Yes, I cited to this paper. 19 Q Paragraphs maybe 113, 115? 20 A Thank you, 113, one -- 21 Q Fifteen. 22 A Fifteen, thank you. Yes, I'm right now

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141 1 trying to -- 2 Q Sure. 3 A There we go I think. Yes, yes. 4 Q Okay. 5 A I have that exhibit in front of me. I 6 think I'm roughly where -- at the place -- 7 Q Sure. 8 A -- I cited. 9 Q Sure. Now, it's your position that this 10 paper would have -- would have -- would have 11 deterred a person of ordinary skill in the art from 12 acetylating the guanosine, correct? 13 MR. SHORES: Objection. 14 A That's what I provided testimony to in 15 paragraph 115. 16 Q Right. 17 A POSA would have understood that the 18 literature demonstrated that adding acetyl to 2 19 prime deoxyguanosine has solubility issues, and 20 therefore, the result was it failed to prepare the 21 N, comma, 3 prime, comma, 5 prime 22 triacetyldeoxyguanosine satisfactorily, yeah.	143 1 A Yes, acetylation of 2 prime -- so the 2 last paragraph on the left -- left column on page 3 3822 -- 4 Q Right. 5 A -- states acetylation of deoxyguanosine 6 so as to prepare the triacetyldeoxyguanosine did 7 not proceed satisfactorily, and yes, there are 8 solubility issues as described in the -- in the 9 footnote. 10 Q Now, this paper is from 1963, correct? 11 A That's -- that's -- received -- there, 12 upper left corner, yes. 13 Q I'm sorry, it was received in '63, maybe 14 published -- 15 A No, it is 60 -- that's what I -- 16 Q Yeah. 17 A Upper left corner says December '63. 18 Q Okay, so this was obviously not using 19 phosphoramidites. 20 A That was not. 21 Q This was not phosphoramidite chemistry? 22 A That doesn't really pertain to the matter
142 1 Q Right, and that's on page 3822. 2 A That's correct. 3 Q Okay. And it's that first -- it's in the 4 last paragraph, first sentence, acetylation -- 5 A Uh-huh. 6 Q -- et cetera. 7 A Uh-huh. 8 Q And there's a footnote there, correct? 9 A Yes. 10 Q Okay, and in the -- 11 A There are two -- there are actually three 12 footnotes. 13 Q Yes, sorry. There's 21 -- 14 A Uh-huh. 15 Q -- which says a part of the cause of 16 failure to accomplish N-acetylation could be due to 17 the insolubility of 3 prime 5 prime di-O, and it 18 goes on. 19 A Uh-huh. 20 Q Which separates from the reaction 21 mixture. Is that what you're saying a person of 22 ordinary skill in the art would be worried about?	144 1 that I opined on because what I'm opining on is 2 nucleoside chemistry at this point, acetylation of 3 deoxyguanosine. 4 Q And so you -- you think -- let me 5 rephrase that. It's your position that a person of 6 ordinary skill in the art, rather than looking to 7 Pitsch's successful acetylation and Fan's data on 8 relative deprotection speeds on acetyl, would look 9 back to this 1963 paper and at the problem that 10 this particular author had and then solved actually 11 in the next sentence of the footnote, right? 12 MR. SHORES: Objection. 13 A So could you repeat your question? 14 Q Well, let's look at the footnote 21. 15 A Uh-huh. 16 Q The second sentence begins more recently, 17 using the base tri -- is it N? Tri-n -- could you 18 pronounce that for me? 19 A Sure, tri-n-hexylethylammonium hydroxide. 20 Q -- to solubilize the nucleoside carrying 21 out the acetylation over prolonged periods, it has 22 proved possible to acetylate the guanine ring in

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1 deoxyguanosine, so -- 2 A I see that. 3 Q So they did get -- they did get it done, 4 but not satisfactorily. Is that -- is that how we 5 read that? 6 MR. SHORES: Objection. 7 A Yeah, so I mean, so it's important to -- 8 to -- to understand here in my paragraph 115, a 9 POSA would have known in general that -- that 10 nucleosides that bear a guanin nucleobase were 11 inherently polar, and it's very well known in the 12 field of nucleoside chemistry that these kinds of 13 nucleosides with a guanin are very polar and can 14 cause difficulties during reactions, during 15 purifications. 16 If one has an amidite, it can cause 17 problems during the introduction of the use of 18 phosphoramidites to build oligonucleotides, all of 19 these steps that can be littered with problems when 20 using guanin, having nucleosides with a guanin 21 nucleobase, and here I cited one example from the 22 -- from the literature that speaks to the -- the	145 1 respect. 2 Q Okay, so -- okay, let's move -- let's 3 move a half a century forward. Can we do Exhibit 4 1029 please? Now, before we do this, what -- what 5 relevance is solubility to SPOS? 6 A I mean, in order for -- I mean, that's a 7 very broad question you're asking me here, which I 8 -- again, I don't think I provided an opinion on in 9 my declaration directly, so sitting here, the 10 phosphoramidite that one uses in -- in solid phase 11 oligonucleotide synthesis needs to be soluble in 12 order to -- in the solvent that is used during the 13 coupling step in order to successfully facilitate 14 coupling. 15 Q And there's some degree of insolubility 16 that would eventually become a problem for that, 17 right? 18 A There's -- there's some -- I'm just -- 19 Q Okay, let me -- 20 A Okay, go ahead. 21 Q Let me rephrase. So every degree of 22 lesser solubility does not present a danger, does
146 1 problems that are associated with the polarity of 2 guanin. 3 Q Okay, and so this -- the polarity is 4 discussed in here? And when I say in here, I mean 5 Exhibit 2012. 6 A Well -- 7 Q Polarity? 8 A Solubility is intricately linked to 9 polarity of a compound. One -- the solubility of a 10 compound depends on its polarity, so they are -- 11 they're linked. 12 Q Okay. So a person of ordinary skill in 13 the art would look to this 1963 article rather than 14 to Pitsch. 15 MR. SHORES: Objection. 16 A I think a person of the skill in the art 17 would know inherently that nucleosides with guanin 18 nucleobases are very, very polar and can cause 19 difficulties and would -- would know that there are 20 challenges associated with -- with these kinds of 21 nucleosides, and this paper here that we're 22 discussing provides -- adds to the evidence in that	147 1 it? 2 MR. SHORES: Objection. 3 A It's a difficult question to answer in 4 the sense of if -- if -- if the -- if -- if the 5 amidite, if the reagent precipitates or forms some 6 gelatinous -- gelatinous structure during SPOS, 7 then that becomes a problem that affects SPOS. 8 Q Well, in the context of SPOS, wouldn't 9 you agree that solubility is more a question of 10 degree than a binary result? 11 MR. SHORES: Objection. 12 A A phosphoramidite cannot be used 13 productively if it precipitates out or it forms 14 gelatinous -- something that's gelatinous in 15 nature. 16 Q Correct, but there must be a whole range 17 of solubility that doesn't -- doesn't produce those 18 circumstances, right? 19 A There's something between gelatinous and 20 miscible, fully soluble. 21 Q Correct. 22 A Sure, there's phosphoramidites.
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149 1 Q And what's your evidence that -- with 2 respect to acetyl, the acetyl's impact on 3 solubility is what caused the gelatinous or the 4 falling out? 5 MR. SHORES: Objection. 6 A In which context? 7 Q In the context which you say it would 8 dissuade a person of ordinary skill in the art. 9 A So -- 10 MR. SHORES: Objection to the extent it 11 mischaracterizes his testimony. 12 A So I provided testimony that the reduced 13 solubility of nucleosides carrying guanin 14 nucleobases and that half and N2 acetyl group that 15 carry into acetyl groups could cause problems 16 during the synthesis and work-up and purification 17 of nucleosides and the intermediates leading up to 18 phosphoramidites as well then as at the -- at the 19 -- at the level of phosphoramidite when it's used 20 in solid phase oligonucleotide synthesis. 21 Q Let me just read that. 22 A Yeah.	151 1 caused it? 2 A The low solubility? 3 Q Yeah. 4 A So in -- the authors, including Nobel 5 Laureate Khorana, stated that they thought that was 6 due to matters of solubility, and certainly that 7 seems like a very logical conclusion to me, given 8 that it's very well known and a POSA would have 9 known that guanin -- that nucleosides with guanin 10 nucleobases are very, very polar. 11 Q Okay, so the person of ordinary skill in 12 the art would go back to 1963 to footnote 21, where 13 they said -- the authors said this could be due to 14 the insolubility, and it goes on and on and on, 15 even though in the next sentence, they came up with 16 a way to do the acetylation, right? 17 MR. SHORES: Objection. 18 A A POSA would know that -- that 19 nucleosides with a guanin nucleobase are very 20 polar. That's -- that's just well known. That's 21 -- that's well known. 22 Q Right.
150 1 Q Okay, so it's theoretically possible that 2 the acetyl group could be so, what, insoluble or 3 soluble as to cause a problem? 4 A That the compound that the acetyl group 5 sits on has such low solubility in organic solvents 6 that it causes synthetic transformations or 7 extractions of purifications to fail and -- and/or 8 that causes the coupling of N2 acetyl protected -- 9 N2 acetyl G nucleosides to -- to fail during 10 coupling. 11 Q Okay, and have you cited any literature 12 documenting that kind of failure for that cause? 13 A I cited Exhibit 2012 for where -- as an 14 example, where it gave difficulties during 15 synthesis of -- during nucleoside synthesis broadly 16 defined. 17 Q Right, and that's -- that's what we just 18 looked at -- 19 A Yeah. 20 Q -- where the -- he didn't -- did he 21 conclude that that's what caused it or did he 22 speculate that -- did he hypothesize that's what	152 1 A And one -- one -- one piece of literature 2 that -- that indicates that, that shows that is the 3 cited paper that we have been discussing, but this 4 is a very well established fact. Any chemist can 5 put in a nucleoside in ChemDraw, for example, and 6 predict properties and see that -- that nucleosides 7 with guanin nucleobases are going to be very polar. 8 Q Okay, and then how do you go with the 9 next step, that using an acetyl protection group 10 would make the reaction that you want fail? 11 MR. SHORES: Objection. 12 A So -- so the literature here gives a good 13 example, right, 2012, that an intended 14 triacetylation of 2 prime deoxyguanosine failed to 15 produce the desired compound because of solubility 16 issues. 17 Q Now, you're familiar with the Donga paper 18 that was attached to Dr. Baran's declaration? I'm 19 going to give you a copy obviously. 20 A Yeah. 21 Q Exhibit 1029. 22 A Could I perhaps ask for a copy of

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153 1 Dr. Baran's petition, which is Exhibit 1003 I 2 believe? 3 Q Certainly. Certainly can. Previously 4 been marked as -- there you go. 5 A Thank you. 6 Q I can give you the question so you know 7 where we're going if you want. 8 A Sure. 9 Q The question is didn't Donga acetylate a 10 guanin base actually in a solution-based chemistry? 11 A Counsel, I must admit that my 12 recollection of this paper is fuzzy at best. 13 Q Okay. 14 A I have not read this paper -- 15 Q Okay. 16 A -- in a very long while. 17 Q Well, I'm certainly not going to ask you 18 to stop everything and read it right now. We can 19 move on. 20 A Okay. 21 Q So the answer to the question is you 22 don't -- you can't tell because you haven't read it	155 1 2009, why is this book relevant? 2 MR. SHORES: Objection to the extent it 3 calls for a legal conclusion. 4 BY MR. MADDOX: 5 Q In your mind, why is it relevant? 6 A In my mind, so I believe that's because 7 the material that I cite to in this work pertains 8 to the known lability, also known prior to 2009, 9 known lability of oligonucleotides that are 10 modified with 2 prime fluoro monomers. 11 Q Okay, so the -- the part you're relying 12 on is directed to 2009, or 2009 or earlier? Is 13 that the idea? 14 A What I'm saying is that it's part of my 15 testimony regarding -- I believe that's where it's 16 cited, secondary indicia for what's called 17 nonobviousness, right? And so let's all go there, 18 around 184 I believe of my -- 19 Q All right. 20 A So -- so the reason I'm citing to this -- 21 to the chapter by -- by Sinha I believe in here is 22 discussing secondary indicia of nonobviousness
154 1 recently? 2 A I have not read this paper -- 3 Q Okay, that's fine. 4 A -- recently for sure. 5 Q All right. Let me look at -- okay, let 6 me give you 20 -- Exhibit 2024. 7 MR. SHORES: That's the forest. 8 BY MR. MADDOX: 9 Q And 2024 is a book chapter that you 10 provided in connection with your declaration. 11 A Yes, I cited to a book chapter, not the 12 book. 13 Q Right, this is actually the book chapter 14 I think. Oh, well, anyway, either way, this is 15 what we -- we got from you all, and it's certainly 16 comprehensive, so -- just wait one second. The 17 first question is you agree that this book was 18 published after 2009, right, if you look on page -- 19 little page IV, the copyright, 2013. 20 A Yes, I see that. 21 Q Okay, and are you saying nevertheless, 22 this book is -- reflects -- well, if the cutoff is	156 1 inasmuch in the '885 patent, the -- the patent 2 owners are describing problems associated with 2 -- 3 with oligonucleotides that are modified with 2 4 prime fluoro modified monomers. 5 The specifications of the '885 patent 6 speaks to two conferences in which such report -- 7 two conference presentations in which these 8 observations were made, and what I'm citing to here 9 is an article from one of the conference presenters 10 that speaks more elaborately about those problems. 11 Q Okay, so what was the -- what -- okay, so 12 what secondary consideration is this relevant to? 13 MR. SHORES: Objection -- 14 THE WITNESS: I mean -- 15 MR. SHORES: -- to the extent it calls 16 for a legal conclusion. 17 THE WITNESS: So -- 18 BY MR. MADDOX: 19 Q Are you saying that this reflects an 20 unexpected result of some sort? 21 A No, no, what I said -- so let's -- 22 perhaps we should go to my declaration --

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Shanghai Hongene Exhibit 1035
Shanghai Hongene v. ChemGenes
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157 1 Q Sure. 2 A -- and paragraph 184 and onward. 3 Q I'm sorry, say the paragraph number 4 again? 5 A 184. So what I said just before, what I 6 testified just before now, it's not -- obviously 7 not going to be verbatim, was that -- that it was 8 well known at the time of the patent pre-2009 that 9 oligonucleotides containing 2 prime fluoro 10 modifications, that there were problems associated 11 with the making of such oligonucleotides, and that 12 is discussed in the '885 patent. The '885 patent 13 cites to conference presentations where that was 14 observed. So that's part of the prior art, and 15 this Exhibit 2024, the section that I refer to 16 there is a more elaborate discussion of those 17 problems that were observed by one of the 18 conference presenters. 19 Q Okay. 20 A So -- 21 Q Bear with me a second. So you're saying 22 --	159 1 A Correct. 2 Q And you think this chapter is 3 sufficiently related to these presentations that it 4 should be considered part of the specification? 5 MR. SHORES: Objection. 6 A I think that book chapter elaborates on 7 the problems that were being observed with the 8 stability of oligonucleotides containing 2 prime 9 fluoro monomers, provides proposed reaction 10 mechanism and -- and -- and so forth, but I do want 11 to point out that -- that '885 in column 11 says 12 the studies as shown in scheme 3, and then it lists 13 the two conference presentations, and then in 14 scheme 3, it shows the -- the effects on quality of 15 oligonucleotides containing 2 prime fluoro 16 nucleosides that, for example, the use of 17 deprotection with methyl amine resulted in. 18 Q Which chapter were you referring to? 19 Maybe you say. 20 A That is a tall ask here, but -- 21 MR. SHORES: Citation there. 22 THE WITNESS: Yeah.
158 1 A So for example, if you go to paragraph 2 187 -- 3 Q Right, that's where I am. 4 A Okay. 5 Q So the patent refers to some 6 presentations, right? 7 A Uh-huh. 8 Q And this book chapter is that 9 presentation? 10 A Sinha -- so Sinha, Nanda Sinha in the -- 11 in the citation that I provide on the -- 12 Q Oh, I -- 13 A -- on top of page 82, Sinha -- Sinha was 14 one of the conference presenters, and same Sinha is 15 the author of the chapter provided here in Exhibit 16 1020 -- 2024. Pardon. 17 Q Okay, and the '885 patent -- 18 A Uh-huh. 19 Q -- was filed in 2010, and this is 20 published in 2013, so they weren't -- they weren't 21 citing to this chapter. They were citing to some 22 presentations.	160 1 MR. SHORES: Paragraph 187, there's a 2 citation to page 83, a pinpoint cite -- 3 THE WITNESS: Thank you. 4 MR. SHORES: -- of 2024. 5 BY MR. MADDOX: 6 Q Eighty-three. 7 A Eighty-three. 8 MR. SHORES: Eighty-three of Exhibit 9 2024. 10 A Must be page 83, right? Yeah, page 83. 11 So where it starts -- 12 Q "There's a growing interest," that? 13 A No. Yeah, yeah, yeah, sorry. Section 14 2.4.4, yeah, that section and the subsequent pages. 15 Q Okay. So this is about 2 fluoro 16 modifications. 17 A And just so you don't get confused, that 18 section, section 2.5.4, refers to two figures, 19 figures 2.41 and 2.42. They're ironically not the 20 next two, but number 2 and 3 that follows. 21 Q Okay, and this is written from the 22 perspective of 2009?

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161 1 A This is by the author Sinha, and the book 2 was published in 2013, so of course, I cannot say 3 -- 4 Q Okay. 5 A -- when he penned this, but it certainly 6 describes the same concerns that are mentioned in 7 the '885 patent in column -- was it 11? Column 11. 8 Q Okay, we can put that aside. 9 A I hope that made it a little clearer. 10 Q Little bit, little bit, sure. Now if you 11 could go to your -- your declaration at paragraph 12 154 -- 13 A Yes, I'm there. 14 Q Okay, I'm not. One second. Okay, now, 15 you say in this paragraph 154 that there was going 16 to be -- the person of ordinary skill in the art 17 would be worried about cleaving; is that right? 18 A Yes, cleaving acetyl groups, yeah. 19 Q Okay, and then in -- I don't see a cite, 20 so why -- why is it -- why is it that a person of 21 ordinary skill in the art would have been worried 22 about cleaving?	163 1 Q Okay. And have you cited any papers 2 where that had occurred? 3 A So I have -- yes. 4 Q Okay. Where -- where can I go for those? 5 A Well, I have cited one paper, for 6 example, that -- that speaks to -- to -- to this 7 effect, and I believe that's Exhibit 2015. 8 Q Okay, I'm looking for that here. One 9 sec. 10 A I will also note while we look for that 11 that I have personal -- literally personal 12 experience, me myself as a student at least that 13 TBAF can cleave -- 14 Q Right. 15 A -- O acetyl groups. 16 Q Right. I'm looking for -- oh, here it 17 is. 18 A My apologies. Sixty-nine, bottom right 19 corner. 20 Q That's the Ober. 21 A Yes, if I could ask for a copy of that? 22 Q Absolutely. We can take a break after
162 1 A So the problem at hand here is that in 2 Dr. Baran's and thereby petitioner's theory of how 3 to reach an N2 acetylated version of compound X, at 4 this point in time in the synthesis, there would 5 have been acetyl groups, if we look at -- at page 6 69, I provided chemical structures there, instead 7 of two isobutyryl groups present as in compound -- 8 example 4-d Roman numeral 2, compound 2, instead of 9 two isobutyryl groups being present at respectively 10 the N2 position and the O2 prime position, there 11 would now have been two acetyl groups. 12 And the concern here is that it was -- a 13 POSA would have known that TBAF, tetra 14 butylammonium fluoride, is a -- is a relatively 15 harsh reagent, what's called -- what chemists would 16 call nucleophilic reagent, that not only would 17 result in the desired deprotection of the 3 prime 18 and 5 prime positions, so-called disilylation but 19 also, there would be a considerable concern that 20 acetyl groups at the N2 and O -- and/or O2 prime 21 position would be cleaved. That's the concern that 22 I have expressed here in this section.	164 1 this exhibit. Sound good? 2 A Yeah, yeah, that's fine by me. Thank 3 you. 4 Q So what proposition -- for what 5 proposition are you relying on Ober? 6 A As it pertains to the general section 7 that we're discussing here of my declaration 8 starting on page 68 and moving forward, we're -- I 9 cited to Ober as an example where there are 10 concerns for the stability of N2 acetyl groups at 11 the N2 position. 12 Q And didn't Ober actually succeed in 13 acetylizing? 14 A They -- they -- so if we go to -- if we 15 go to page 18144 -- 16 Q Uh-huh. 17 A Right column towards the end -- well, 18 second -- third sentence of the last paragraph, the 19 subsequent. So speaking of compound 5, previous 20 sentence, the subsequent deprotection of the TBDMS 21 groups proved to be difficult due to the parallel 22 cleavage of the acetyl protecting groups under

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165 1 basic fluoride deprotection conditions, such as 2 TBAF and THF. 3 Q Right, and with respect to compound X -- 4 A Uh-huh. 5 Q -- are we talking about a TBDMS group? 6 A It's -- it's -- so if we go to the 7 structure that's -- that I provide in section 154 8 of my declaration, what we can call compound 2 as 9 well, that -- there's a name, there is a silyl 10 protecting group. A silyl, S-I-L-Y-L, silyl, 11 silyl. I think Americans pronounce it silyl. I 12 think Britain say silyl. There's a silyl 13 protecting group protecting the 3 prime and 5 prime 14 positions, and the TBDMS is also a silyl protecting 15 group. 16 Q Okay, but -- well, let's take -- let's 17 take a siloxane group. Maybe they call it 18 siloxane. You know what I'm talking about? 19 A Well, actually, let's agree what we're -- 20 Q It's S-I-L-O-X-A-N-E. 21 A Siloxane group. 22 Q Siloxane group.	167 1 A I think out of respect of this process, I 2 need to -- to know exactly what we're talking about 3 and -- when -- when I'm answering this question. 4 Q Let me come at it this way. Is there 5 such a thing as a siloxane group? 6 A From the -- I'm sure there is, and 7 perhaps that is the name of the protecting -- would 8 be what one would call the protecting group 9 spanning the 3 prime, 5 prime position of compound 10 2. Sitting here right now, I actually don't know 11 if that's the term that's being used. I don't use 12 that term, but doesn't mean that it isn't correct. 13 Q Could we go to Ober at -- 2015 at 18144? 14 I think we were already there. 15 A Ober 18144, uh-huh. 16 Q Right. The last sentence of the 17 paragraph you directed us to -- 18 A Uh-huh. 19 Q The cleavage reaction was finally 20 possible with pyridine buffered pyridine - HF 21 complex and ethyl acetate. 22 A That's correct, it says that.
166 1 A So that is -- that -- the silyl 2 protecting group of compound 2, is that where 3 you're going? 4 Q Well, I'm going where -- well, wasn't it 5 true that TBDMS was known to be difficult to 6 remove? 7 MR. SHORES: Objection. 8 A TBDMS? 9 Q Yeah. 10 A I would not characterize a -- give me a 11 second here. I would not characterize TBDMS as a 12 protecting group that's difficult to remove, no. 13 Q Would you characterize it as one that's 14 more difficult to remove than a siloxane group? 15 A So if you -- because I think it's a 16 trivial name you're using there. Do you mean the 17 silyl protecting group of compound 2? 18 Q I'm afraid I'm at the very outer limits 19 of my knowledge and I -- I kind of need to mean 20 what I say, siloxane group. If you can't answer it 21 because it doesn't make sense, I understand, but 22 that's --	168 1 Q Okay. So was there a cleavage problem 2 that they couldn't overcome? 3 A There was a cleavage problem that -- 4 introduced by TBAF, and then that required 5 experimentation and -- and -- and effort to 6 overcome, but they switched -- it seems that -- 7 that Ober switched -- then switched to this 8 particular reagent in order to facilitate 9 deprotection of TBDMS. 10 Q In order to overcome the problem. 11 A Chemists are there to overcome problems, 12 and Ober, through experimentation, found a way to 13 convert in for them satisfactory manner supposedly 14 compound 6 to compound 7 using these conditions, 15 the pyridine buffered pyridine hydrogen fluoride 16 complex. 17 Q And this extensive experimentation he 18 conducted, where is that described? You say -- 19 MR. SHORES: Objection. 20 BY MR. MADDOX: 21 Q -- he had to do a whole bunch of 22 experimentation to come with the solution.

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169 1 MR. SHORES: Objection to the extent it 2 mischaracterizes the witness' testimony. 3 A I'm saying that they probably -- I'm 4 speculating here. They probably went into the lab 5 and tried alternative conditions for deprotection 6 of -- of silyl protecting groups. The greater 7 point here was using TBAF as such did create a 8 problem, as I have observed in my own research. 9 Q And whatever problem it created here, 10 Ober overcame. 11 A It -- it -- sitting here looking at this, 12 it -- it seems that by -- I will note that they say 13 the cleavage reaction was finally possible with 14 pyridine buffered pyridine hydrogen fluoride 15 complex, so perhaps the word finally possible 16 indicates that there was considerable 17 experimentation. 18 MR. MADDOX: Okay, let's take a break. 19 THE VIDEOGRAPHER: We are going off the 20 record. The time is 2:56 p.m. 21 (Recessed at 2:56 p.m.) 22 (Reconvened at 3:20 p.m.)	171 1 targeting RNA and studying them in clinical studies 2 and so and so forth, I would say. We synthesize 3 oligonucleotides. 4 Q Right. Some are ASOs, some are not? 5 A I don't -- we have never had one of our 6 oligonucleotides tested for -- at least not that we 7 have published I think, for activity in terms of 8 biological activity. 9 Q Okay. 10 A So I don't -- I don't know if others 11 would categorize what we do as ASOs. We synthesize 12 oligonucleotides. 13 Q Okay, and could you just give me a little 14 background on how -- how -- how you go about doing 15 that, how you go from wanting to synthesize an 16 oligonucleotide to getting there. 17 A So that's a very broad question, but -- 18 okay, so assuming that there's some sequence of an 19 oligonucleotide that we want to make, typically in 20 my -- this is now not speaking in the context of 21 the '885 -- 22 Q Right.
170 1 THE VIDEOGRAPHER: We are back on the 2 record. The time is 3:20 p.m. 3 BY MR. MADDOX: 4 Q Okay, Doctor, you're familiar with the 5 acronym ASO? 6 A ASO? 7 Q Yes. 8 A In the context of my field, it's used for 9 antisense nucleotide. 10 Q Right, and you synthesize ASOs, you and 11 your group? 12 A I mean, it depends on what you in the end 13 call an AS -- what constitutes an ASO. We 14 synthesize oligonucleotides. 15 Q Right, and there are ASO approved drugs, 16 yes? 17 A Yes, there are compounds that are 18 categorized as antisense oligonucleotides that are 19 being used to that. I would like to add a little 20 comment just to what I said before. I mean, ASOs, 21 antisense oligonucleotides, indicates that one is 22 designing them with a clear-cut purpose for	172 1 A -- patent, so -- so speculating here on 2 the fly, what we would do is to decide that there's 3 some sequence that we want to make of a particular 4 oligonucleotide, typically some chemical 5 modifications, and then -- well, there are many 6 steps -- 7 Q Okay. 8 A -- involved in that, but that'll be kind 9 of -- yeah. 10 Q So you have an oligonucleotide in mind. 11 A Sure. 12 Q Okay, and then what -- what is sort of 13 the phases of development there? 14 A Well, first off, you need to make sure 15 you have a DNA synthesizer. 16 Q Okay. 17 A Next you need to make sure you have the 18 requisite phosphoramidite reagents and all of the 19 other reagents that are necessary for 20 oligonucleotide synthesis, and then depending on 21 the nature of the oligonucleotide that one sets out 22 to synthesize, one can employ machine-assisted

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173 1 oligonucleotide synthesis using the -- what 2 colloquially is called DNA synthesizers, and in my 3 lab, we have a mix of commercially available 4 deoxyribonucleotides, DNA monomers, if you will, 5 that we program the machine and says add these -- 6 these nucleotides, and at some point we would add 7 our modifications and do the typical purification 8 -- processing and purification that is involved, 9 and that is our chemically modified oligonucleotide 10 as in my group. 11 Q Right. 12 A Those are some of the practical steps, by 13 no means a all-encompassing process. 14 Q And how do you go about selecting the 15 reagents? 16 A Well, that is not necessarily a 17 straightforward question. There are many steps to 18 consider, what kind of solid support does one want 19 to use, what type of solid support, pore size, what 20 -- what chemical nature should the chemical support 21 have, price, where do I want to buy it from. Those 22 are some considerations.	175 1 read that. I'm sorry, folks. One second. 2 A Yeah, afterwards direct me to where we 3 are because I don't know where you are. Oh, there. 4 MR. SHORES: Where are we in the 5 document? 6 BY MR. MADDOX: 7 Q Oh, we're in column 10 of Exhibit 1001, 8 line 36, there's a note that I somehow thought we 9 wanted to look at, but I'm not sure anymore. Can I 10 have a highlighter? Do you have a highlighter? 11 Maybe that will make it pop. Okay, never mind. 12 We'll come back to that when we can read it. 13 Unbelievable. You're familiar with the term 14 "enantiomers," correct? 15 A Yes. 16 Q Okay, and do you agree that enantiomers 17 have the same physical and chemical properties with 18 respect to achiral reagents? 19 A Enantiomers as a pair of enantiomers will 20 be expected to -- will have -- it's not expect. 21 Will have identical physical properties, such as 22 boiling point, melting point and so on, so forth.
174 1 Then there are considerations about other 2 certain coupling reagents that I would have to 3 choose one or the other, a coupling reagent, that 4 depends on what modification one is using. There 5 are considerations whether one wants to do capping, 6 oxidation, capping. So the synthesis cycle, there 7 are many considerations there. There's coupling 8 time. There's lots of parameters that one needs to 9 consider, and which we consider every time when we 10 make chemically modified oligonucleotides. It's 11 not a black box push a button and out comes an 12 oligo in my lab. 13 Q Okay. Bear with me one second. Now, 14 excuse me. Could we look at the '885 patent? If 15 we could go to column 10, line 36 -- 16 A Okay. 17 Q I don't know if you can read it. It's 18 pretty faint. 19 A What's that? 20 Q We can -- you can see this is a sequence 21 diagrams, but at one point, it says compound 22 structure 6 is produced by -- man, I can't even	176 1 They will interact differently with entities that 2 are chiral, biological molecules, other chiral 3 molecules, and they will be synthesized from 4 different starting materials. That's also what I 5 provided testimony on to that effect. 6 Q But the actual finished enantiomers will 7 have the same properties with respect to achiral 8 materials. 9 A I don't know fully what you mean here by 10 achiral materials, but two enantiomers will have 11 identical physical properties in the sense of 12 melting point, boiling point, yeah, but again, they 13 will interact differently with other chiral 14 entities, and they are made differently, 15 substantially differently -- 16 Q Okay. 17 A -- in the sense they would start from 18 different starting materials. The synthesis would 19 start from a different starting material -- 20 Q Okay. 21 A -- normally. 22 Q Understood. Let's take a look at --

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177 1 excuse me, the '991 patent, which is 1020. 2 A Yeah, if I may -- 3 Q Sure. 4 A I'm getting confused with all the 5 exhibits we have. 6 Q Absolutely. 7 A I thought we had covered it. We haven't. 8 Q We've looked at the '031 and the '885. 9 A Yeah. 10 Q And there are not many others. Here we 11 go. 12 A Many other exhibits. 13 Q Yes, indeed. Here you are. 14 A Thank you. 15 Q Now, this is -- I'll represent to you 16 this is the -- Exhibit 1020, it's the '991 patent 17 that there's been some testimony, some declaration 18 testimony about. 19 A Sure. 20 Q And in particular, there's been 21 declaration testimony about compound 5 in figure 22 16, which --	179 1 figure 16, compound 5, asks -- if one goes to the 2 figure legend of figure 16, which can be found on 3 column 16, it states figure 16 shows that 4 illustrated -- shows the illustration of 2 prime 5 fluoro L cytosine phosphoramidite based on 2 prime 6 fluoro L uridine. So condensing my answer, clearly 7 this is a -- a L configured nucleoside -- 8 nucleoside phosphoramidite that we're looking at. 9 Q Okay, and if it -- isn't it -- isn't the 10 L configured nucleoside the enantiomer of a D 11 configured nucleoside? 12 A Yes, L and D, their relation -- if you 13 have -- it's mirror image. The compound 5's mirror 14 image would be a D -- a D -- the D configured 15 nucleoside within the cytosine and -- and acetyl 16 and all of that. 17 Q And with respect to non-chiral 18 interactions, wouldn't you expect them to have the 19 same properties? 20 A As I mentioned before, D and L, two 21 enantiomers will have same chemical properties, 22 boiling point, melting point, that kind of stuff,
178 1 A Yeah. 2 Q -- you can find on page -- 3 A I'm there. 4 Q You're there. Good for you. There, 5 okay. Now, you have in your declaration recited a 6 number of reasons why you don't find Dr. Baran -- 7 you don't agree with Dr. Baran about this patent, 8 about this compound. 9 A Correct. 10 Q One of them is that -- is one of them 11 that -- that this is L configured, and the X -- 12 compound X is D configured? 13 A There are several reasons why I -- I 14 disagree with Dr. Baran here, that there are two 15 key differences between compound 5 of the '991 16 patent and compound X. One is unequivocally -- 17 well, both are unequivocal. Let's start first, 18 what we're looking at here in compound 5 has a 19 cytosine base that is protected with an acetyl at 20 the N4 position, a completely different nucleobase 21 than -- than a guanine. 22 Secondly, and completely unequivocally,	180 1 but their syntheses will differ. How you get to 2 those compounds will differ substantially. And 3 then in the context we're speaking here in the '885 4 patent also, we're -- we're talking about SPOS, 5 solid phase oligonucleotide synthesis, and that 6 inherently does not include achiral compounds. It 7 entails nucleoside -- phosphoramidite's a growing chain 8 of an oligonucleotide that is chiral. 9 Q Okay, so -- 10 A So they would -- as I testify, would 11 behave differently. 12 Q I see. 13 A Made differently, behave differently. 14 Q Okay. So SPOS involves chiral 15 interactions. 16 A Yeah, that -- I mean, in the vast 17 majority of cases, the way that we're thinking 18 about oligonucleotide chemistry, it entails 19 inevitably nucleosides that have chirality 20 associated with them, so yes, that would entail 21 interactions between two -- between chiral 22 molecules, not achiral molecules.

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181 1 Q So -- so if you filed -- excuse me. If 2 you follow example 6 in the '991, which -- which on 3 its face says that that's how you get to compound 5 4 -- 5 A Could you direct us to -- 6 Q Yeah, let's take a look together, work 7 this out together. Let's look at example 6. Hang 8 on. I'll get you a -- 9 A Yeah, no, no, you're good. Sorry. 10 Q No, example 3, example -- sorry, I'm 11 still looking. 12 A You're good. 13 Q Example 4. Example 5 on column 41. 14 A Forty-one? 15 Q No, I'm sorry, my mistake. Example 6 we 16 need. Sorry. Example 6 on 45. 17 A Okay, I'm there. 18 Q Okay, so this is synthesis of L2 fluoro 19 phosphoramidites, right? 20 A That's the title -- 21 Q Right. 22 A -- of that section, yes.	183 1 could -- could -- could follow. 2 Q Hang on a second. Can we go back to 3 Exhibit 2014? It's the Guschlbauer paper. 4 A Guschlbauer. 5 Q Guschlbauer. I think I gave it to you, 6 but I could be wrong. 7 A No, I don't think you did. 8 Q Okay, well then let me reach into my box 9 of documents then. Why am I having trouble with 10 this? 11 A Thank you, Counsel. 12 Q Actually, I don't have this paper. Okay. 13 Now, do you recall generally why you cited this 14 document? 15 A Generally, yes. 16 Q And why was that? 17 A It was -- so let's go perhaps to my -- 18 Q Sure. 19 A So give me a second. Yeah, it's -- allow 20 me a second. 21 Q Sure. 22 A I know where I want to go. I just want
182 1 Q Right. And in a POSA's understanding of 2 this, what -- does this example 6 lead you to 3 compound 5? 4 MR. SHORES: Objection. 5 A I haven't provided testimony to that 6 effect I believe, but sitting here, I can speculate 7 and look at this. 8 Q I don't want you to speculate. If you 9 haven't -- if you -- if you'd be unable to tell 10 without doing, you know, detailed reading and so 11 forth, just tell me. That's fine. It's not a 12 reading test. 13 A Reading the first line or two, it 14 suggests -- it says the synthesis -- the second 15 line would seem to suggest 2 fluoro-L-uridine was 16 synthesized according to, and then it gives a 17 citation to a paper from 1964, and I note it says 18 there it's synthesized from L-arabinose. 19 Q Okay. 20 A So this probably seems to suggest a -- a 21 -- this -- this seems to suggest to me sitting here 22 right now a -- some guidelines that the reader	184 1 to find it, so -- 2 Q That's fine. 3 MR. SHORES: I think I know, but I don't 4 want to be -- 5 MR. MADDOX: If you want to -- 6 MR. SHORES: Yeah. 7 MR. MADDOX: Go ahead. 8 MR. SHORES: So it's -- 9 THE WITNESS: 168 I think. 10 MR. SHORES: And 171 as well -- 11 THE WITNESS: Yeah. 12 MR. SHORES: -- which is -- 13 THE WITNESS: I found it just as you -- 14 MR. SHORES: -- incorrectly cited there, 15 so -- 16 BY MR. MADDOX: 17 Q So where should we go? Paragraph -- 18 A Roughly around 168. I'm not committing 19 to 168 though. 20 MR. SHORES: Just on page 76, there's -- 21 it says Exhibit 2016, but I think that should be 22 2014.

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185 1 THE WITNESS: Yeah, that's correct, so I 2 miss -- miscited in my report on page 76 paragraph 3 178 where it says Exhibit 2016, 1421, that should 4 have been Exhibit 2014, 1421. Yeah, so -- 5 MR. SHORES: I think you said paragraph 6 178? 7 BY MR. MADDUX: 8 Q Yeah, you did. 9 A Oh, I did not mean to. I -- I apologize. 10 Paragraph 171. 11 Q Ah, okay. 12 A My apologies. Where it says -- 13 Q Ah, got it. 14 A -- Exhibit 2016 -- 15 Q Yeah. 16 A -- should be Exhibit 2014. 17 Q Oh, okay, this makes more sense now, 18 okay. 19 A And yes, so in this paragraph, I deliver 20 testimony speaking against the assertion that -- 21 the first sentence of paragraph 171 basically goes 22 to the effect of -- that I'm opposing the viewpoint	187 1 nature of the sub -- what that -- 2 A Substituent? 3 Q Yeah, no, I'm dealing with her shorthand 4 as well, which -- 5 A Yeah, uh-huh. 6 Q It can have an effect on its reactivity, 7 okay. Can have an effect on its reactivity, okay, 8 and the possibility of this effect would deter a 9 person of ordinary skill in the art from -- 10 MR. SHORES: Object to form. 11 BY MR. MADDUX: 12 Q -- using the 2 fluoro? 13 MR. SHORES: Sorry. 14 THE WITNESS: The point that I'm -- 15 MR. SHORES: Object to form. 16 THE WITNESS: The point that I'm trying 17 to make is that a POSA would know that a 2 prime 18 fluoro 2 prime deoxyguanosine is a very different 19 molecule than a 2 prime deoxyguanosine -- 2 prime 20 deoxyguanosine at least as one can speak to the 21 effect of nucleoside confirmation. It's very well 22 known by a POSA that the effect -- so-called
186 1 that 2 prime or 2 prime dioxyguanosine would react 2 -- would react similarly to a, quote unquote, 3 regular 2 prime dioxyguanosine, which is a position 4 that petitioner and Dr. Baran have taken, and what 5 I'm mentioning at the end of paragraph 171 in the 6 hopefully now corrected citation to the correct 7 exhibit is that at a very minimum, a POSA would 8 know that the nature of the substituent at the 2 9 prime position impacts the confirmation that a 10 nucleoside adopts and thereby can have effect -- 11 effect on its reactivity. 12 Q And so this possible effect on 13 reactivity, how would that influence the behavior 14 of a person of ordinary skill in the art? 15 MR. SHORES: Objection to the form. 16 A Could you rephrase the question? 17 Q Hang on. 18 A Your question as you stated made very 19 little sense to me, it impacted a POSA. 20 MR. SHORES: The behavior. 21 BY MR. MADDUX: 22 Q One second. A POSA would know that the	188 1 stereoelectronic effect that impacts the 2 confirmation of a nucleoside, that's driven by the 3 -- in part by the 2 prime substituent. 4 BY MR. MADDUX: 5 Q So did this paper, 2014 -- 6 A Uh-huh. 7 Q -- compare the reactivity of 2 fluoro -- 8 2 prime fluoro 2 prime deoxyguanosine to that of 2 9 prime deoxyguanosine? 10 A So this paper provides -- where is it? 11 Right there. This paper provides information, for 12 example, in -- in figure 4, how the -- how the 13 nature of the substituent at the 2 prime position 14 affects confirmation, and then in the discussion of 15 this paper, there's -- there's considerable 16 discussion how the confirmation of a nucleoside can 17 interact with water molecules, for example, in a 18 DNA duplex, how that has an effect on that. 19 Q But there's no comparison of the 20 reactivity of the 2 fluoro -- 2 prime fluoro 2 21 prime guanosine versus the 2 prime deoxyguanosine? 22 A There is -- there is -- there's a general

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189 1 -- there's a general discussion how nucleoside 2 confirmations translate to duplexes, I believe it's 3 DNA duplexes here, and how -- DNA duplexes, RNA 4 duplexes, and how they interact with water 5 molecules that are surrounding the duplex, so their 6 interactions with water. 7 Q I'm sorry, did you say so their 8 interactions with water? 9 A Water. 10 Q Is -- is water -- 11 A If -- sorry, I was just perhaps wanting 12 to guide you. 13 Q Is -- may I ask, is -- 14 A Go ahead. 15 Q Is water a standard reagent used to 16 convert nucleosides to N protected 17 phosphoramidites? 18 A No, water is not a -- 19 Q Okay. 20 A -- standard reagent. 21 MR. MADDOX: Understood. Why don't we 22 take a ten-minute break and we'll have a short	191 1 for compound 5 except started with a guanin 2 material in the D configuration instead of a 3 cytodine material in the L configuration? 4 MR. SHORES: Object to form. 5 A I haven't -- repeat your question please. 6 I want to make sure I get this right. 7 Q Isn't it true that a person of ordinary 8 skill in the art could have used the same procedure 9 as for the compound 5 except started with a guanin 10 material in the D configuration instead of a 11 cytodine material in an L configuration? 12 A I haven't provided any testimony to -- to 13 -- to that fact, and I'm not willing to sit and 14 speculate here on this -- on the spot towards that 15 end. 16 Q With respect to the ASOs we were 17 discussing, are the monomers used to generate 18 oligonucleotide considered the lead compounds? 19 MR. SHORES: Object to form, object to 20 the extent it calls for a legal conclusion. 21 BY MR. MADDOX: 22 Q By you.
190 1 session and be done. 2 THE VIDEOGRAPHER: We are going off the 3 record. The time is 3:49 p.m. 4 (Recessed at 3:49 p.m.) 5 (Reconvened at 4:01 p.m.) 6 THE VIDEOGRAPHER: We are back on the 7 record. The time is 4:01 p.m. 8 BY MR. MADDOX: 9 Q Doctor, if you could go to your 10 declaration, paragraph 207 -- 11 A Yes. 12 Q And -- and in paragraph 207, you write 13 with respect to -- this is with respect to compound 14 5 in the '991 patent and compound of claim 2. 15 A Uh-huh. 16 Q You write, "A POSA would have understood 17 that these molecules were totally different, would 18 have been prepared completely differently, and 19 would have had opposite stereochemical 20 configurations and would have required different 21 starting materials for the synthesis." Is it true 22 that a POSA could have used the same procedures as	192 1 A As -- as I believe I provided testimony 2 to before, it depends on the context that we're 3 sitting in whether an amidite or the 4 oligonucleotide is a lead compound. What I 5 provided testimony on was in looking at the '031 6 patent -- sorry. Yeah, '031 patent, I provided 7 testimony that one would have selected an 8 oligonucleotide as the lead compound, specifically 9 the one -- the one that I referred to in my 10 declaration. 11 Q Prior to this lawsuit, and excluding any 12 other lawsuits in which you -- 13 A Okay. 14 Q -- paid expert -- 15 A Uh-huh. 16 Q -- have you ever referred in your 17 writings to a monomer as a lead compound? 18 A I provided testimony to this earlier in 19 this deposition here in which I said something to 20 the effect, and I hope I'm -- remain consistent. 21 It's certainly my intent, that I don't know for 22 certain whether or not we use the term "lead

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193 1 compound" in anything, but I hope that the 2 introduction set forth very clearly what -- what it 3 was that we were trying to accomplish, what prior 4 work inspired us and that we potentially wanted to 5 -- to -- to extrapolate from. 6 Q So is it fair to say that sitting here 7 today, you don't have a specific recollection of 8 referring in writing to a monomer as a lead 9 compound? 10 MR. SHORES: Objection. 11 THE WITNESS: Counsel, I have published 12 72 papers I believe it is, the majority of which 13 related to oligonucleotide, and sitting right here, 14 I don't remember the exact phrase that I may or may 15 not have used across those papers, so I cannot 16 answer your question. 17 MR. MADDOX: Okay. Nothing further 18 subject to recross after redirect if there's any 19 redirect. 20 MR. SHORES: Can we take a break? 21 MR. MADDOX: Sure. 22 THE VIDEOGRAPHER: We are going off the	195 1 ACKNOWLEDGMENT OF DEPONENT 2 I, Patrick J. Hrdlicka, Ph.D., do hereby 3 acknowledge that I have read and examined the 4 foregoing testimony, and the same is a true, 5 correct and complete transcription of the testimony 6 given by me, and any corrections appear on the 7 attached errata sheet signed by me. 8 9 10 (DATE) (SIGNATURE) 11 12 13 14 15 16 17 18 19 20 21 22
194 1 record. The time is 4:06 p.m. 2 (Recessed at 4:06 p.m.) 3 (Reconvened at 4:32 p.m.) 4 THE VIDEOGRAPHER: We are back on the 5 record. The time is 4:32 p.m. 6 MR. SHORES: Patent owner has no 7 redirect. 8 MR. MADDOX: Then I guess I have no 9 recross. Then we're done. 10 MR. SHORES: Concludes this deposition. 11 MR. MADDOX: It does. 12 THE VIDEOGRAPHER: This concludes the 13 video deposition of Patrick Hrdlicka. We are going 14 off the record. The time is 4:32 p.m. 15 (Off the record at 4:32 p.m.) 16 17 18 19 20 21 22	196 1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC 2 I, KAREN YOUNG, Court Reporter and Notary 3 Public within and for the District of Columbia, do 4 hereby certify: 5 That Patrick J. Hrdlicka, Ph.D., the 6 witness whose deposition is hereinbefore set forth, 7 was duly sworn by me before the commencement of 8 such deposition, and that such deposition was taken 9 before me and is a true record of the testimony 10 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 Patrick J. Hrdlicka, Ph.D. occurred at the offices 16 of Rothwell, Figg, Ernst & Manbeck, P.C., 901 New 17 York Avenue, Northwest, Washington, D.C., on 18 Wednesday, December 20, 2023 commencing at 9:44 19 a.m. to 4:32 p.m. 20 I further certify that I am not related 21 to any of the parties to this action by blood or 22 marriage, I am not employed by or an attorney to

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1 any of the parties to this action, and that I am in
2 no way interested, financially or otherwise, in the
3 outcome of this matter.

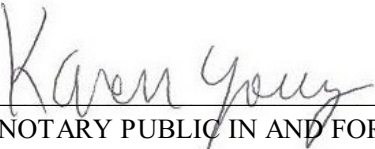
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5 IN WITNESS WHEREOF, I have hereunto set my hand
6 this 26th day of December, 2023.

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10  NOTARY PUBLIC IN AND FOR THE

11 DISTRICT OF COLUMBIA

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13 My commission expires:

14 July 31, 2024

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