

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORP.,
Petitioner,

v.

CHEMGENES CORP.,
Patent Owner.

IPR2023-00490
Patent 9,884,885 B2

Record of Oral Hearing
Held: April 23, 2024

Before JOHN G. NEW, ZHENYU YANG, and
CYNTHIA M. HARDMAN, *Administrative Patent Judges*.

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The above-entitled matter came on for hearing Tuesday, April 23, 2024, commencing at 1:00 p.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P-R-O-C-E-E-D-I-N-G-S

(1:12 p.m.)

JUDGE NEW: Welcome to the Board, I'm Judge New, and with me today via video are my colleagues Judge Yang and Judge Hardman. We're convened this afternoon to hear an oral argument to be a matter of IPR2023-00490, Shanghai Hongene Biotech Corporation versus ChemGenes Corporation. This hearing relates to claims one to five of U.S. patent number 9,884,885 B2. We'll begin by asking counsel for each party to introduce yourselves. When doing so, please spell your name for the court reporter, and we'll begin with Counsel for Petitioner, Shanghai Hongene.

MR. EDWARDS: Thank you, Your Honor. My name is Jeremy Edwards from the law firm of Procopio, here on behalf of the Petitioner, my name is spelled Jeremy, J-E-R-E-M-Y, last name Edwards, E-D-W-A-R-D-S.

JUDGE NEW: Thank you. Good morning -- good afternoon, I mean. And for Patent Owner, ChemGenes Corporation?

MR. SHORES: Yes, good afternoon Your Honor, my name is Dan Shores, I'm Lead Counsel for ChemGenes Corporation in this IPR. With me here today, also from our firm Rothwell Figg, is Adam Nicholais and Aydin Harston.

JUDGE NEW: Good afternoon, Mr. Shores, welcome to the Board. Consistent with our joint hearing order, each party has a total of 60 minutes for its presentation. Petitioners may reserve a portion of up to 20 minutes of their time to respond to arguments presented by the Patent Owner, and the Patent Owner is also authorized to reserve a similar portion of its time for rebuttal. I ask you to be mindful of the court reporter that's transcribing this hearing, and so when referring to a particular demonstrative exhibit, please clearly identify it

1 orally by slide number so it will be reflected in the hearing transcript. This is
2 also important for my colleagues who are here on the panel who are unable to
3 see the projection screen in the hearing room, so they can follow along with
4 their own copies of the demonstratives, but it's important that you mention the
5 slide number when referring to each.

6 Please know that this hearing is open to the public and that the parties
7 will refrain from disclosing any confidential information during the hearing, or
8 including any confidential information in a demonstrative exhibit. Now
9 Counsel for Petitioner, you may proceed with your argument after indicating
10 any time you would like to reserve for rebuttal.

11 MR. EDWARDS: Thank you, Your Honor. I would like to reserve 20
12 minutes of my time for rebuttal, please.

13 JUDGE NEW: Very well.

14 MR. EDWARDS: Thank you for the opportunity to present this
15 argument today. I of course have remarks prepared, but if the panel has any
16 questions they would like to begin with, I'm happy to start wherever you'd like.

17 JUDGE NEW: Why don't you just begin with your presentation?

18 MR. EDWARDS: Thank you. This IPR relates to the '885 Patent, which
19 has five claims, on which the IPR was instituted. Claims one -- and if we can
20 bring up slide two of our demonstratives, Petitioner's demonstratives. This is
21 just summarizing the grounds and the claims involved and the basis for which
22 we're seeking declaration of unpatentability. As you can see, claims one and
23 five were instituted on anticipation grounds. Fundamentally, those bases were
24 not contested by the Patent Owner, and we believe that the panel should find
25 them unpatentable for the reasons in the papers. Won't belabor those bases
26 today, but I will touch on them briefly. The other three claims, Claims two,

1 three, and four, we are dealing with a set of obviousness positions, and we will
2 get into those in greater detail. The priority date of the patent was in 2009, and
3 in this IPR there are no disputes about whether there is or is not prior art. So
4 it's going to be a very straightforward discussion about what the prior art shows
5 and doesn't show.

6 If we could turn to slide four, here we have shown the language of Claim
7 1, highlighted, and then on the right the corresponding structure. I'd like to
8 presume, if I may, that the panel is familiar with the basic nomenclature of
9 these compounds. If I get ahead of you all and you need a clarification, please
10 let me know, but we are short on time so --

11 JUDGE NEW: It's a fair assumption to make, we are familiar with the
12 material.

13 MR. EDWARDS: Okay, thank you. So as you can see, we've got a
14 claim to a phosphoramidite. Phosphoramidites have been used since the early
15 1980s as standard reagents for conducting what's called solid-phase
16 oligonucleotide synthesis, I'll call that SPOS today, for short, and I'll refer to
17 oligonucleotides and their modified versions, oligonucleosides, for short as
18 oligos today. As the panel is probably aware, oligonucleotides, oligos, are
19 chains of connected building blocks. These phosphoramidites are used to
20 introduce them in the SPOS process into a growing chain to come up with an
21 ultimate product.

22 So essentially, a phosphoramidite is a modified nucleoside or nucleotide
23 that's used in this process. They have some standard features associated with
24 their nomenclature, if we can look at petition page 19, there's a nice diagram
25 here talking about nucleotide substructures. Just want to point out what we'll
26 be talking about a lot today. On this basic sugar ring with the oxygen in the

1 middle, we've got these prime positions, one through five prime, they are to
2 denote the carbon and then what's attached to them. Two prime position in this
3 model on Figure 2, as shown as X, that's going to be much of the discussion
4 today, is about what shows up at the two prime position. Also these nucleotides
5 and nucleosides have at the one prime position a base. The base can be any of a
6 number of different possible bases. Above you can see depicted the so-called
7 canonical nucleobases. The three in the middle comment at both DNA and
8 RNA all have these exocyclic NH₂ groups, or exocyclic amine groups. Those
9 groups are reactive and need to be protected and then de-protected as the
10 process of SPOS is unfolded. So we'll be talking about what is used to protect
11 those exocyclic amine groups as well throughout today.

12 We can go to slide five, quick depiction, claim one being anticipated by
13 the '039 Patent, not disputed, enablement was shown as well as being
14 presumed. This is anticipation of one of the species in the genus of this claim
15 and therefore anticipates the genus, again we should find this claim
16 unpatentable as it's not really opposed. Next, slide seven, we're showing a
17 similar comparison with -- well, we're showing the language of claim five. I
18 want to pause here for a second and just point out that we've shown some
19 modifications to the claim language, these are not controversial. We've
20 changed M from being potentially a succinyl group to an ethyl group to make
21 this claim make sense, and we've added this phrase, capable of being attached,
22 et cetera. The parties don't disagree, this is the proper construction of this
23 claim, and we submit that it should be construed that way or corrected that way
24 at the panel's discretion, we think it's quite straightforward and not
25 controversial.

1 If we can look at slide eight, this is a side by side depiction of claim five
2 with the item of prior art, the Guar reference that anticipates it. It requires a
3 little more unpacking, but it's again, not disputed, and the panel should find
4 claim five unpatentable. I would like to turn now to where our focus is going to
5 be today, and that is claim two of the '885 Patent. If we could show slide 10
6 please, a side by side here, we've got the text of claim two, with the
7 corresponding structure, when you choose guanine-N-acetyl as the base, and
8 it's color coded for convenience. You can see in the top right of the structure
9 this exocyclic amine grouping protected by an acetyl group, and in pretty prime
10 position you've got this standard phosphoramidite group, nobody really
11 disputes that that's a standard group. Of interest in this claim, and there will be
12 a lot of talk about this, is the two prime position, occupied by a fluorine atom. I
13 can tell you right now, it wasn't new to put a fluorine here at the two prime, and
14 it wasn't new to put an acetyl group on a guanosine base in a phosphoramidite.
15 What the patentee seems to have believed was new and non-obviousness was
16 having both of those at the same time, but neither were new, and as we'll show,
17 it's an obvious combination.

18 If you could turn now, please Mr. Kressman, to slide 11 -- actually if you
19 could go back to two slides before just to mention the obviousness basis -- back
20 one more. One more, slide six. Oh, I'm sorry slide seven. Okay, we seem to
21 be missing a slide. I'll just say it, Claim 2, Ground 2, is based on three
22 references, the '031 Patent, specifically compound X, the reference called
23 Pitsch, which you'll hear a lot about, and a reference called Fan, so this is those
24 three in combination, rendering Claim 2 obvious.

25 If we can jump back to slide 11 and look here at compound -- on the left
26 we've got Claim 2, when you have this acetyl protecting group on guanosine,

1 and on the right, this is the '031 Patent compound X, this is a key compound for
2 our discussion today. It's protected not by isobutyryl, or not by acetyl or
3 isobutyryl. That's the sole difference between the claimed compound and this
4 prior art compound, is one is on the exocyclic amine of the guanosine base. We
5 submit that this difference is insubstantial and obvious to, or would have been
6 in 2009, to a person of skill in the art. So let's talk about compound X and the
7 '031 Patent, why would anyone at the time be interested in that? Well, for a
8 whole host of reasons.

9 First of all, compound X is immediately recognizable as a
10 phosphoramidite, known to be useful for SPOS, and this use is specifically
11 contemplated in the '031 Patent. We submit that this alone was a sufficient
12 reason to select compound X for use and potential improvement, but there's
13 much more to the '031 Patent than that, that would be of interest to a person of
14 skill at the time. The '031 Patent touts two prime fluoronucleosides as
15 preferred and particularly useful for increasing the binding affinity of the oligos
16 to which they are inserted. We can see this at column 11 of the '031 Patent,
17 that's Exhibit 1017, PDF page 12, we've highlighted some of this for you here.

18 This passage clearly points out what I just said, and first in the list of preferred
19 substituent groups of the two prime to increase this binding affinity is the
20 fluoro. On the next column, column 12, there's an entire paragraph that starts
21 with this sentence. A particularly useful two prime substituent group for
22 increasing the binding affinity is the two prime fluoro group.

23 JUDGE NEW: Is there a slide number for that, Mr. Edwards?

24 MR. EDWARDS: This is directly from the Exhibit 1017, Your Honors.

25 JUDGE NEW: All right, very good.

1 MR. EDWARDS: I'll also note that there are contextual clues that would
2 have taken a person of skill straight to compound X in the '031 Patent.
3 Compound X is the end product of example 4D in that patent, it's not merely an
4 intermediate plucked out, it's the end result of one of the examples. We can see
5 this in Exhibit 1017 at columns 27 to 28, and that's where we get the name
6 compound X, it's the 10th step in a lengthy synthesis of this compound that is
7 disclosed in the '031 Patent.

8 What's even more interesting, Your Honors, is that compound X is the
9 only two prime fluoro guanosine phosphoramidite disclosed in the whole '031
10 Patent, it's the only one, and Dr. Hrdlicka, the patentee's expert agrees with
11 that. As a result, compound X is necessarily used to make oligonucleotides
12 according to four different examples in the '031 Patent, and those examples are
13 12iii, 13iii, 13v, and 14i. Let's take a look at one of those, for example, that is
14 example 12iii. Could you put that up on the screen? Still at Exhibit 1017,
15 columns 43 to 44. Here is an example in the patent where they say you can go
16 ahead and make two prime fluoro substituted oligos in the manner of something
17 called Example 8, which we'll get to. You can make a chimeric oligo having
18 two prime fluoronucleosides in its so-called wing segment, and they say that
19 that's a thing you can do. The only way to insert that as a guanine base with a
20 two prime fluoro substitution is to use compound X, and it's done in four
21 different examples here in the patent. Now, all four of those examples say
22 something similar about inserting the two prime fluoro into the wing segment of
23 the oligo that is of interest.

24 As mentioned, all four of these examples also say that when you prepare
25 these oligos containing the two prime fluoro substitution in the wing segment,
26 you do that in the manner of example 8. So let's look at Example 8, because it

1 in turn contemplates the use of these wing segments and the use of guanine in
2 particular. We're showing here column 40 in the '031 Patent, example 8.
3 We've highlighted for your reference there that it's contemplating making five
4 prime and three prime wings, and it's contemplating inserting guanine into the
5 oligos that are being made.

6 Now I'll pause here and say that it seems that ChemGenes has to my
7 mind feigned confusion about how someone would go about incorporating
8 doing the examples that we just mentioned in the manner of example 8. A
9 person of skill would not have been confused by this at all, the examples clearly
10 say to do it in that manner, and a person of skill reading example 8 would know
11 how to plug in the correct phosphoramidites that are disclosed at length in the
12 earlier parts of the patent, when they were performing the syntheses of the
13 oligos that are described in those examples and refer them directly and
14 explicitly to example 8. There is really no confusion to be had here, we think
15 that's manufactured by the Patentee here.

16 So if you'll continue to look down further in example 8, you'll see, I just
17 want to point out, they've explained here that when they went to de-protect the
18 bases, when they made these oligos, they did that in methanolic ammonia for 24
19 hours at room temperature. This is important. 24 hours, quite a long time, and
20 a person of skill in the art would see that and immediately think hey, how can I
21 do better? Can I do this any faster? The answer comes clearly and
22 emphatically in the form of a Pitsch reference that is the second reference in
23 this combination. The Pitsch reference came along in 2001, and it clearly
24 teaches to use the acetyl protecting group, which is the claim protecting group
25 in Claim 2, because it's faster, you can de-protect faster. A person who is
26 interested in compound X would have seen Pitsch, seen its teachings of use of

1 acetyl group and clearly been motivated to make that switch. If they did that,
2 they would arrive at Claim 2.

3 JUDGE NEW: Mr. Edwards, these reference, we can find both deal with
4 ribonucleic based phosphoramidites, but not deoxyribonucleic
5 phosphoramidites that use the synthesis of RNA oligonucleotides. Is there a
6 specific difference between those two types of molecules, deoxyribo and ribo
7 that would actually play into both the, how the protected groups are added and
8 the length of protection time? I struggle to see the relevance of Fan in this,
9 because of looking at somewhat different molecule, and the protection times,
10 I'm wondering if they are at -- how would you compare those two what we see
11 in deoxyribo-based phosphoramidite?

12 MR. EDWARDS: How would I compare the de-protection times
13 demonstrated in Fan?

14 JUDGE NEW: Well, yeah, I mean what's the relevance of Fan if it's
15 dealing with a different type of oligonucleotide?

16 MR. EDWARDS: Well, the relevance of Fan in our position has been
17 largely motivational, to show a direct comparison between the de-protection
18 times of an acetyl group versus an isobutyryl group. It actually isn't required in
19 our combination, although it is part of our combination, because all of the
20 elements of the claim are disclosed in compound X and in Pitsch, Pitsch
21 contributing the acetyl group. The relevance of Pitsch to the '031 Patent is
22 quite clear, because the use of two prime fluoro substituted nucleosides is hand
23 in hand and side by side with the insertion of RNA nucleosides, okay? There's
24 the Kawasaki reference, Your Honors, that clearly shows that chimeric oligos
25 are made using both kinds. So a person of skill looking to make that sort of
26 chimeric oligo would be pleased to read Pitsch and see that you could get an

1 acetylated nucleoside into an RNA kind nucleoside, and they would like to
2 apply that, and would have loved to apply that to the two prime fluoro substitute
3 nucleoside when making chimeric oligos.

4 So let's take a quick look at Pitsch, it's a remarkable piece of work by a
5 group out of Zurich, and if we can pull up Exhibit 1018 at PDF one, it's right
6 there in the title that they came up with a reliable synthesis of RNA oligos, and
7 it was published in a very influential journal, Helvetica Chimica Acta. They're
8 reporting here some really extensive and rigorous work on oligo synthesis, and
9 let's jump right to where they talk about the acetyl group, PDF page six.

10 They've explained here that they chose acetyl because it was already used for
11 cytosine, and that it was used for the convenient de-protection scheme, and that
12 they determined the half-lives of de-protection of not just acetyl protected
13 cytosine, but also guanine and adenine. The data they say right here in this
14 paragraph indicates that they got complete de-protection of their resulting
15 oligos in an hour, not the 24 hours reported in the '031 Patent, one hour. And
16 they say, remarkably, that the acetyl group, according to their data is, suited for
17 a labile, universal nucleobase protection. In their own words, they are telling
18 the field, acetyl is a pretty darn good protecting group for essentially any use
19 you would like to put it to.

20 JUDGE NEW: Mr. Edwards, how do you respond to the Patent Owner's
21 argument that acetylation of the phosphoramidite, in this case using it as a
22 protecting group, substantially decreases the solubility of the molecule as an
23 organic solvent?

24 MR. EDWARDS: Yeah, we believe that's an irrelevant distraction, Your
25 Honors, and if you'll permit me just a moment, I'll jump that that in my notes.
26 It's both vague and speculative and it's a red herring, and it refutes itself. What

1 they've said is it could have negatively affected purification and caused the
2 synthesis to fail. There's no literature showing that, none of the literatures
3 shows a failure due to the insolubility of an acetyl protected phosphoramidite,
4 and it's contrary to Pitsch itself. Pitsch got very good results, and they did it
5 with acetylated, the three canonical acetylated nucleobases and got extremely
6 good results. As Dr. Baran points out in response to this solubility argument,
7 all of the subsequent solvents in the scheme of example 4D in the '031 Patent
8 are highly polar, there's no expectation of any solubility issue. But moreover,
9 this is an argument that's a red herring because it's only about purity or yield, it
10 can't affect the reasonable expectation of success, but this claim is directed to a
11 compound per say, there is no yield, no purity requirement of anything. If you
12 can reasonably expect to get any of it, you can reasonably expect and you check
13 that box in the obviousness analysis. Not for nothing, there's also purification
14 steps that are involved in all of these steps, and Pitsch and Pitch number two,
15 Exhibit 1021, they disclose those kinds of things. So we think that's a red
16 herring here.

17 Just wanted to get back and touch on the rigors of Pitsch, they got great
18 results. If we could turn to PDF pages eight through 10 of Exhibit 1018, this is
19 back at Pitsch. They got quantitative removal of their protecting groups, they
20 got a uniform product under short time de-protection, they empirically
21 determined their de-protection conditions, and they say they never observed
22 incomplete de-protection. That, coupled with telling the world this is a great
23 uniform protecting agent, it's hard to imagine a better advertisement for using
24 the acetyl protecting group.

25 I'd like to turn to Fan, just for a moment, and mention again, there's a
26 criticism of Fan that it used different conditions and that it's not predictive of

1 the de-protection times for the resulting oligos into which the monomers are
2 inserted. That's another distraction, Your Honors. A person of skill in the art,
3 as Dr. Baran explained, would be well aware that the point of Fan was to do the
4 one to one comparison, isobutyryl versus acetyl, and to show relative de-
5 protection times of those nucleosides. And the literature reflects that people of
6 skill in the art used those kinds of comparisons to predict the relative de-
7 protection times of the resulting oligos, you can see that as reflected in the
8 Schulhof paper that is Exhibit 2013.

9 I'd like to turn to the expectation of success prong of this analysis, and do
10 a little level setting, because there's some undercurrent in the Patentee's briefs
11 that is inconsistent with the true inquiry here. What matters is a reasonable
12 expectation of success in making the claimed compound. As I mentioned, this is
13 a compound per se, the expectation does not need to be absolute, it needs to be
14 merely reasonable. And what we're talking here about is the installation of an
15 acetyl protecting group instead of an isobutyryl protecting group. As Dr. Baran
16 explained, this would have been very straightforward for a person of skill in the
17 art at the time, and you don't have to take his word for it, because the art
18 reflects that.

19 We presented two examples in our petition that are reflective of that
20 reasonable expectation of success. One is simply following along with example
21 4 in the '031 Patent where they made compound X, and simply changing the
22 excipient used to attach the isobutyryl group to the corresponding reagent used
23 to attach the acetyl group. If you note that, we can pull up Exhibit 1017, PDF
24 page 19 here, they explain in the '031 Patent they use isobutyryl anhydride,
25 that's how they attach the isobutyryl group. Well, as Dr. Baran explained, a
26 person of skill would know you could use acetyl anhydride here instead to

1 attach the acetyl group. In fact, this is exactly how Pitsch did it. If we could
2 pull up Pitsch, Exhibit 1018, at PDF page three, they're explaining, that's the
3 Ac20, right there, they acetylated their guanosine in the same exact way. As
4 Dr. Baran also mentioned, a person of skill in the art would have regarded
5 acetyl as even easier to install than isobutyryl, because acetyl is smaller with
6 lower molecular weight.

7 The second example we've provided, illustrative of the expectation of
8 success in making the claimed compound was by starting with a precursor
9 compound disclosed in Sivets, which is exhibit 1028, and if we could pull up
10 PDF page four, here's that compound. You can see it's a two prime fluoro
11 guanosine, it doesn't yet have the phosphoramidite group or the five prime
12 DMT group, but people of skill in the art were well versed in how to attach
13 those groups as of 2009. Again, Pitsch references how to do this and even gives
14 a nice diagram. If you look back at Pitsch, PDF page three, we show scheme
15 one, that top left, if I could use the pointer, I hope this helps you at least, Judge
16 New, if not the folks following along remotely. Top left, guanosine as acetyl in
17 step C, and then step D you attach the five prime group, and then through steps
18 E, following down along to the right, step F, that's how you attach the
19 phosphoramidite cyanoethyl group. Very straightforward and reported in
20 Pitsch. If instead you had a two prime fluoro instead of the two prime OH, you
21 would arrive at the compound of claim two. As Dr. Baran explained, having a
22 two prime fluoro there instead of a two prime OH would actually make this
23 synthesis easier, because the OH is reactive, requires protecting group
24 chemistry. The two prime fluorine does not, and doesn't require that.

25 The Patentees -- I don't have time to perhaps jump out ahead of
26 everything they might say about reasonable expectation of success, but I will

1 put in perspective what I think encapsulates the bulk of their arguments, say of
2 a half dozen or so. They are some combination of either unsupported and
3 speculative, contrary to the literature that they cite, or they speak to yield, as we
4 discussed, and not the ability to actually make some of the claimed compound.
5 If we have time at the end, we'll come back and address some of that.

6 I'd like to turn now to Ground 3, which is also directed to Claim 2, the
7 same species of Claim 2 that we just talked about. This combination is through
8 use of the '991 Patent and again, Pitsch. If we can go to slide 13, here is a side
9 by side comparison of Claim 2 and the compound 5 of the '991 Patent. The
10 difference here is which nucleobase is being used. Claim 2 uses the guanine,
11 compound 5 uses cytidine. The other difference, which we think is
12 inconsequential, is the stereochemical configuration, which for Claim 2 is a
13 native integration of a D configuration, and for compound 5 is the L
14 configuration, and we've tried to denote that here in the slide by showing you
15 that the two prime, three prime positions are visually switched, that's just the
16 easiest way to render this.

17 Now compound 5, just like compound X would have been of particular
18 interest, largely for the same reasons, it's a two prime fluoro phosphoramidite,
19 which we've discussed were famously useful for inserting into chimeric oligos
20 with RNA. This is reflected in the '991 Patent itself, which touts compound 5
21 as useful. The synthesis is shown in example six, and the structure is disclosed
22 in Figure 16. Up on the screen now are those particular excerpts from the '991
23 Patent. A person of course would have been motivated to make a guanosine
24 version of compound 5, because that's another one of the very few canonical
25 nucleobases. If you're building an oligo, you want to have those handy.
26 Whatever your sequence is, it's likely to require guanosine. And of course,

1 Pitsch underscores the desirability of acetylated guanosine in particular, so
2 we've already discussed the reasons why you would want acetyl.

3 As for the different stereochemical configurations, we think this is a
4 distraction again. The '991 Patent itself explains why you would want both
5 configurations handy, depending on your use case. If we could pull up Exhibit
6 1020, that's the '991 Patent, at PDF page 81, column 11, here is a passage
7 discussing how either can be useful. Absolutely it discloses in passing a
8 preference for the de-configuration, but then it goes on at length to say well,
9 what about the other configuration? And at the bottom you can see it talks
10 about potential functions for that other configuration, interaction with other
11 molecules, for example, allowing immobilizing, cross-linking proof or
12 ethylation. As for expectation of success on this ground, it's the same
13 compound, we've already discussed that at length in connection with Ground 2.

14 Turning now, as I'm getting short on time, to Claim 3, which is Ground
15 4. The obviousness combination here is the same as we've discussed, with the
16 addition of a fourth referenced, called Scaringe. Up on the screen is slide 15,
17 we've got the claim language as corrected by the parties, side by side with the
18 resulting structure when you make the choice of guanine and acetyl and the use
19 of the ribo fluoro. This is the species that we're focusing on in this analysis.
20 As you can see, the only difference between this species and the species of
21 Claim 2, that we've already addressed, is at the three prime position we've got a
22 linker, a succinate linker. For the reasons we already discussed, you would --
23 beg your pardon, let me back up. Yeah, if you can go to the next slide, slide 16,
24 here's a side by side comparison, comparing the prior art compound X that
25 we've already discussed, to the compound of Claim 3. We've already

1 discussed why you would want to use the acetyl protecting group instead of the
2 isobutyryl, and here the other difference is this phosphoramidite group.

3 Attaching a three prime phosphoramidite group was absolutely standard
4 in 2009, it's how you began SPOS. It's used to attach is to the solid substrate,
5 the S, solid, in that process. This is not really a dispute in this IPR that that's a
6 standard thing, and that it's standard to attach it. As for a reasonable
7 expectation of success in making this compound, Scaringe itself details how to
8 attach the three prime succinate. The Patentee mostly relies on Claim 2 for its
9 arguments against obviousness of Claim 3, and we've already addressed those.
10 They do offer one argument that's sort of cursory and unique to Scaringe,
11 which is that Scaringe itself doesn't teach acetyl protected compounds to two
12 prime fluoro substitutions or de-protection rates. This is again an irrelevant
13 deflection, Your Honors. The two prime fluoro is disclosed in compound X,
14 the '031 Patent, and the advantage of the acetyl protecting group is taught by
15 Pitsch and Fan. The point of Scaringe in this combination is simply to reflect
16 the standard attachment of a three prime phosphoramidite group.

17 Dr. Baran explained that the presence of a two prime fluoro on the
18 precursor when you're trying to make this succinylated nucleoside doesn't
19 affect the expectation of success in making this, in fact with the TBDMS group
20 at two prime, it provides more steric hindrance to attaching something at the
21 three prime position than the fluorine atom would. Patentee has not disputed
22 that characterization by Dr. Baran.

23 Turning now to Claim 4 which is Ground 5, if we can -- again, this is an
24 obviousness combination, the same three, Scaringe, Pitsch, and Fan, if we can
25 show slide 18, that shows you the structure when you make the selections that
26 are highlighted here on the left, color coded on the right. We're no longer

1 talking in Claim 4 about a two prime fluoro phosphoramidite or a two prime
2 fluoro succinyl type nucleoside. Attached at the two prime position in Claim 4
3 is OTBDMS, which was a standard two prime protecting group for RNA
4 nucleosides. If we can turn to slide 19, Scaringe compound 5c is on the right,
5 and compare it to the compound of Claim 4 on the left. The sole difference,
6 again, is the protecting group. Scaringe using an isobutyryl.

7 Of course a person of skill in the art would be interested in Scaringe
8 compound 5c, because as mentioned, they would know that this would be a
9 useful nucleoside, derivitized nucleoside for attaching to a solid support for
10 SPOS. And of course, Scaringe reported doing exactly that as part of successful
11 RNA oligo synthesis, and gave data on that. If we could pull up Scaringe,
12 which is Exhibit 1022, at PDF pages two to three, and page eight, this is where
13 that's discussed. And you can see here, as highlighted, they are describing
14 having made supports coupled to compounds 5a through d, of course that
15 includes 5c. So they did this, they used 5c to begin their solid phase, and
16 therefore began some of their syntheses with the guanine nucleoside. The
17 motivation to get from Scaringe compound 5c to Claim 4 is the same as we've
18 discussed for Pitsch and Fan, and for Claim 3, with respect to the succinyl
19 group at the three prime location.

20 The expectation of success flows mainly from what we've already
21 covered, Scaringe actually doing it, and as explained in connection with Claim
22 3, the succinyl group attachment was routine. And again, you've got this
23 OTBDMS group instead of a two prime fluoro, but that would not affect
24 installation of the acetyl protection group way up there on the nucleobase. I'll
25 note in passing that the Patentee offers no secondary considerations in support
26 of Claim 4.

1 JUDGE NEW: While we're on that, Mr. Edwards, I'd like you to
2 address the secondary considerations arguments that the Patent Owner makes
3 with respect to Grounds 3 and 4.

4 MR. EDWARDS: Absolutely, Your Honor, happy to. As an initial
5 matter, they've based the entirety of their assertive secondary considerations on
6 their own statements in their own patent. They don't point to any commentary
7 in the field, pointing out some long felt need, or problem in the art, or failure of
8 others, or unexpected results, they point to their own statements in their patent.
9 That's entitled to less weight.

10 JUDGE NEW: But doesn't a disclosure in the background section of a
11 long felt need go in some ways towards meeting that requirement?

12 MR. EDWARDS: I'm not saying --

13 JUDGE NEW: As it reflects that state of the art of the field as a person
14 of skill in the art would understand it?

15 MR. EDWARDS: I'm not saying it's irrelevant, Your Honors, I'm
16 saying it's entitled to less weight, because it's not someone out there in the
17 industry just interested, saying hey, we've got a longstanding problem and we
18 really need to solve it. It's the Patentee saying here's what we came up with
19 and selling it to a degree. They do cite some presentations by others when they
20 say what they came up with, but those don't mention the reaction conditions at
21 play and what they were struggling with. The Patentee must have had those
22 handy, otherwise they couldn't have cited them in the application, but they
23 haven't produced them in this IPR, we'll never know what those reaction
24 conditions were. You can only wonder why they wouldn't have produced
25 them.

1 There is absolutely no evidence of any failed attempts by anybody to
2 overcome this supposed problem that they cite, and in the literature that they
3 point to outside of the patent actually shows that there was not this degradation
4 problem with two prime fluoro oligos. They point to this reference called
5 Sinha, Exhibit 2024, and if we can pull that up, PDF page 107, this is not saying
6 there's a big problem, they're saying the lability of the two prime modification
7 must be taking into consideration. If you look then beyond that, in the same
8 reference, to pages 109 to 110, they've said well let's take it into consideration,
9 and then what did they do? They said well, you can avoid these side reactions,
10 and here's how. You can minimize them using ethanolic ammonia, for
11 cleavage and de-protection, that's what C and D is there.

12 So the alleged problem had a workaround, according to the prior art
13 itself. This workaround had variations. The Kawasaki reference, Exhibit 2025,
14 if we can go to PDF page three, says you can work around this problem with
15 methanolic ammonia. And by the way, example 8 in the '031 Patent used that
16 workaround, it de-protected with methanolic ammonia, as we saw earlier. By
17 the way, if the problem was degradation under strongly basic conditions, then
18 it's simply not surprising to use the acetyl protecting group, because it was
19 known to facilitate de-protection under less stringent basic conditions. The
20 Patent Owner sort of pivot from there, and says well, it's not so much that there
21 was this blanket problem of degradation of two prime fluoro, but that there was
22 a problem of having limited reagents available, because methylamine was a
23 problem. But that's not even what their patent says, and it's certainly, you
24 don't see in Kawasaki or Sinha, you don't see them or anyone else clamoring to
25 use methylamine, they seem content with their workaround. So it's not quite

1 adding up what they say the problem was, when there's clear workarounds with
2 no external clamoring to get back to methylamine.

3 I'd like to point out one -- since I have about a minute left before my time
4 is up, I'd like to point out one additional side reason why it's curious that
5 they're arguing a person would not select compound X because it's a two prime
6 fluoro nucleoside. The Patentee itself, as early as 1999, was touting two prime
7 fluoro and selling two prime fluoro nucleosides. Exhibit 2030, at PDF page 70,
8 this is their catalogue, and here they're talking about two prime fluoro cytidine
9 and two prime fluoro uridine, and at the bottom they're explaining how
10 interesting these are, they're used as versatile probes, and they impart very
11 interesting biological properties to fluorinated oligomers. Notably, they're not
12 selling the guanosine version, all the more reason for a person to be interested
13 in making a guanosine version that's two prime fluoro substitute. That's the
14 amount of time for my opening statements.

15 JUDGE NEW: Thank you, Mr. Edwards, let me just check with my
16 colleagues to see if they have any questions. Judge Hardman? All right, thank
17 you very much, Mr. Edwards. I think we'll now hear from counsel for Patent
18 Owner, ChemGenes.

19 MR. SHORES: Thank you, Your Honor. Judge New, do you have a
20 copy of the slides?

21 JUDGE NEW: Right here in front of me.

22 MR. SHORES: Okay, obviously Judges Hardman and Yang, I can't
23 provide those, at least in this day and age.

24 JUDGE NEW: We all have copies of the demonstratives.

25 MR. SHORES: Thank you very much. Thank you, Your Honor. Let's
26 see if we have our slides here. If we could go to slide 32, please? Your

1 Honors, ChemGenes corporation is a longstanding nucleoside and
2 phosphoramidite innovator that has served the pharmaceutical industry since the
3 1980's, since the early days of SPOS, and it was a husband and wife founded
4 team, and in fact the inventor on the '885 Patent -- well, let me just say, we
5 have here today representatives from ChemGenes, we have Anuj Srivastava,
6 who is the Chief Operating Officer from ChemGenes corporation, as well as
7 Kevin O'Connor, who is the General Counsel of ChemGenes corporation, and
8 Suresh Srivastava is the named inventor on the '885 Patent.

9 JUDGE NEW: Mr. Shores, I'm going to interrupt you briefly, do u want
10 to reserve some time for rebuttal?

11 MR. SHORES: Yes, I apologize, Your Honor, yes I do. I would like to
12 reserve 20 minutes of rebuttal time. I apologize, I had that in my notes, but I
13 didn't --

14 JUDGE NEW: That's fine. Let's proceed.

15 MR. SHORES: Thank you, Your Honor. So I think what I'd like to do
16 is there are a number of arguments that the Petitioner has made that you know,
17 we claim we disagree with, and I'd like to address some of them up front, and
18 then I think through the presentation I think you'll see the contrast in the
19 viewpoints between the parties here. So let's talk about compound X, let's talk
20 about binding affinity for compound X, and if we can pull up the '031 Patent,
21 which is where compound X is identified. And if we can please pull up, it's
22 column 12. Actually, if we could please go to slide 59. Apologies to my
23 colleague here.

24 Let's talk about the '031 Patent, so the '031 Patent is the patent that has
25 compound X as one of the examples of two prime fluoro phosphoramidites
26 listed. The example 4D is the two prime fluoro, two prime deoxyguanosine

1 phosphoramidite that is compound X. In the disclosure of the '031 Patent,
2 there's no data that relates to compound X, and this is something that
3 Petitioner's expert, Dr. Baran, had acknowledged during his deposition.
4 Furthermore, with respect to, if we could go to slide 60, with respect to example
5 8 and example 12, okay, so this is what Petitioner has not disclosed. Two prime
6 fluoro monomers, there are several two prime fluoro monomers that are
7 disclosed in this application, one of them is the subject two prime fluoro
8 monomer phosphoramidite, which is two prime fluoro, two prime
9 deoxyguanosine. Well, there were three others as well, and if we look here in
10 example 12, in the lower left hand corner of this slide, we see yes, there are
11 mention of two prime fluoro nucleosides, but there's no specific reference to
12 any base, guanine or any other base. And if we look at example 8, Petitioner's
13 expert, Dr. Baran states, testifies, that example 8 describes using
14 phosphoramidites to introduce two prime fluoro monomers in the wing
15 segments of the oligonucleotides, but plainly, as Patent Owner's expert Dr.
16 Hrdlicka's testified, there is absolutely no mention to two prime fluoro
17 monomers in example 8, and so this is patchwork analysis, patchwork
18 perspective. And this is not attorney argument, this is Dr. Hrdlicka interpreting
19 this passage and saying a person of ordinary skill in the art would have been
20 confused. Dr. Hrdlicka was a person of ordinary skill in the art in the 2009
21 timeframe, he spent his entire career synthesizing building blocks, and his
22 testimony is that a POSA would have been confused when comparing example
23 12 to example 8, and therefore --

24 JUDGE NEW: But, excuse me sir.

25 MR. SHORES: Yes, Your Honor?

1 JUDGE NEW: This reference, the '031 Patent, does disclose a two
2 prime fluoro monomer that is compound X, does it not?

3 MR. SHORES: It does.

4 JUDGE NEW: It's right there, so where is the confusion come in? I'm
5 afraid I don't understand.

6 MR. SHORES: The confusion comes in with this argument that relates
7 to binding affinity, and so if we can go to -- the question, Your Honor, is
8 whether, is what the patent actually highlights, and it's actually more
9 specifically whether the patent actually highlights compound X.

10 JUDGE NEW: But do the claims actually recite binding affinity? Is that
11 relevant to this? Are we speaking to motivation here?

12 MR. SHORES: Well, I'm actually responding to the Petitioner's
13 argument that binding affinity would have been a rationale for a person of
14 ordinary skill in the art to have selected compound X, and I must add as well
15 that none of this was in the petition. A Petitioner is the master of this petition,
16 none of this was in the petition, and actually the Petitioner side-stepped the lead
17 compound analysis on an erroneous basis, and we can talk about that. But this
18 is in order to buttress their argument that a person of ordinary skill in the art
19 would have selected compound X in the first instance. The only mention of the
20 characteristics of compound X in the petition related to its usefulness in SPOS.
21 Well it's undisputed that there are thousands of phosphoramidites and
22 nucleosides available in the prior art that had similar utility. Thousands. And
23 so how is that going to match with the lead compound analysis where there's
24 some reason or motivation to select compound as the lead in the first instance?

25 And if we can go back to the disclosure, if now my colleague, if we can
26 go back to the '031 Patent, Petitioner has argued two prime fluoro monomers,

1 they have increased binding affinity. And it is true that in the '031 Patent, it
2 discloses that two prime fluoro monomers, once installed -- now, there's a
3 difference between what we're talking about here. There's oligonucleotides,
4 which are really what that refers to, two prime fluoro monomer on an
5 established, built, oligonucleotide, had shown to have increased binding affinity
6 in some situations, but we're not talking about oligonucleotides, we're talking
7 about the building blocks of phosphoramidites that are used to install the two
8 prime fluoro. And if we look more closely at this patent, and if we can go to
9 column 12, lines 50 to 59, and if we can somehow zoom in on that. Your
10 Honor, may I approach, so I can see, reading here?

11 So if we look at -- thank you, Adam. If we're looking at this column 12,
12 you can see the sentence, the passage that says, certain of these nucleobases --
13 now we're talking about two prime fluoro group, but there's another group
14 that's also on the installed oligonucleotide, which is the base group. And so
15 here, in this passage, which Petitioner did not disclose to you, certain of these
16 nucleobases are particularly useful for increasing the binding affinity of
17 oligonucleotides, these include, they list the adenine, uracil, cytosine, do not
18 mention guanosine. And if you go to example 4D of this patent, could you go
19 to example 4D?

20 So what Petitioner is telling you is that the only two prime fluoro
21 guanosine phosphoramidite disclosed in the '031 Patent is compound X, but
22 what Petitioner is not telling you is that this is example 4D. If we go up to
23 example 4A, what do we have? In example 4A we have an adenine base, in
24 example --

1 JUDGE NEW: Mr. Shores, is there anything extraordinary about any of
2 this? I mean, you're going to need all four of the canonical nitrogenous bases
3 when you're making DNA nucleotides, are you not?

4 MR. SHORES: Your Honor, thank you for that question, Judge New.
5 Yes, the point here is that when we're talking about the lead compound
6 analysis, it's whether compound X, whether one would have reviewed this
7 disclosure and found that compound X was special, it was something useful to
8 enhance its properties. And what this disclosure demonstrates is that amongst
9 the four two prime fluoro phosphoramidites that are disclosed, compound X
10 isn't even mentioned, but as guanosine, isn't even mentioned as having
11 specifically, you know, significant properties relating to binding affinity, and
12 therefore --

13 JUDGE NEW: This is a structural claim now, and we're not talking
14 about a situation like Takeda, where we've got a million possible compounds.
15 This is a compound, compound X, that is a specific embodiment disclosed in
16 the specification, it's used in several examples, isn't that sufficient enough to
17 make it stand out from thousands of anonymous phosphoramidites to tell a
18 person of ordinary skill, this one might be worth looking at?

19 MR. SHORES: Your Honor, respectfully, it is not disclosed, as Dr.
20 Baran testified, this is an attorney argument, it is not disclosed in any examples.
21 A study and a review of this --

22 JUDGE NEW: Right, but the methods of synthesis are there, in this
23 patent --

24 MR. SHORES: But nothing of synthesis is present for compound X, but
25 let's discuss that. Your Honor, the other piece of this is that that particular
26 compound, compound X, had known degradation issues relating to it. And if

1 we can go to slide 61. So the question here is whether this group was in the
2 lead, whether one of ordinary skill in the art would have looked at compound X
3 and said, we want to develop this compound further. Well, as Dr. Hrdlicka
4 testified, compound X itself had known degradation problems. This compound,
5 both the '031 Patent and the Kawasaki reference were identified as originated --
6 you can go to slide 90, were identified as originating from the same company,
7 Isis Pharmaceuticals.

8 As Dr. Hrdlicka analyzed both the Kawasaki reference, dated 1993, and
9 the '031 Patent, they had overlapping synthesis schemes for compound X, and
10 therefore is direct evidence that compound X itself, as reported in Kawasaki,
11 had these known degradation problems. And if we can go to slide 62, this is
12 something that Dr. Baran admitted that he did not consider in his opening
13 declaration, he didn't consider the issues related to degradation and compound
14 X in his opening declaration, and therefore a person of ordinary skill in the art,
15 when looking at the, first of all, the thousands of phosphoramidites, the
16 thousands of nucleosides, the only thing that Petitioner stated was utility, for,
17 you know, and then also looking at '031 Patent itself, no data, no statement that
18 it's not amongst the other based phosphoramidites that are useful for binding
19 affinity. And then when a POSA's reading this, in comparison to Kawasaki,
20 that compound X had these known degradation problems.

21 JUDGE NEW: What about Petitioner's argument that Kawasaki teaches
22 a workaround to the degradation problems?

23 MR. SHORES: Well, a workaround -- Your Honor, methylamine, in
24 other words, Kawasaki can't be used with -- I mean, compound X can't be used
25 in certain de-protection conditions. It's like saying, you can buy my coffee, but
26 you just can't use it with sugar. There's a limitation, and it's standard fare, Dr.

1 Baran, the Petitioner's expert witness stated that it's standard fare, so amongst
2 the tools that you have to de-protect, and one of them is standard, is
3 methylamine, but you can't use compound X. So we're not talking -- we're
4 talking about motivation. And so for all of those reasons, compound X simply
5 does not stand out as a lead compound, and again, none of these arguments for
6 lead compound were made in the petitioner, because Petitioner intentionally
7 ignored and sidestepped that analysis on erroneous grounds. Compound X
8 simply would not have been viewed as a lead compound by a person of
9 ordinary skill in the art.

10 JUDGE NEW: The question I have here, really, seems again to sort of
11 come out of cases that you cite, Otsuka, Altana and then Takeda as well, that --
12 I mean, is the lead compound analysis really appropriate here? Because all
13 we're doing is swapping out one known protecting group from another. That's
14 really what this whole ground devolves to, and it seems to me that the fusion
15 one patent's disclosure of the isopropyl protecting group and the acetyl
16 protecting group, that's claimed in the patent and is talked about by Pitsch and
17 Fan, it just seems to be a fairly simple substitution, and in view of KSR, that
18 doesn't seem to be a terribly big jump to get to obviousness.

19 MR. SHORES: Your Honor, respectfully, and I really appreciate the
20 question, it's important that we have this conversation, Your Honor, this is
21 exactly what represents the dangers of hindsight. This is what represents the
22 dangers of -- yes, they're similar compounds, but when you really look at this,
23 what Petition did was select a structurally similar, as structurally similar a
24 compound as possible, and then apply the analysis. And if I may, Your Honor,
25 to your question on whether the lead compound analysis should apply, we

1 submit it absolutely should apply. It's longstanding Federal Circuit law, it
2 applies to new chemical compounds.

3 And the other issue I wanted to bring up is that the Petitioner had stated
4 in his opening that this wasn't a new compound. Well, we're in obviousness, I
5 believe it's not disputed that this is a new compound. But when you talk about
6 the case that was cited, that Judge Yang was -- the decision on NOF Corp, or
7 NOF Corp, or however you pronounce that case, in the NOF Corp ruling did
8 not eschew the lead compound analysis. In that circumstance, the way we read
9 it, and we didn't have firsthand experience on that case, but the way we read it
10 was that the patent owner was demanding that the Board adopt lead compound
11 as the exclusive test for obviousness, and it's not the exclusive test for -- you
12 can't ignore KSR. And I believe that KSR flexible should apply, but they're
13 not mutually exclusive. The lead compound analysis exists within the
14 framework of KSR in order to protect against hindsight. This is the exact --

15 JUDGE NEW: Well I understand that, and your point is well taken.
16 However, even in a lead compound analysis, it doesn't mean we have to choose
17 to best one, particularly we've got numerous exemplary embodiments that we
18 have here, and this is not like Petitioner is plucking this particular molecule,
19 compound X, out of a long, long list of undifferentiated chemicals, as was the
20 case in Takeda. Here, we're taking one known compound and it's also known
21 in the art that we've got protecting groups that could be acetyl base or isopropyl
22 based, they're well known in the art, and here we're simply substituting one
23 known substituent group for another known substituent group, and that seems to
24 me to generally lead to obviousness.

1 MR. SHORES: Well, Your Honor, again, I submit, and respectfully, this
2 is the, you know, represents the dangers of hindsight with Takeda. You know,
3 that's millions of compounds.

4 I don't know if that's the standard, but I mean here -- but we do, we do --
5 we do hold, we do hold the position that this compound was plucked out of
6 thousands. There's no dispute, there were thousands of other phosphoramidites
7 and nucleosides available for use in SPOS.

8 And because this had a structural similarity, then this is why this was
9 selected to, in this case.

10 JUDGE NEW: How many exemplary embodiments of the final
11 phosphoramidite, not just the one we're talking about -- but final. Because they
12 talk about synthetic schemes, so we'll leave the intermediates out of it. How
13 many phosphoramidite exemplary embodiments are there in the '331 patent?

14 MR. SHORES: Your Honor, I will have to check, double check, but my
15 recollection is there are, I believe there, it's in our briefing, I should say, I think
16 there are 40 or so, dozens, 40, you know, to that effect. But --

17 JUDGE NEW: And out of all of those, how many have synthetic
18 schemes? Do we know?

19 MR. SHORES: Actually, Your Honor, I don't know in terms of how
20 many have synthetic schemes.

21 But I will say that, and is as Dr. Hrdlicka has testified, that our expert
22 witness has testified, that there were other RNA compounds disclosed where
23 data was disclosed in the '031 patent that -- and that would have been more
24 appropriate as lead compounds, based on that, you know, but based on the 031 -
25 - 1 disclosure.

1 And you know, we submit that, again, that compound x simply would not
2 have been a lead compound.

3 JUDGE NEW: And thank you for correcting me. When I was saying
4 331, I mean 031.

5 MR. SHORES: Okay.

6 JUDGE NEW: With all these numbered patents, sometimes it's easier
7 maybe we could just call it Cook. That might make it easier for us.

8 Anyway, please continue.

9 MR. SHORES: Okay. Okay, so we kind of went in a lot of different
10 directions. We've got some time here.

11 I'd like to, I guess we can pick up --

12 JUDGE NEW: Well, actually, while we're here, I have another question
13 for you. And I'd like for you to enlarge perhaps a little bit on your argument
14 concerning the secondary considerations.

15 MR. SHORES: Yes, Your Honor, thank you. That's fine, I'm happy to
16 do it this was as well, because I want to entertain all your questions.

17 Sure, the secondary considerations. This was, you know, there was,
18 despite what Petitioner had said, there was a known degradation, you know,
19 problem.

20 I mean, it's not just as stated in the '885 patent. I mean, the '885 patent
21 identifies a few studies.

22 These are scientists, they attend studies. They attend conferences, excuse
23 me. They see that -- they know colleagues, it's a small world.

24 And the presentations were made out at the TIDES Conference, this is a
25 very popular scientific conference, and other conference.

1 And this was identified by colleagues as an issue. And but these,
2 meaning, and there was depyrimidination, which is you have a chimeric
3 oligonucleotide, which is a oligonucleotide comprised of -- it's non-natural,
4 right.

5 There's, and some of the sub monomers are two prime fluoro. Others
6 could be 2 prime OH with cytosine.

7 Others could be, you know, 2 prime H with guanine, etc., etc., right. So
8 these are chimeric synthesized oligonucleotides.

9 And then under standard conditions, under standard-based protection
10 conditions, the resulting oligonucleotide when using a two prime fluoro
11 monomer, would degrade.

12 You would lose the hydrogen as hydrogen fluoride. Of the fluorine,
13 excuse me, as hydrogen fluoride. You would -- the bases would detach.

14 And so there was this problem when you just use your standard methyl --
15 protection conditions to clean the oligonucleotide once it was synthesized.

16 And so there was an industry problem. I mean, I -- to me, that should not
17 be disputed. Apparently it is disputed.

18 This is corroborated by Sinha, this is corroborated by Kawasaki.

19 And what the inventors did was the inventors invented a new molecule, a
20 new compound, that's not disputed that it's new.

21 And this configuration, while apparently simple of just switch out acetyl
22 for isobutyryl, solved this problem.

23 And so therefore, while there may be workarounds, there was no
24 workaround that resulted in the change of the configuration of the molecule.

25 And therefore that molecule has --had inherent advantages and
26 unexpected results as compared to the closest prior art, compound x.

1 JUDGE NEW: And is there any extrinsic evidence that your particular
2 molecule, from the '885 patent, that's recited in claim 3 -- claim 2, is there any
3 extrinsic evidence to show that that has met with commercial success as a result
4 of solving this alleged problem?

5 MR. SHORES: We didn't -- that, there's no evidence in the record of
6 commercial success, right. So it's long-felt need and unexpected results.

7 JUDGE NEW: But no industry plaudits or anything like that either?

8 MR. SHORES: Well, not that we're aware of. I'm not saying there
9 wasn't that, I'm not saying that that didn't occur, I was just --

10 JUDGE NEW: But there's no evidence of record for that.

11 MR. SHORES: There is an evidence of record and we have word limits
12 and we want to pick our spots. And we felt, you know, unexpected results is
13 pretty clear.

14 But also long-felt need. The Kawasaki reference that identifies this
15 degradation issue was dated in 1993. So the filing date of this patent was 2009.

16 And so for at least 16, or if I'm doing my math correctly, I may not be,
17 but you know, 16 years of -- of this issue, at least that existing, and it was
18 solved by this new compound.

19 JUDGE NEW: Thank you very much.

20 MR. SHORES: You're welcome, Your Honor. Okay, if we can -- I'm
21 sorry, Your Honor, I just want to make sure I'm following how you want to
22 proceed. But I can --

23 JUDGE NEW: You may proceed.

24 MR. SHORES: Discuss motivation or you know. With respect to
25 motivation, if we can go to slide 68, please.

1 There are a number of really separate and independent reasons why a
2 person of ordinary skill in the art would have been motivated by -- would not
3 have been motivated by Pitsch and Fan to modify compound x to reach the
4 claimed invention.

5 You know, I think sort of the most clear, you know, one is that Pitsch and
6 Fan really were RNAs.

7 I mean, they weren't -- here we have a 2 prime fluoro, 2 prime deoxy
8 guanosine molecule that is a deoxyguanosine.

9 And Pitsch and Fan, which had limited studies to TOM-protected across
10 phosphoramidite, which is that large 2 prime group.

11 And then a precursor molecule in Fan, we believe those references are
12 sort of, you know, limited to their -- and I'll reference a slide in a second, Your
13 Honor, I know --

14 JUDGE NEW: Sure, sure, yeah, I want to talk to you about the slide --

15 MR. SHORES: Yes.

16 JUDGE NEW: Because I'm --

17 MR. SHORES: Yes.

18 JUDGE NEW: Hard-pressed to see the relevance of it. First off, it's,
19 well, by scientific standards, antediluvian. I mean, it's from 1972 as a reference.
20 And things have progressed quite a bit since then, including the development of
21 phosphoramidites.

22 I mean, he's talking about a method of synthesis using phosphoramidites
23 that's completely different from the synthetic scheme that's proposed in the
24 '031 patent and in your patent.

25 He's working basically in another synthetic scheme using different
26 modules. And then this was before phosphoramidites were even developed.

1 So I'm hard-pressed to see the relevance of this.

2 MR. SHORES: Yes, Your Honor, thank you for that question. And it's
3 an important question.

4 You could take my word for it, you could take Petitioner's, you know,
5 attorney argument. But we have Dr. Hrdlicka.

6 Okay, so when this case was brought, Petitioner's expert, Dr. Baran,
7 made an argument relating to Pitsch and Fan, and a very simple argument
8 relating to Pitsch and Fan.

9 And our expert, you know, dug into this. And he dug into this to
10 understand why.

11 Because he knew that the standard protecting groups to protect the N²-
12 position of guanine included isobutyryl, included a number of other protecting
13 groups. PAC, which according to Fan, deprotected 57 times or -- please refer to
14 the briefing, I'm just speaking extemporaneously here, faster than acetyl.

15 And so what our expert did was go back and look at the scope and
16 content of the prior art. And it goes back to Khorana.

17 Now, Khorana did use phosphodiester chemistry, that's correct. That was
18 the state of the art at that time.

19 And but they were the same molecules. Acetyl was acetyl then, it's acetyl
20 now. And the nucleosides that they were constructing and oligonucleotides they
21 were constructing were the same then as they are now.

22 And the argument that, the actual argument that's being -- that Petitioners
23 made is that well, this is old. This is old and, I think -- if you go to the next
24 slide, I think, you know, Dr. Baran, or the next slide after that, please.

25 Dr. Baran say well, if you -- if you go back far enough in the literature,
26 you can be convinced the Earth is flat.

1 Khorana is really useful literature in the classroom. No one would have
2 picked Khorana reference for anything other than historical understanding.

3 But yet, in the SPOS era, Beaucage references Khorana as establishing
4 isobutyryl as the standard protecting group for guanine and guanine-based
5 nucleosides.

6 Hogrefe, 2013, which I understand it's not prior art, but it's also more
7 contemporaneous than anything else we have here states Khorana introduced
8 the protecting groups for the nucleoside amidites that are known today as the
9 standard protecting groups for isobutyryl and isobutyryl for guanosine.

10 And if we go back a slide, if we could, and here is a timeline of the
11 literature showing from Khorana into the phosphor -- into the SPOS era, P(III)
12 era.

13 The references, Schulhof, Beaucage, you know, Sinha, Scaringe, Culf,
14 Hogrefe, Iyer, all showing numerous protecting groups. And this is in the
15 record, these are exhibits, numerous protecting groups to protect guanine but
16 none are using acetyl.

17 And yes, we do have Pitsch and Fan. Pitsch and Fan, as we've discussed,
18 they are -- they are not deoxyguanosine, which is what Khorana had studied.

19 So one of ordinary skill in the art, looking at -- looking at Khorana,
20 understanding Khorana, and the rest of this literature, this wealth of literature
21 that would not have, you know, that would not have deviated from these
22 teachings, the broader scope and content of the prior art would not have
23 deviated from these teachings because of these limited studies of Pitsch and
24 Fan, the two prime TOM-protected nucleoside. Which Dr. Baran admitted, Dr.
25 Baran admitted that there was no data in TOM -- in Pitsch, other than for the
26 TOM-protected nucleoside.

1 So I think the proposition that somehow -- that somehow Pitsch
2 discovered that acetyl could be used on any nucleobase, so virtually any
3 nucleoside, it's simply absurd, Your Honor.

4 JUDGE NEW: Well, Khorana teaches, in fact, Khorana expressly states
5 that acetyl has all but disappeared as a protecting group as of 1972 in the
6 phosphodiester synthetic scheme.

7 Then, 29 years later, we've got Pitsch coming up and using a different
8 synthetic scheme, basically says that the acetyl group, in combination with
9 methyl nitrite is -- not methyl nitrite, methylamine, is indeed suited for a labile,
10 universal nucleobase protection.

11 Doesn't that tell a person of ordinary skill in the art that it's -- it will
12 work on any nucleobase, and that includes our four canonical ones, including
13 guanosine.

14 MR. SHORES: Your Honor, respectfully, we don't see it that way. We
15 see Pitsch as a study that -- as a study of the 2 prime TOM-protected
16 nucleosides, RNA nucleosides, they have studied.

17 There's no data other than the 2 prime TOM-protected nucleoside.

18 And so to extrapolate the teachings of Pitsch to apply to any potential,
19 you know, any possible nucleo -- any combination of any nucleoside with any
20 nucleobase, it's just not supported, and that's the only sentence.

21 And when we asked Dr. Baran this, Your Honor, during his deposition,
22 we asked him what is your, and I lost my track of my slides here, but we asked
23 what is his basis for, you know, what is his basis for that statement that acetyl is
24 a universal nucleobase protecting group. And he referenced Webster's
25 Dictionary, the definition of.

1 And there's no other basis other than that's in Pitsch and it's limited to its
2 teachings.

3 JUDGE NEW: Mr. Shores, I've been badgering you with a lot of
4 questions and we still have several grounds to cover, and time is running short.

5 MR. SHORES: Yes, Your Honor.

6 JUDGE NEW: So let's move on and --

7 MR. SHORES: Yes, Your Honor.

8 JUDGE NEW: Go to grounds 3 and 4.

9 MR. SHORES: Thank you. And I will say we're not going to be able to
10 get through all of our 122 slides, but I'm happy that we -- that we, you know,
11 addressed some of the key issues.

12 If I can hit on a couple of the ones, then I have a -- I want to have a few
13 minutes to discuss an important issue in this case.

14 With respect to the reasonable expectation of -- so if we could go to slide
15 82. Doctor -- I'm sorry, if we go to slide 83. Actually, if we can go to slide --
16 yeah, 83.

17 So Your Honor, just speak to this and it's in the deck here. But what Dr.
18 Baran's testimony was, in order to -- in order for the reasonable expectation of
19 success argument was that one of ordinary skill would have simply substituted
20 acetic anhydride in step 2 of the example 4D.

21 And then magically you'd have compound at 12 -- I'm sorry, the claimed
22 compound.

23 So compound x has isobutyric anhydride. You'd simply drop in acetic
24 anhydride, and that would have resulted.

1 Well, as Dr. Hrdlicka quite frankly just, this was really the first argument
2 that he seized upon. This just would not have -- would not have resulted in a
3 claim compound. There are multiple independent reasons for that.

4 First, according to Fan, the acetylation of compound 1 would have
5 resulted in dark reaction mixtures, as stated in Fan.

6 And step 2, where you have the more labile protecting groups, protecting
7 N²-position of guanine, and then the two prime, the two prime group in the '031
8 patents, example 4D, that's isobutyryl.

9 When you have acetyl there, TBAF, it's a very harsh condition. TBAF
10 would have cleaved those acetyl groups.

11 And this isn't just Dr. Hrdlicka's testimony. He has cited literature that
12 supports.

13 Now, Dr. Baran did not cite any literature. Dr. Baran just cited, just had
14 his own testimony. And if we can go to the next slide, please.

15 The step 2, this compound, the compound 2, I guess, or compound 3,
16 would have had acetyl groups attached to those positions and would have had
17 significant solubility problems.

18 And I'm not sure we're going to get a chance to fully get into the
19 solubility, unless Your Honor has a question and we can address it quickly.
20 Step 3 has, you know, no insolubility issues.

21 And Your Honor, may I ask, we reserved?

22 JUDGE NEW: Twenty minutes.

23 MR. SHORES: Twenty minutes. So I might push over in my --

24 JUDGE NEW: If you want to rush through your time --

25 MR. SHORES: Rush through my time -- I didn't plan on doing that, I
26 agree with you.

1 JUDGE NEW: My mistake. If you want to extend your time over in your
2 reserve time --

3 MR. SHORES: Okay, thank you, Your Honor.

4 JUDGE NEW: It's up to you.

5 MR. SHORES: Thank you, Your Honor. And I'll try to keep it in, within
6 the time, but I may have to use some more time.

7 JUDGE NEW: Sure.

8 MR. SHORES: If we go into the next slide. The sodium hydroxide, this
9 is a selective deprotection step. Which means that in the '031 patent on this
10 step, the use of sodium hydroxide removed one of the isobutyryl groups, but left
11 the isobutyryl group on the N²-position of guanine intact.

12 Here, as Dr. Hrdlicka testified, the harsh sodium hydroxide conditions
13 would have cleaved both groups.

14 And these area separate and independent reasons for failure of the
15 scheme. And so any one of these would have derailed the -- the synthesis
16 scheme according to Dr. Hrdlicka.

17 Okay, we discussed secondary considerations. Your Honor, if we can go
18 to -- or my colleague Adam, if we could go to claim 2 for ground 3, and that's
19 slide 10.

20 JUDGE NEW: I understand Dr. Hrdlicka's objections to this. But --

21 MR. SHORES: Go back.

22 JUDGE NEW: It seems to me that the '031 patent sets out a pretty
23 straightforward, for organosynthesis, synthetic scheme, that it would be
24 relatively -- a person of ordinary skill in the art would be relatively confident
25 that you could synthesize -- you'd synthesize compound x.

1 MR. SHORES: Yes, Your Honor. And Dr. Hrdlicka didn't feel that way.
2 This is Hongene's burden, this is Dr. Baran's burden, or Dr. -- it's Hongene's
3 burden.

4 But there's Dr. Baran's testimony that they relied upon. And you know,
5 we -- as we articulated in our briefing, we don't feel that that was the
6 appropriate scheme.

7 So if we can talk about -- if we can go to slide 97.

8 Okay, so here are the compounds. We've got compound -- claim 2 from
9 the '885 patent, and we've got the '991 patent.

10 You know, the Petitioner stated in his papers, these are almost identical.
11 Well, an L-configured cytosine is not almost identical to a D-configured
12 guanine, and in the claims.

13 And even their -- Petitioner's expert Dr. Baran did not support this
14 characterization. As you can see his testimony, I wouldn't say, I wouldn't use
15 any of that language that they're substantially identical.

16 And therefore, these are just not the same, the same compounds.

17 In the -- in the reply brief, Petitioner's reply brief, Petitioner argues that
18 they're homologs. Well, these are not homologs.

19 I mean, by definition, textbook chemistry, and Dr. Baran did not support
20 that.

21 So the fact that they would argue they're homologs is a purely attorney
22 argument.

23 And the '991 patent teaches and claims L-configured pyrimidines, not D-
24 configured purines, like in -- like as claimed.

25 And so essentially what it boils down to in my time here is that
26 Petitioner's argument is that a person of ordinary skill in the art is going to

1 select the L-configured cytosine as a lead, and then turn it into a D-configured
2 two prime fluoroguanine.

3 And Your Honor, I submit this is the poster child for hindsight.

4 And I'd like to also just touch on a few other --

5 JUDGE NEW: Well, I'd like to -- I'd like to ask you a couple questions
6 about that.

7 MR. SHORES: Yes, Your Honor.

8 JUDGE NEW: Because first off, as Petitioner argues, wouldn't a person
9 of ordinary skill in the art realize that there's use for both D and L enantiomers
10 in these types of organic syntheses?

11 MR. SHORES: If we can go to the next slide, please, Your Honor, I'll
12 address your question.

13 JUDGE NEW: Okay.

14 MR. SHORES: Okay, so this is what the argument Petitioner made.
15 Petitioner says the nucleic acid -- argues that, in their reply, they say the nucleic
16 acids, according to present invention, had to be D nucleic acids or L nucleic
17 acids.

18 But they've admitted they immediately -- that they quoted the patent, but
19 then they admitted the immediately following sentence, which says nucleic
20 acids according to present invention can either be D or L the Nucleic acids are
21 preferably L nucleic acids.

22 And when you look at the claims of the invention, the claims are
23 claiming L nucleic acids.

24 The patent also talks about issues relating to the instability of L, of D
25 nucleosides, which we would have claimed.

1 So it's just, the reference does teach it, but if you're just, the plain view
2 of these compounds. In addition to this, the claimed view of these compounds is
3 they're just -- they're just very different.

4 I mean, they have different bases, different configurations. And we just
5 feel that this is not a viable argument, Your Honor. In time if I can --

6 JUDGE NEW: If a person was building an oligonucleotide, you're going
7 to need cytosine as well as a guanosine as well adenine and thymine, right, for
8 the vast majority of these purposes.

9 And the only difference between these two molecules besides the
10 chemistry, is one nitride is based, canonical nitride is based, the purine, or
11 pyrimidine being or, you know, pyrimidine, yeah, being substituted with the
12 purine and arriving at the compound.

13 That doesn't seem again like something that would be beyond the
14 knowledge of a person of ordinary skill needing phosphoramidites using all four
15 of the canonical nitrogenous bases.

16 MR. SHORES: Your Honor, I think if you'd reconstruct it in that way I
17 think, and with that rationale and with having the problem to be solved in mind
18 at first, I think that's true.

19 But I also think that that's hindsight. And I think that's exactly why we
20 have any compound analysis, which is -- which is applicable here.

21 One last thing on the grounds, and then I need to move onto one last
22 issue. The -- if we can go to slide 112, please.

23 Hongene just simply failed to show any, make any argument in its
24 petition, or it bootstrapped an argument in its -- in its reply that, of any
25 argument relating to the reasonable expectation of success for synthesizing the
26 claim 4 compound.

1 Therefore, it just fails as, for that reason alone, that that -- and this is in
2 our briefing.

3 And Your Honor, in the interest of time, if I can move on to another
4 issue?

5 JUDGE NEW: Please do.

6 MR. SHORES: So Your Honor, this is, you know, someone with an
7 unusual -- unusual situation in the sense that, you know, bias very rarely, and I
8 think very rarely comes before the Board and the panel.

9 But if we can go up to -- if we can go to slide 41.

10 Your Honor, when --

11 JUDGE NEW: All right, I'm going to stop your right here --

12 MR. SHORES: Yes, Your Honor, thank you.

13 JUDGE NEW: Counsel, because some of this information is redacted in
14 your brief. And anything that comes out in the transcript is going to go out to
15 the public.

16 So I'm just going to caution you before you proceed on that. You
17 shouldn't be discussing confidential redacted information in the brief unless
18 you want it to go public, because the transcript will become part of the public
19 record.

20 MR. SHORES: Yes, Your Honor. Thank you for that, and we respect
21 that, very much so. And this Petitioner's confidential information, and which
22 why we've only included public versions of these materials.

23 In this case, Petitioner filed this petition on January 19, 2023. The day
24 after that, Dr. Baran was solicited, was contacted by Hongene to quote, begin
25 working together. And this is in Exhibit 2033.

1 On August 7, 2023, Hongene agreed to take -- to pay Dr. Baran \$70,000
2 a year to serve on its advisory board. This was not disclosed to ChemGenes,
3 this was not disclosed in Dr. Baran's deposition on September 18, 2023.

4 This was not disclosed in Dr. Baran's declarations. It was not disclosed in
5 his CVs. It was not disclosed -- it was discovered on his second deposition in
6 2022.

7 And then in parallel to this, as we learned through limited document
8 discovery, there were other discussions that were occurring between Dr. Baran
9 and Hongene which were not disclosed all the way up until January 22nd.

10 Not, some of these were discovered through document production on
11 February 15. Not, and then you know.

12 So we have this pattern, Your Honor, we have this pattern. The facts are
13 clear and they're in the briefing that, first of all of bias.

14 This is very, to us, this is a very serious issue. I mean, if you look at the
15 colorful remarks from the witness, and they're in the slides, we, you know,
16 which we referred, Your Honors to, this is as relevant as our -- as my favorite
17 color sweater, that's what Dr. Baran says.

18 Well, we disagree with that, Your Honors. We disagree that this is -- this
19 is irrelevant. We think this is very relevant.

20 First, it's relevant as it relates to the financial interests, the entrenched
21 entanglements, the financial interests, that their extra witness has with Hongene.

22 It also implicates the duty of disclosure before the USPTO.

23 In the Ferring case, the similar conduct for affiant, and the affiant and the
24 relationship with the affiant and the patent owner was found to be -- was found
25 as grounds for unethical conduct.

1 And so we weren't being told about this, these. And when we discovered
2 it, it was, you know, a lot of hand-waving. And I think we've seen that both in
3 the, and we can see it in the deposition transcript, we can see it in the -- in the
4 briefing.

5 Judge Weinstein has said, you know, this type of bias, this type of
6 evidence is, you know, it's not -- it's proved circumstantially.

7 JUDGE NEW: Mr. Shores, for the record, can you say -- can you say for
8 the record what this slide number is?

9 MR. SHORES: Yes, Your Honor, excuse me. This is slide 47.

10 JUDGE NEW: Thank you very much.

11 MR. SHORES: So according to Judge Weinstein, the relationship of --
12 the relationships, the financial and business relationships between a witness and
13 a party is always significant in assessing credibility.

14 And that's the risk that the underlying relationship in certain
15 circumstances will operate on the witness to determine whether a modification
16 of the witness's testimony is a probable, a probable human reaction.

17 Here we have Dr. Baran. He struck a \$70,000 per year deal with Hongene
18 during this case, which was hidden from the record.

19 He had other discussions with Hongene relating to licensing and other
20 collaborations with Dr. Baran where Dr. Baran had the prospect of receiving a
21 financial benefit. That was hidden from the record.

22 And we submit that the SAB deal, the other dealings, whether
23 consummated or not, would naturally affect Dr. Baran's objectivity as a witness
24 in this case.

1 And we talked about the implications of the duty of disclosure. And we
2 have sophisticated parties here. Dr. Baran is a tenured professor at a well-
3 known institution. He serves on multiple corporate boards.

4 Counsel was well aware of their duties here. When, if we go to slide 46,
5 when we were asking Dr. Baran straightforward questions relating to his
6 financial and business affiliations, he testified, as you see there, check my
7 DNA, etc. Whatever you like, sir, it's all irrelevant. I think it's all funny.

8 This demonstrates to us a contemptuous, unprofessional attitude towards
9 this process. And we believe it bears on his -- it bears on his credibility and his
10 bias because he demonstrated in numerous occasions the propensity for
11 overstatement.

12 And we ask Your Honors to keep that in consideration.

13 And I think I'm at my time here.

14 JUDGE NEW: Just for the record, Mr. Shores, I want to clarify that you
15 have not --

16 JUDGE HARDMAN: Judge Hardman, just a quick question. At Dr.
17 Baran's first deposition, were there questions asked of him that you think
18 should have elicited this information, such that he concealed it or hid it during
19 that first deposition in response to specific questions?

20 MR. SHORES: There was, Your Honor.

21 If we can move back to a slide here, to slide 44. And this was a slide
22 where I have found it more difficult to argue with relating to, you know,
23 because there's confidential information at issue.

24 So this is briefed, but he had invited, you know, the question that would
25 have invited its disclosure, we also -- I mean, this was a fundamental, this
26 disclosure obligation is fundamental.

1 You update your CV. You advise, and you submit, when you submit your
2 declaration, you advise as to what your affiliations are.

3 And so whether we, respectfully submit, whether we asked it or, we
4 submit that there was -- there was a duty to notify us.

5 But if we go to slide 42, when I ask -- when we asked Dr. Baran you
6 didn't disclose your \$70,000 per year contract with Hongene, he said he didn't
7 think it was relevant. And that his counsel knew about it.

8 But that they -- so there was evidence here of an intentional decision to
9 withhold this information in this case.

10 And so we think this is very serious. We think it's very relevant. We
11 don't think it's funny.

12 JUDGE NEW: I just would like to clarify for the record, Mr. Shore,
13 Patent Owner has not moved to exclude or to strike Dr. Baran's declaration or
14 deposition testimony, have they?

15 MR. SHORES: That's correct, Your Honor, we have not moved to
16 exclude. We understand from the rules the broad standards that PTAB has for
17 accepting expert testimony, which we respect.

18 And we just ask the court to take all this into consideration when
19 evaluating the credibility of this witness's testimony, as well as the weight of
20 this testimony.

21 And also as comparison to Dr. Hrdlicka, which has spent his entire, you
22 career in this space, has no financial entanglements.

23 And there's a summary slide here, and we can finish with that, and it's
24 slide 50. This provides a summary of the comparison of -- between these
25 witnesses.

26 So Your Honor, I'd like to reserve some time at least at the end.

1 JUDGE NEW: Yes, you have nine minutes remaining.

2 MR. SHORES: Thank Your Honor.

3 JUDGE NEW: Thank you.

4 MR. EDWARDS: Mr. I resume the podium?

5 JUDGE NEW: Mr. Edwards, please do. You have 20 minutes left for
6 rebuttal. And you may proceed when you're ready.

7 MR. EDWARDS: Thank you, Your Honors.

8 I'd like to address this whole issue of bias first. It's largely a one-sided
9 situation in front of Your Honors at the moment, because this was first
10 introduced in the sur-reply.

11 So let's talk about Dr. Baran's service on the Hongene advisory board.

12 There's been no attempt to explain how or why his service could have
13 biased his opinion in this case. That's because he reached his opinions in this
14 case before he was ever contacted by Hongene.

15 And you saw he wasn't approached until after he submitted his
16 declaration in this case.

17 There is no way in which something that happened later could have
18 influenced something that happened before.

19 The advisory board arrangement is a separate fee for a separate service.
20 It's not tied in any way to this IPR.

21 His work in that had nothing to do with the subject matter of this IPR.
22 This is all going to be in his most recent deposition.

23 And unfortunately, we haven't had an opportunity to brief this. So either
24 we're going to -- either you're going to gratuitously grant that to us, or I invite
25 you to read the deposition transcript. Because I think it's more illuminating than
26 the snippet-based approach to presenting this that the Patentee has provided.

1 Dr. Baran has not even discussed the existence of his work in this IPR
2 with his folks at Hongene that he's working with on the advisory board. He
3 testified to that as well.

4 Incidentally, there's nothing unusual about Dr. Baran serving on a
5 scientific advisory board for Hongene. He is a world-famous chemist and a
6 serial entrepreneur.

7 His credentials are sparkling. There can be no dispute that he is one of
8 the world's leading organic synthetic chemists.

9 His expertise is highly sought after by all the household names in the
10 industry. It's no surprise that he was approached to serve on yet another
11 scientific advisory board, of which he serves on several.

12 As for allegations that he supposedly concealed this service, those are
13 simply wrong. It wasn't mentioned in his first declaration because he hadn't
14 been approached yet.

15 He didn't testify about it in September because he wasn't asked about it.

16 If you looked at slide 44, and Mr. Kressman, can you bring up Patentee's
17 slide 44?

18 He was asked if a company would consider licensing some technology to
19 Hongene. He's not being asked there about his advisory board service.

20 But in any event, he's explaining that he doesn't think they legally can.

21 He wasn't asked are you engaged in any other arrangements with
22 Hongene at this point during his deposition at that time. That's why it wasn't
23 disclosed in his deposition.

24 They may later have regretted not asking that question, but it's not that he
25 concealed it in his deposition.

1 Now, we do admit there was a clerical error that resulted in the second
2 version of his CV submitted with his reply declaration not being updated at all.

3 And if you look at his deposition testimony, he explains that that was an
4 error that he took responsibility for.

5 The Hongene advisory board service wasn't the only thing that wasn't
6 updated. Another advisory board service wasn't updated. His title wasn't
7 updated. Numerous things hadn't been updated.

8 This was not an attempt to conceal anything in particular or anything at
9 all.

10 They asked -- you saw a deposition snippet up there that doesn't tell the
11 whole story. Later on in that same deposition, and we should pull this up.

12 Let's go to Exhibit 2035 at PDF page 157-158 or transcript page 156-
13 157.

14 Counsel for Patentee followed up about hey, what about that Hongene
15 advisory board service. And he explained further here, on page 156, line 11, it's
16 not that I didn't feel I needed to represent that. I didn't even look at my CV.
17 Shelly -- his administrative assistant -- handled it.

18 And then he goes on to explain about this oversight.

19 When asked directly later, his answer was clear. Let's go to page 158-
20 159.

21 I asked him in follow-up, did you intentionally withhold any information
22 about your service on Hongene's scientific advisory board in this matter? No.

23 Let's take a step back. The hallmark of Dr. Baran's conduct in this case
24 has been extraordinary candor and cooperation.

25 From the moment he was first asked about the advisory board, he
26 testified openly and at length about it. He produced every document he has.

1 And what's more, and this is striking, he conducted multiple, on-the-fly
2 investigations during his depositions to facilitate the accuracy and fulsomeness
3 of his responses.

4 In January, starting at page 119 in his deposition Exhibit 2032, he's
5 looking in his computer, finding all his emails, sending them to me, and we're
6 producing them.

7 He's doing that again in February in the deposition in one of the related
8 IPRs.

9 He's going on the fly in his deposition and doing a factual investigation
10 so he can be sure full disclosure is available as soon as possible.

11 Regarding this nascent licensing discussions, these refer to discussions
12 between Hongene and a company that Dr. Baran has a piddly ten percent stake
13 in.

14 These discussions never went anywhere. And they never could have,
15 which is exactly what Dr. Baran said when he was first asked about it.

16 No money has changed hands between that -- between Hongene and that
17 potential licensor. There is no entanglements.

18 This is all smoke and mirrors by the Patent Owner in an attempt, frankly
19 a regrettable one and desperate one, to distract from the merits of this IPR.

20 I want to turn now to the merits of this IRP.

21 Let's talk about the lead compound analysis. That's Tab C. I'm going to
22 refer to some tab numbers for my colleague here as I jump around.

23 Hang on a sec. Yeah, okay, so with respect to selecting compound x,
24 Patentee is accusing us of bootstrapping in. that's simply not correct.

25 If you look at Exhibit 1003, page 45, PDF page 48, this is in the petition.
26 I'm sorry, the Baran declaration associated with the petition.

1 Describing the '031 patent and indicating that the patent discloses several
2 nucleoside amidites that had useful properties.

3 In their Patent Owner's response, they said absolutely no reason to
4 choose compound x. And in our reply, we expanded on this exact principle.

5 Our reply arguments expanding on our petition arguments didn't take a
6 new direction, it's not a new theory. It's directly in response to the accusation
7 that there was no reason to select compound x.

8 Let's talk about the lead compound analysis that was mentioned during
9 Patentee's presentation quite a few times.

10 And I'm not quite, I couldn't quite follow whether they're arguing that it
11 must apply here, but of course that is inconsistent with KSR.

12 Judge Yang's final written description in the NOF Corp IPR is
13 instructive. That case dealt also with reagents, just like this '885 patent deals
14 with. And that board rejected the application of the lead compound analysis in
15 that context.

16 And that makes sense here of course too. These are not therapeutic
17 evidence, they're research tools. They're used to make oligonucleotides, which
18 themselves are research tools.

19 Sure, those oligos can perhaps be used as therapeutics, but we're talking
20 about tools for making tools.

21 We're not talking about necessarily about therapeutic compounds.

22 So as a result, there can be a variety of motivations at play, and it's
23 context and use case dependent, as I alluded to in my opening remarks.

24 There is ample evidence here regardless. Regardless of whether the board
25 applies the lead compound analysis or not to find these claims unpatentable as
26 obvious.

1 We are not advocating that this court -- that this panel apply -- reject and
2 apply only the generalized obviousness framework for all reagent cases.

3 We're saying it's more appropriate here, but we're also saying these
4 claims are obvious under either rubric consistent with KSR.

5 I'd like to respond to some comments regarding degradation. I sort of
6 previewed those when I pointed to Kawasaki and Sinha as overcoming the
7 supposed degradation problem.

8 And if I hear Patentee likening it to coffee with no sugar, anybody who's
9 been to a café in the last 20 years can pick up that packet of sugar and what's
10 left on the table are three other packets, the pink, the blue, and the yellow.

11 There are alternatives. It doesn't mean there's a persistent problem.
12 There's no persistent problem with sweetening coffee, and there was no
13 persistent problem with arriving at and using two prime fluoro monomers in
14 oligo synthesis.

15 Regarding secondary considerations, I wanted to just tack on a little bit
16 about the use of methylamine.

17 The '885 patent says generally that they can use methylamine, but they
18 don't provide any data. There's no data hook to show here are some real world
19 unexpected results about using methylamine with two prime fluoro substituted
20 derivatives.

21 So it seems to be a bit of a reconstruction and a sort of straw man
22 problem that they're alluding to here. They didn't actually report any actual
23 science of doing this in the patent, in the patent itself.

24 I'd also like to respond to some discussions about the applicability of
25 Pitsch and Fan, because they were dealing with RNA.

1 The Patent Owner here stands alone trying to wall off Pitsch from the
2 '031 patent and compound x.

3 And what you know, I think you'll notice as you look in the briefs,
4 there's nobody else in the literature saying hey, you know, this stuff's not
5 applicable. This is apples and oranges.

6 That's just Petitioner, I mean just Patent Owner, excuse me.

7 There was a mention, I want to turn to another mention that was made by
8 Patent Owner in their argument. And if we could turn to Tab 16, Mr.
9 Kressman.

10 There's a reference to phenoxyacetyl being faster than acetyl.

11 I think the implication of what you see in the briefs is the argument that
12 well, a person of skill looking at Fan would have seen that phenoxyacetyl is
13 way faster.

14 The implicit argument there is that you would -- they would have
15 selected phenoxyacetyl instead of acetyl.

16 First of all, that's pure attorney argument in the sur-reply, not supported
17 by any expert testimony.

18 Second of all, the only expert testimony on this is the deposition
19 testimony of Dr. Baran, who explained that that's not necessarily the case. That
20 the choice of acetyl or phenoxyacetyl is based on a variety of factors.

21 Phenoxyacetyl might be too labile, and you might want to minimize the
22 molecular weight and go with acetyl instead, or it might be based on
23 commercial availability.

24 I think it's a red herring to point to another option and say well, that's a
25 reason to not choose acetyl when there's clearly a teaching of the utility of
26 using acetyl.

1 I'd like to turn now to a discussion of Khorana and response to that.

2 We think that pointing back to Khorana is antediluvian. And it's a
3 wishing away of the teaching of Pitsch and Fan.

4 It also ignores the recent use acetyl protecting groups on guanine more
5 recently by none other than ChemGenes itself.

6 If we can pull up Exhibit 1043, we're at Tab 19, Mr. Kressman.

7 This is ChemGenes' own patent, 5,525,719. And if we can go to PDF
8 page 8, column 4.

9 ChemGenes is describing their invention in this patent, and they are
10 defining N2 protection of guanosine as including a seal.

11 And then if you look further down, PDF page 15, column 17-18, the very
12 first claim in the patent, they're claiming it. They don't say acetyl here, but
13 they're using the definition of N2 protected.

14 So they're claiming N2 acetyl protected guanosine phosphoramidites
15 here in their patent.

16 The idea that someone would look back to Khorana and not use an acetyl
17 protecting group can't be squared with ChemGenes' own patent.

18 I want to talk now about some reference to the dark reaction mixtures
19 that Fan encountered.

20 Yet again, they've pointed, Patentee has pointed to literature saying
21 there's a problem, when the literature itself, in a couple sentences later, says
22 here's the workaround.

23 Can we go to Tab 21, Mr. Kressman, and pull up Fan Exhibit 1019 at
24 PDF pages 1-2.

25 Sure, they got dark reaction mixtures and unsatisfactory yields. But what
26 did they do two sentences later?

1 They sorted it out using TMSCL. And what did they get? Smooth
2 acylations without generation of dark mixtures.

3 There was a references to the use of TBAF in connection with making
4 the compound of claim 2.

5 Mr. Kressman, could you turn to Tab 22?

6 By the way, there's no evidence that this ever happened. And all that
7 they've said and their expert has said is there is a quote unquote risk.

8 The only support they offer is citation to a paper by Ober. But yet again,
9 Ober overcame this.

10 If we can pull up Exhibit 2015, this is the literature support they cite.
11 This is Ober at PDF page 2.

12 Again, two sentences later, after saying oh, we got this unfortunate
13 parallel cleavage, they say well, we sorted it out using this complex, pyridine-
14 buffered pyridine HF complex, 8 ethyl acetate.

15 By the way, they just said it was difficult in the first instance, they didn't
16 say it was impossible. And then they solved with the difficulty anyway.

17 That can't inure to a lack of success, that's a success.

18 There was a reference to the lesser solubility of the acetylated guanosine.
19 Their argument, if you read their briefs carefully, is that acetylated
20 intermediates would be less soluble in organic solvents and could negatively
21 affect purification.

22 And I think I actually addressed this in my opening remarks, so I'll keep
23 it short here.

24 You know what, I now realize that I addressed that ahead of time, so I
25 will move to the next topic.

1 There was a reference by Patentee's counsel regarding the use of sodium
2 hydroxide. We're at Tab 24, Mr. Kressman.

3 The argument that sodium hydroxide would derail the synthetic
4 procedure for making the compound in claim 2 is refuted by the literature and
5 again, conflates yield with the ability to obtain the claimed compound, Your
6 Honors.

7 First of all, it's refuted by Pitsch, because Pitsch used sodium hydroxide
8 when they acetylated guanosine.

9 Here we can see on the right, Exhibit 1018, that Pitsch at PDF pages 15-
10 16. There you are, treating it with 10 molar aqueous sodium hydroxide.

11 By the way, in the '031 patent, that's what they did too, sodium
12 hydroxide.

13 So the reference that Patentee has pointed to for this supposed derailment
14 for sodium hydroxide actually shows good yield, not failure. It's the opposite of
15 what they say it is.

16 Let's go to Exhibit 2020. This is the Buchi reference at PDF page 29.

17 Here, they're comparing the stabilities of acetylated guanosine over time
18 to a different item B in that table below.

19 But you can see in the top line the acetylated guanosine treated with
20 sodium hydroxide for two hours, 82% yield.

21 That's not a failure, that's a pretty good yield. There's no answer to this
22 in the sur-reply because there's no answer to it on the merits.

23 It appears that I am out of time.

24 JUDGE NEW: You have six seconds left, Mr. Edwards.

25 MR. EDWARDS: I want to thank everyone for their time today.

26 JUDGE NEW: Thank you very much.

1 MR. SHORES: I believe I have nine minutes left, Your Honor?

2 JUDGE NEW: That is correct, Mr. Shores. You may begin when you're
3 ready.

4 MR. SHORES: Let me just start where, kind of where Petitioner started.
5 First of all, there was really no -- if you go to slide 42. You'll note there
6 was really no explanation provided as to -- about this apparent decision to
7 withhold this information.

8 So I'll just, just want to make that point, okay. I'm not going to -- I'm not
9 going to --

10 JUDGE NEW: Well, let me just ask you one more question --

11 MR. SHORES: Yes, Your Honor, if you would.

12 JUDGE NEW: If these contractual undertakings in service of Dr. Baran
13 with Hongene were all undertaken after the submission of his declaration, then
14 how does that go to undue influence when the depositions, the reply declaration
15 all refer back to the deposition, they stem from that?

16 So in other words, there's the deposition testimony, or the declaration
17 testimony, I should say, was given before there was any relationship between
18 Hongene and Dr. Baran.

19 How does that poison what flows from that in terms of the reply
20 declaration and the first and second deposition?

21 MR. SHORES: Thank Your Honor. So if we can go to slide 41. So the
22 facts are important here.

23 If I may approach this screen?

24 JUDGE NEW: Yes, please. Go right ahead.

25 MR. SHORES: So this is when, on January 19 is when the petition was
26 filed. And that included Dr. Baran's first declaration.

1 The evidence that we collected in limited discovery showed that the very
2 next day, one of Hongene's representatives reached out to Dr. Baran to begin
3 working together.

4 Time passes. Eventually a relationship relating to service on the Hongene
5 advisory board is consummated. A contract is executed on August 7, 2023 that
6 includes a payment of \$70,000 per year.

7 It's a one-year contract that's coterminous with these -- this case and the
8 other two IPRs that the parties are involved with.

9 Dr. Baran's -- so at the time of Dr. Baran's first deposition, at the time of
10 Dr. Baran's both is his reply declaration, which included his CV, on January 19,
11 2024, this affiliation of the contract, the service on the SAB, was not disclosed
12 in those declarations or in, to us in any capacity.

13 And while the Petitioner seeks to diminish these other discussions that
14 went on between Hongene and, as Petitioner said, a company that Dr. Baran has
15 a financial interest in and that he testified that he has a ten percent stake in, that
16 these discussions, these separate -- so we have a relationship with his service in
17 the SAB.

18 Then there's the prospect that a company that Dr. Baran has an
19 ownership interest in would have led to a licensing agreement.

20 So you know they say this agreement wasn't --

21 JUDGE NEW: Mr. Shores, I'm going to interrupt you briefly.

22 MR. SHORES: Yes, sir.

23 JUDGE NEW: When you step away from the podium, I've been told
24 that the sound decrease.

25 MR. SHORES: Oh, I apologize.

26 JUDGE NEW: If you're going to use --

1 MR. SHORES: I'll just do my best. I guess there was a pointer, but I
2 don't know where it is here, so.

3 So if we look at -- so in other words, the -- on January 19, the petition
4 was filed.

5 The next day a representative from Hongene contacted Dr. Baran to
6 begin working together. On August 7, 2023, an agreement was executed, a
7 contract for Dr. Baran's service on the Strategic Advisory Board was executed,
8 which included a payment of \$70,000 per year.

9 And it's a one-year term agreement, which could be renewed, but it's
10 coterminous with this case. It's coterminous with the other two IPRs.

11 Dr. Baran had a deposition on September 18. It was not disclosed in his
12 deposition on September 18. He corrected some of his declaration, but he didn't
13 correct his CV, and the record demonstrates that in that deposition.

14 On the -- on the reply declaration, so there were two other declarations
15 that were submitted, one to support Patent Owner's -- the Petitioner's reply, the
16 other was to support the motion to amend two declarations.

17 The arrangement, the SAB arrangement, the \$70,000 SAB arrangement
18 was not disclosed in those declarations, those declarations that you signed under
19 oath did not disclose that contract, \$70,000 contract that he had with Hongene.

20 In addition to that, in parallel, if you look below, there are separate
21 discussions occurring.

22 And this is represented in the deposition testimony and also in the
23 documents, some of the documents that we cited and that were produced.

24 A separate licensing discussions that were being had between Dr. Baran
25 and his company that Dr. Baran owns an interest in that he would financially

1 benefit from. He admitted that he would financially benefit from. And a success
2 of this company that he has an interest in.

3 Discussions with Hongene that Petitioner says, well, those haven't been,
4 you know, consummated.

5 Well, it doesn't matter. There was a prospect of an additional
6 independent relationship.

7 So we have the service as an expert witness, supposedly an objective
8 expert witness, that's the, I guess the assumption that we make in this process
9 for \$750 an hour.

10 We have on top of that a \$70,000 a year contract that was not disclosed.
11 On top of that, we have a potential licensing deal that was not disclosed.

12 And it took us a lot of effort to discover this information despite the
13 cooperation that Petitioner has -- we didn't want to involve the board.

14 We think they produced about 20 documents in addressing the
15 Petitioner's complaint that this was the first time that, you know, it was, this
16 issue was raised for the first time in the sur-reply.

17 Well, they didn't finish producing some of the documents that we
18 requested until the day before our sur-reply was due. This is entirely their
19 doing.

20 And there's no admission, there's no -- and there's no throwing
21 themselves on the mercy of the court for intentionally withholding this
22 information, Your Honor.

23 And I submit to you that's not appropriate. That's not a proper example
24 to set for our bar.

25 And so we think it's serious. And in that regard, but also with respect to
26 the credibility of this witness.

1 And when the Petitioner has -- argues that, you know, Dr. Baran has
2 cooperated, and if we can go to slide 46, this is what we're met with, personal
3 attacks.

4 This is so irrelevant to the case. I think it's sad. I feel sorry for your client
5 that this is what you're doing. It's irrelevant. Why would I put that in the
6 declaration? It's irrelevant. None of this is relevant to the case. I'm sorry your
7 client is paying for this.

8 I'll know you'll strive, that you'll strike it from the record, go ahead, etc.,
9 etc.

10 And so, you know, we've not --
11 (Simultaneous speaking.)

12 MR. SHORES: Yes, Your Honor.

13 JUDGE NEW: I understand your position on this.

14 MR. SHORES: Yes, Your Honor.

15 JUDGE NEW: I just want to be absolutely clear on this. You are not
16 alleging that there was any sort of financial arrangement enacted or even
17 contemplated prior to the 18th of January 2013, when Dr. Baran signed his first
18 declaration, is that correct?

19 MR. SHORES: His first declaration. And what we're saying is we don't
20 know. But the evidence of record indicates that the relationship began a day
21 after his declaration.

22 And so this gets to your question, Your Honor, and I apologize, I want to
23 answer your question.

24 At a minimum, based on the evidence of record, subsequent to that is
25 where you have the, you know, the issues of these possibilities, these payments
26 as bearing on this witness's testimony.

1 And unfortunately because of the -- we probably spent a lot more time on
2 this, Your Honor, but there are numerous areas in his testimony where in one
3 instance he's saying, Dr. Baran is saying, well, the two prime fluoro, two prime
4 deoxyguanosine compounds at issue here are just like, are DNA like.

5 And then later in another -- to suit another argument, they're RNA
6 like.

7 And we addressed these in our briefings, but we submit to you that
8 there's, again, with Judge Weinstein establishing bias is a circumstantial matter
9 and we think there's significant circumstantial evidence.

10 And then again, we just put it before the court and we're asking the court
11 to take into consideration in weighing his testimony.

12 JUDGE NEW: Thank you, Mr. Shores. We're out of time. Do you want
13 to make a very brief final summation? Like less than a minute?

14 MR. SHORES: Excuse me?

15 JUDGE NEW: Do you want to make a brief final statement of your case,
16 less than a minute, before we adjourn?

17 MR. SHORES: Yes, Your Honor.

18 In terms of in this case, what we have here is a inventor's, a family-
19 founded company, an inventor who developed a new chemical compound. And
20 the chemical compound solved a longstanding problem in the industry.

21 It was a reconfiguration of the -- of the, you know, it was a new
22 compound that was used to solve a longstanding problem. And it demonstrated
23 unexpected results.

24 And they have been profitable with that compound. And we have a party
25 who's -- who wants to sell that compound, who's -- we have evidence that they
26 have done that in the past.

1 And the obviousness arguments we feel are very, you know, very, you
2 know, specious, to be quite honest.

3 JUDGE NEW: All right, thank you very much.

4 MR. SHORES: Yeah, thank you.

5 JUDGE NEW: Are there any other questions from the panel?

6 Judge Yang? Judge Yang, I think you may be muted. Do you have any
7 further questions?

8 JUDGE YANG: No, I don't, thank you.

9 JUDGE NEW: Judge Hardman?

10 JUDGE HARDMAN: No. Thank you, Counsel.

11 JUDGE NEW: All right. Well, being there are no more questions, I
12 would like to thank you all for a very interesting and stimulating discussion. It
13 was ably argued by counsel for both parties.

14 We've now taken this matter under advisement, and a decision will be
15 entered in due course.

16 We stand adjourned, but I'm going to ask you to please remain to answer
17 any spelling questions that the court reporter may have.

18 (Whereupon, the above-entitled matter went off the record at 3:17 p.m.)

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