UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Patent Owner.

Case IPR2018-00680 (Patent 9,404,127)
Case IPR2018-00739 (Patent 9,364,435)

Record of Oral Hearing
Held: June 6, 2019

Before SHERIDAN K. SNEDDEN, SUSAN L.C. MITCHELL, and RICHARD J. SMITH, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE PETITIONER:

C. MACLAIN WELLS, ESQUIRE
MORGAN CHU, ESQUIRE
MICHAEL R. FLEMING, ESQUIRE
Irell & Manella LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, California 90067
310-277-1010

ON BEHALF OF THE PATENT OWNER:

MICHAEL T. ROSATO, ESQUIRE
SONJA GENRARD, ESQUIRE
FRANKLIN CHU, ESQUIRE
Wilson Sonsini Goodrich & Rosati
701 Fifth Avenue, Suite 5100
Seattle, WA 98104
206-883-2500

The above-entitled matter came on for hearing on Thursday, June 6, 2019, commencing at 1:00 p.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, VA 22314.

P R O C E E D I N G S

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(Proceedings begin at 1:00 p.m.)

JUDGE MITCHELL: Thank you. You may be seated. Sorry.

Good afternoon, everyone. We have a final hearing this afternoon in two cases, IPR 2018-00739 and IPR 2018-00680. I'm Judge Mitchell and seated to my left is Judge Snedden, and with us by video conference is Judge Smith, who should be here. Is Judge Smith on?

JUDGE SNEDDEN: Uh-huh.

JUDGE SMITH: Uh-huh.

JUDGE MITCHELL: Oh, great. Sorry.

JUDGE SMITH: Hello.

JUDGE MITCHELL: Great, thank you.

I would like to get appearances for the parties on the record, and if we could start with the Petitioner.

MR. FLEMING: Good afternoon, Your Honor. I'm Mike Fleming with Irell & Manella, and with me is Morgan Chu, as well as Maclain Wells.

JUDGE MITCHELL: Great.

MR. FLEMING: And we all three will be arguing.

JUDGE MITCHELL: Great. Thank you.

MR. CHU: Good afternoon.

JUDGE MITCHELL: Good afternoon. And for Patent Owner, please.

MR. ROSATO: Good afternoon, Your Honor. Mike Rosato on behalf of Patent Owner. I have with me for the counsel table Sonja Genrard, as well as Franklin Chu. Thank you.

JUDGE MITCHELL: Thank you.

Let me get a quick clarification from both of you-all, because as I understood from your requests for oral hearing, I think Patent Owner requested the two cases be separate, which is fine. It's just we could do the 739 first, adjourn for a short bit, and come back and do the 680, and have one record that gets submitted for both cases, so that you can rely on -- you know, if claim construction issues are similar, you're going to want to have that discussion in both cases. So I want to make sure I understood right or if you really do want separate transcripts.

Petitioner?

MR. FLEMING: Your Honor, we have prepared for having separate hearings.

JUDGE MITCHELL: Okay.

MR. FLEMING: Because I will be arguing the 739 and --

MR. CHU: All right. The way we're going to proceed is Mr. Fleming and I will argue '435.

JUDGE MITCHELL: Okay.

MR. CHU: And Mr. Wells will argue the '127 Patent, referring to the patent numbers, but having a single unified

transcript as constituting the official record --

JUDGE MITCHELL: For both cases.

MR. CHU: For both cases makes sense.

JUDGE MITCHELL: Okay. And -- and Patent Owner?

MR. ROSATO: We have no objection to this suggestion, You Honor. I mean --

JUDGE MITCHELL: Okay. Okay. So we will go forward with the '739. We'll take a short break and then come back on but have one complete record for both cases.

We set forth our procedure for how we're going to handle this oral hearing in our order, but I want to go over a couple of things as a reminder.

Each party will first present argument in the '739 case, and each party will have an hour for that case, and then we will have a second hearing for the '680 case, and that case, there's a 40, 45 minutes per side of total time.

And to assist Judge Smith in following along with your argument and for the clarity of the record, it is very important that you refer to an exhibit. When you refer to an exhibit, that you state the exhibit number and the page number to which you are referring, and when you're referring to a demonstrative, that you state the slide number.

Petitioner has the burden of showing the unpatentability of the challenge claims in both cases, so the Petitioner will go first. The Patent Owner will then have an opportunity to present its response and may reserve a small

amount of time for some rebuttal.

We have reviewed Patent Owner's notice of objections to Petitioner's demonstrative exhibits. We're not going to exclude any of the demonstratives at this time for the hearing. The Patent Owner may certainly address any objectionable demonstrative in your argument time, if you choose.

We also want to furthermore note for the record that demonstratives are evident -- or not evidence and will not be considered as such. They're used for the benefit of those in this room and for the benefit of the transcript that will become part of the public record.

The Panel will distinguish evidence in the record from argument appearing in demonstrative exhibits and all arguments must be supported by evidence; already of record and relied upon in the briefing. The Panel will not consider arguments or evidence appearing only in the demonstrative exhibits.

So with that, let me ask Petitioner if you'd like to reserve time for rebuttal.

MR. FLEMING: Yes, Your Honor. So our understanding, that is when we go first, we'll be addressing both the principal case as well as the motion to amend.

JUDGE MITCHELL: Yes, I'm sorry. Yes, of course.

MR. FLEMING: And --

JUDGE MITCHELL: Well -- yes.

MR. FLEMING: Or --
JUDGE MITCHELL: I'm sorry, yes.
MR. FLEMING: Would it --
JUDGE MITCHELL: That's correct.
MR. FLEMING: Would it be better that we do the principal case and then later, the motion to amend?
JUDGE MITCHELL: I mean, however you've decided to do it, we'll -- we'll take the argument whatever you're comfortable doing. So that's fine, however you do.
MR. FLEMING: Okay. We'll -- we plan to reserve. If we're going to go forward with the principal case and the motion to amend first, we will reserve 30 for rebuttal.
JUDGE MITCHELL: Okay. Whenever you're ready.
MR. FLEMING: Your Honor, may I --
JUDGE MITCHELL: Oh, sure.
MR. FLEMING: Approach the Bench and present hard copies?
JUDGE MITCHELL: Please.
MR. FLEMING: We might need the -- evidently the --
JUDGE MITCHELL: Oh, is it not working?
MR. FLEMING: Well, it was working just a minute ago.
JUDGE MITCHELL: Oh, no.
MR. FLEMING: This is (indiscernible).
JUDGE MITCHELL: Would you like some help?
MR. FLEMING: Yeah, Your Honor. Could we get

technical assistance?

JUDGE MITCHELL: Can we have like a (indiscernible).

FEMALE TECHNICAL STAFF: This equipment that they have it hooked up to, I can't mess with the equipment if they have it hooked up to --

JUDGE MITCHELL: Oh, okay.

FEMALE TECHNICAL STAFF 1: Because surely if somebody -- because it was up and then you shook it. It came up and it (indiscernible).

JUDGE MITCHELL: Whenever you're ready.

MR. FLEMING: Thank you, Your Honor. Appreciate the patience. We should have it up here.

Okay. I'm ready, Your Honor.

JUDGE MITCHELL: Go ahead.

MR. FLEMING: Okay. Good afternoon. May I have Slide 4, please?

The Petition challenges just Claims 1 through 20 of the '435 patent.

And if I can have Slide 6, please? Here is the independent claim before you. It's important to note that what we have is a nucleic acid lipid particle comprising a nucleic acid, a cationic lipid with this particular range and non-cationic lipid with the 13 to 49.5 range and a conjugated lipid from 05 mole to 2 mole range.

The key here, as far as patentability goes, it's the cationic lipid comprising the range of 50 mole percent to 85

mole percent.

I want to point out that the claim is not directed to a particular use or how effective the particle is, and it doesn't require that the particle is to be non-toxic or that it is in vivo or in vitro.

If I have Slide 5, please.

JUDGE SMITH: Counsel, could you speak up or perhaps be moved closer to microphone?

MR. FLEMING: Yes, Your Honor. Can you hear me now?

JUDGE SMITH: Yes. Thank you.

MR. FLEMING: Just to test, can you hear me now?

JUDGE SMITH: Yes.

MR. FLEMING: Okay, great. I'll speak up.

If I can have Slide 5. There's no dispute that the nucleic acid, the cationic lipid, the non-cationic lipid, and the conjugate lipid are all known in the art.

If I can I have Slide 9, please? So turning to claim construction. The term in the preamble is at issue, and that's the nucleic acid lipid particle.

And the board's construction is correct. The nucleic acid lipid particle is a particle that comprises a nucleic acid and lipid, where the nucleic acid may be encapsulated.

Now Slide 11, please. The intrinsic evidence supports this construction in Column 11, Lines 14 through 22. The '435 Patent defines lipid particle has a lipid formulation

that can be used to drive nucleic acid for the nucleic acid making it encapsulated in the lipid.

A person of ordinary skill in the art would derive that the nucleic acid lipid particle comprises a nucleic acid and a lipid. And I want to point to Dr. Janoff's testimony in his reply declaration on Page 13 that affirms this.

May I have Slide 15, please? The '435 Patent in Column 11, Lines 23 through 46 also define a stable nucleic acid lipid particle, SNALP, as a particle made from a lipid, wherein the nucleic acid is fully encapsulated.

So the term nucleic acid lipid particle encompasses SNALP, but does it -- but is not so limited.

JUDGE MITCHELL: What happens to your case, if we agree with Patent Owner and we think that Claim 1 is limited to a SNALP?

MR. FLEMING: Your Honor, as we point out in our petition, that the 554 Publication actually teaches encapsulation of the nucleic acid in the particle. So as you're correctly pointing out, even if they do get this narrower term, which I don't believe is the broadest reasonable, it still won't matter as far as what the prior art teaches.

May I have Slide 19, please? Which really takes me to Ground 3. And Claims 1 through 20 are anticipated by or obvious in view of the 554 Publication.

If I can have Slide 21, please? There is a formula

that was tested, and that is L054 that reads on the claim. The first thing is that it teaches that the nucleic acid lipid particle in Table 4 and in Example 17 encapsulates siNA.

May I have -- can you pull up the Example 17?

MALE TECHNICAL STAFF: I can't get back into that.

MR. FLEMING: Oh, okay. Well, not a problem.

Example 17 is -- explains the preparation of the nanoparticle that encapsulates siNA formulation that's shown in this Table 5 -- 4.

May I have Slide 22, please? So you can see in the Table 4, it teaches a cationic lipid that it's 50 percent -- 50 mole percent, which is within the range.

If I can have Slide 23, please? It also teaches a non-cationic lipid. That's 48 percent. That's within the range.

And if I could have Slide 24, please? It also teaches a conjugated lipid. That's two percent. That's also in the range.

JUDGE MITCHELL: So are these all referring to a starting formulation and not necessarily a particle?

MR. FLEMING: No, Your Honor. This is referring to a particle. And in the art -- and we have testimony for both the experts that that's how they refer to the particle, but, indeed, it was formulated as a particle.

So if we can go to Slide 30, please? We also have overlapping ranges, and we can establish a prima facie case of

obviousness.

So if I can go to Slide 32, please? The 554 Publication teaches, in Paragraph 0313, the nucleic acid particle formulation that in -- formulation that encapsulates siNA and if we have the overlapping ranges.

And if I could have Slide 31. This summarizes and shows side-by-side the overlapping ranges.

If you could go to Slide 61, please? I want to point out that the Patent Owner has not been able to establish unexpected results, and the key here is that looking at Example 3, which they relied on heavily, there's really only three points that are within the range -- within the scope of the claim. And those three points don't show that it's commensurate in scope with the entire range of the claim.

But even if you look closer at what the table is teaching you, if we can go to Slide 62, please? Here, what we have is the Figure 2 that shows all the groups in the comparison. And so Groups 2 through 10 and 12 have cationic lipids less than 50 percent mole. So if you look at Figure 2, it shows the test results of each of these groups. And so what is going on here is you have -- for each group, four mice were administered 1:57 SNALP.

And the upside-down T, if I can show second slide of 62? Can I have the next slide? When you have the upside-down T, it represents experimental error between these experiments. So when you consider the experimental error, Groups 2 through

5 have similar results compared to 14.

So if we can have the next slide, please. So the other aspect of this figure that is important to understand is the vertical axis; lower is better.

Can I have the next slide, please, and the next slide. You don't? Is that all I have?

MALE TECHNICAL STAFF: Yeah, it's all for 62.

MR. FLEMING: So if you look on the Y-axis, the vertical axis, lower is better because what that is showing is that it's showing how effective the formulation is in silencing the target gene, so you want a lower value there to show that it's more effective.

Okay. So if you look at -- if I can go to the next slide? So the prior art is 2:40, and that's the 40 percent cationic lipid and 2 percent conjugate. And that's what you need to compare to determine whether you have unexpected results because that is the closest prior art.

And there, you see, that for Group 7, it's really -- can I have the next slide? See if it does -- so if you look at Group 14, it's worse than the prior art, and if you look at -- if you go to the next slide, please? If you have Group 13, it's no better or worse than the prior art.

If I have next slide, please? And if you look at Group 12 versus Group 11, it's pretty close. So, at best, all you have is one point, but it's certainly not surprising unexpected results. It's very close to what was the prior

art.

May I have the next slide, please? The Patent Owner is relying on surprising results for the placebo. But the problem there is it's not proper to compare to the procedural or placebo. You need to compare to the prior art.

So if we could go to Slide 67? What is not addressed by the Patent Owner is the fact of how broad this claim is. So to be considered -- to be commensurate in scope with this claim, it's not only showing how effective the particle is, but what you also have to show -- well, what about all the payloads? It could be -- because you have a very broad term, nucleic acid, which can be a bunch of different payloads.

So they certainly haven't shown surprising and unexpected results for all the payloads. And, again, there's only a few lipids that were tested and only a few formulations. So there's a problem here. It's just not -- they're showing us -- this is not commensurate in scope for the claim. I'm going to --

JUDGE MITCHELL: Is it your position that -- you know, I'm trying to figure out how much testing would they actually have to show to basically show that they have the full range of their claim? I mean, what is -- what is your suggestion? I mean, they can't possibly formulate every lipid particle that would be within the claim. I mean, we don't hold them to that kind of a standard to say that they already

achieve or at least support the scope of a particular range in a claim.

MR. FLEMING: Yes, Your Honor. What would be required would be enough testing to show that -- to one of ordinary skill in the art that these surprising and unexpected results would result -- you know, that you'd have enough test to show that you would have a same -- unsurprising unexpected results for the entire range, for one. But the other issue though is, again, you also need to show that you have testing across the nucleic acid as well. So here we only have siNA payloads.

So, again, this claim is very, very broad, Your Honor, and so there lies the problem.

If there's not any further questions, I'd like to turn it over to Morgan Chu to argue the motion to amend.

MR. CHU: Good afternoon again, Your Honors.

I want to start with what the Patent Owner argues are two new limitations and then later, I'll go to the modified ranges.

The first alleged limitation is adding to new independent Claim 21, the phrase, serum-stable. And as Your Honors will know, looking at that new proposed Claim 21, serum-stable appears in the preamble.

Now, this is not a lonely patent prosecutor who's overworked writing claims for many different patents. This is a team of lawyers in a hotly contested IPR proceeding where if

they wanted serum-stable to be a limitation, it would have been easy to put it in the body of the claim.

Now, let's suppose for the moment they did that, which they didn't do. If you have your copy of the '435 Patent handy, I want to show that serum-stable does not add a limitation that the claim must be in vivo or involves systemic delivery.

And the second argument that the Patent Owner is making about the term serum-stable is that it requires encapsulation. Those two arguments.

So if you have your patent handy and can go to Column 13, Line 32, or I can pull it up on the screen. We'll do both. Okay. Column 13, Line 32, and then let's highlight that language, third -- Line 32 through 37. Column 13, 32 through 37. And we'll highlight the word -- okay.

You see, serum-stable is defined by the Patent Owner in a particular manner. It is a defined term in the '435 Patent. And if you look at that language, there is nothing in that language that requires in vivo use or systemic delivery whatsoever. Indeed, if you go to the following lines in Column 13, starting at Line 38 through 41, it's the beginning of the definition of another defined term, quote, systemic delivery. And if you look at that language, systemic delivery is intended to be in vivo.

So if the Patent Owner, in proposing amended claims, wanted to have the claims limited to in vivo or systemic use,

instead of using serum-stable, which doesn't include an in vivo limitation, he could use the next definition, systemic delivery. They chose not to do so.

JUDGE SNEDDEN: In the definition for serum-stable, you have a reference to assays that can be used to test whether or not the particle is serum-stable.

MR. CHU: Yes. And we will see actual testimony by Dr. Thompson after I leave the language of the claims where he is saying that the claim includes in vitro, so we will get to that. It can include it. But remember where we are. We're looking at some words added to the preamble, so although there can be an argument that they are -- could be read, as being a limitation, the general law is, no, you start out, it's just the preamble, and unless it's necessary to give life, and meaning, and vitality to the claim, it's just a preamble. It's not a limitation. If the Patent Owner wants it clearly to say it is limited to in vivo, they could have used the definition, systemic delivery.

Second point, on encapsulation. The serum-stable definition we were looking at in Column 13, line -- beginning at Line 32 did not say encapsulate. If the Patent Owner wanted the new proposed Claim 21 to require encapsulation as a limitation, there's a handy word to do that, and that is to add the word encapsulate. But in addition --

JUDGE SNEDDEN: That --

MR. CHU: Yes?

JUDGE SNEDDEN: That would suggest that you can have a serum-stable particle without it being encapsulated.

MR. CHU: Yes, I agree.

JUDGE SNEDDEN: Okay.

MR. CHU: Okay.

JUDGE SNEDDEN: And then --

MR. CHU: But --

JUDGE SNEDDEN: Then the next question will be, how would something pass these assays and also be serum-stable if it was not encapsulated?

MR. CHU: Okay. So let me get to that. But I just --

JUDGE SNEDDEN: Okay.

MR. CHU: I'm told there's some problem if I try to switch to --

JUDGE SNEDDEN: Sure.

MR. CHU: Some pre-prepared slides from the language of the patent. Let me just show you what else the Patent Owner could have done --

JUDGE SNEDDEN: Okay.

MR. CHU: If it wanted to say encapsulate. There's a limitation.

So there's the possibility of using the word encapsulated. There's another possibility. And it includes the possibility of defining the new Claim 21 as a SNALP because if you go to Column 11 starting at Line 23, the term

SNALP is also a defined term, which includes being fully encapsulated.

So quick points, one, serum-stable was just in the preamble. It's no limitation. If we pretend for the moment it was a limitation, which it is not, the choice of the defined -- particular defined terms and not others and not using clear words would not limit the claims to either in vivo or encapsulation.

So let me go to some of the slides. And maybe we'll just go to 78 for a second, and you can see serum-stable there in the preamble.

And then let's go to the next slide. I'm going to do my own work. It's a different definition of full-service lawyer. Someone who's going to advance the slides himself.

So these are the changes that I will be discussing, and I will try to answer Your Honor's questions along the way here. And just to look for a moment at the Whereas clause, there's an argument being made about the Whereas clause possibly adding a limitation other than what the plain language states. And, here, it's pretty clear that this can be done in a Petri dish. So contrary to the lawyer's argument, this is not suggesting anything about in vivo for degradation. And this was Slide 86. Okay.

Let me go to 87, and this is just showing of the three principal references, the 554 Publication, Exhibit 1004, the 196 PCT, which is Exhibit 1002, and the 198 publication,

which is Exhibit 1003 on the Slide 87, that the nuclease degradation resistance was disclosed in the prior art, so the wherein clause is not adding anything new.

Let me go to the new narrow ranges. You see them in blue highlighting in Slide 88. You can tell from the brackets, it shows the original range. So for the cationic lipid, the original range was from 50 to 75 percent of -- the original was from 50 to 85 percent, and the new range is from 50 to 75 percent. And as Mr. Fleming already addressed in the 554 Publication, this is Slide 89, we see the range covered as well as the second range in Slide 90.

And the next Slide 92 shows that the prior art still overlaps for the proposed cationic lipid range from 50 to 75.

And in Slide 93, we show the actual overlap and note that the relative amount of overlap is greater than it was in the original claim, which was from 50 to 85. By narrowing the original claim, there's relatively more overlap as shown in 93.

And then the point about the lack of surprising and unexpected results can be shown in Slide 96. You've seen this before, Figure 2. You see Group 7, and Group 12 is the prior art, 14 is worse than the two pieces of prior art, 13 is worse than Group 12 and about the same as Group 7, so neither worse or no better. And if you compare Group 11 to Group 12, it's hard to tell whether there is any meaningful statistical difference between the two because of the error bars. And, in

fact, Dr. Janoff discusses the fact that in his opinion, looking at the figure, it's hard to read of course. In this tight comparison, he said in effect, it's likely not statistically significant. It's very close.

But let's for the moment, for the purposes of argument, say that the Patent Owner has one data point for this very broad range of 50 to 75 cationic percent.

In answer to Judge Mitchell's question earlier, it cannot be the case for that broad range. A single data point is commensurate with the scope of the range. Indeed, that 50 to 75 percent includes 70 to 75 percent no data point that the Patent Owner points to is in the 70 to 75 percent. And the record is replete with the fact that slightly different combinations can lead to grossly different results.

So even if the Patent Owner has one data point that shows or maybe shows somewhat better results, it is not commensurate with showing surprising and unexpected results for the entire range.

So you've seen the -- we call the PBS, the inert of placebo standard.

And before I go to the next point, I think Judge Snedden, you asked a question, and chemically modified siRNA, for example, can avoid the degradation. I believe that's in the record, and maybe someone's going to find the exact paragraph for that.

If you go to --

JUDGE SNEDDEN: Before we read the spec, is there anything that spec about a chemically modified nucleic acid or a particle?

MR. CHU: We will look that up, and if I don't get to it in the little bit of time, I have here --

JUDGE SNEDDEN: To me, the amended claim essentially refers -- but -- it recites serum-stable, you go to the definition of specification, it -- it gives you a brief definition of that, and what -- in that is that it must survive exposure to nuclease.

MR. CHU: So --

JUDGE SNEDDEN: And you have referenced here DNA's, RNA's acid. And if you read that in the context of the specifications, it seems the only way that they're attempting to achieve that with this invention is through encapsulation; is that correct or --

MR. CHU: Because I've run over the time, let me just on a somewhat different --

First of all, we will answer your question. My colleagues are --

JUDGE SNEDDEN: Okay.

MR. CHU: Looking through the spec and other references now, and when I get up -- stand up to give rebuttal testimony, hopefully, I'll have a cogent answer to that.

Let me just finish by saying there are other slides as well as in our briefs.

Because this is a contingent motion to amend, then Section 112 comes into play. And we put forth in the papers why the written description requirement is not met and the claim -- the amended claim as proposed is not enabled. And if need be, I'll come back and address those in greater detail.

So I have your question in my journal.

JUDGE SNEDDEN: Sure.

MR. CHU: Thank you.

JUDGE MITCHELL: Thank you.

MR. ROSATO: Before I get started, a question on -- a clarification --

JUDGE MITCHELL: Sure.

MR. ROSATO: -- that the order on granting oral hearing, you mentioned the ability that you mentioned here today, Your Honor, to receive a short amount of time?

JUDGE MITCHELL: Yes.

MR. ROSATO: What do you mean by short?

JUDGE SNEDDEN: I think you have a maximum of five minutes of rebuttal time that you can save.

MR. ROSATO: Okay. I'll reserve five. Thank you.

Let start out on Slide 3. So this is actually a point of clarification on the slides that were submitted. I think that this listing of original Claim 1 inadvertently had a typographical error, including the term serum-stable that appears only in the amended claims of course, but that's been corrected here. I hope nobody has a problem with that, but

we're showing the actual claim here.

But just looking at the '435 Patent, and very briefly, these are directed to lipid particles designed for the delivery of nucleic acid (indiscernible) payloads. And the '435 Patent is a very important patent for a number of reasons, but it's -- one of which is it's listed in the FDA's orange book as covering the Patisiran Onpattro commercial product, which was the first in class -- first nucleic acid delivery drug that's been approved by the FDA and is now approved for use in humans in Europe, as well as the United States.

This is of course important because this has been characterized in the literature, and in the industry, as a game-changing development and because Patent Owner's delivery technology has been specifically credited in the literature as a vital component of that success.

There are a number of challenges that have been advanced; each of them fail for a number of reasons. I'm going to attempt to address. It's a little bit out of order on the slides, but I'm hoping following the order that was presented is more convenient for everyone.

So with that in mind, I want to turn to Ground 3, which is at Slide 21 in the demonstrative exhibits.

So while we're getting there, ground -- we know that Grounds 1 and 3 both presented an obviousness theory, and I'll return to the obviousness theory, but I wanted to address

first the anticipation theory that's raised in Ground 3. And that specifically is alleged anticipation over this L054 mixture. And as Your Honor, Judge Mitchell, correctly pointed out, L054 mixture is a lipid mixture for making particles, not a particle itself. There's never been any dispute on that until today.

I was surprised to hear counsel incorrectly characterize the L054 of Table 4 as a particle. That is categorically false. The evidence is uniformly supportive of the falsity of that charge. It's not a particle. It's a starting lipid mixture for making particles. There is never any discussion in the petition materials about any particle. This appears to be a complete oversight and misinterpretation on behalf of Petitioner and the petition materials, but it's not been challenged. In fact, I'm going to bring up Petitioner's demonstrative Exhibit 25.

This issue -- again, this has not been challenged until today, so I was surprised to hear this. Even Dr. Janoff, in his reply declaration, readily admits that the -- the 554 Publication is describing input percentages as opposed to the composition of the final particles.

Their only response to that is, Well, that might all be true, but everybody did that, so that's conventional. So there's -- as far as the factual matter, it's not disputed that that is a lipid mixture, not a particle. In terms of the response that everybody did this and this was conventional,

it's not responsive to the point.

The claims are directed to nucleic acid lipid particles. They're not -- they do not recite a starting mixture for making particles. So pointing to the starting mixture is not sufficient to establish anticipation with this aspect of the claim. And this all matters, of course, because as set forth in the briefing and established with evidence of record, one does not simply assume that the particles that result from a process have the exact same lipid composition as the starting material. And that's particularly important in the context of 554 for a number of reasons, which, again, are laid out in the record and well supported with evidence.

It's particularly important because in 554, there is no disclosure of particle composition. They don't report any, they don't characterize any, and they don't claim to characterize any. It's also important because there were very specific reasons to call into question the -- what the 554 particle composition, whatever those resulting particles look like, there are reasons to call into question the -- exactly how much they would deviate from the starting materials. And there are a number of reasons as explained -- by both the literature explained by Dr. Thompson, agreed upon by Dr. Janoff, that you would expect significant deviations because different components -- different lipid components, given the processes, the limited amount of detail of the processes in 554, you'd expect different incorporation

efficiencies for different lipid components. And that's going to result in particles that throw out of whack the lipid composition compared to what the starting material was.

This is all very well-documented, supported with evidence, not just attorney argument, and doesn't fit in, as far as I can tell, is not opposed anywhere in the record, and for -- in fact, agreed upon as illustrated by Petitioner's own evidence.

Let me turn to that claim construction issue, and I'll go to Slide 4. So as everybody here knows, as part of the Petitioner's responsibility as moving party, they bear the requirement of the statute and the relevant board rules to set forth and establish exactly how claims are to be construed. So we're talking -- we're going to talk about the construction of the term nucleic acid lipid particles. And for that term, there have now been advanced by Petitioner, three different constructions. The first is the construction that was advanced in the petition materials. The second is a construction that is advanced by Dr. Janoff during cross-examination, where he repeatedly testified that he believed that the claim particles were very specifically defined as SNALPS, and we'll go through that testimony. And then third, in the reply, and this was surprising when the reply materials came in, despite having advanced two different constructions, the reply comes out with an entirely conclusory comment that the Board's preliminary construction is appropriate. There's

no analysis as to why that is or why they believe that to be the case. There's no discussion of why that's appropriate in view of the specification or any other piece of evidence. It's entirely conclusory argument as to just a statement that it's appropriate.

I think there is some additional argument or attempted argument to substantiate that here. The lack of explanation is an issue we specifically raised in our sur-reply materials that there was no argument or evidence substantiating this agreement. So to the extent they're trying to add argument here today, that's obviously improper. But there are reasons why it's not appropriate, and we address that in our briefing. I'm happy to address that in further detail here today, but I want to go through each of these constructions in order, and the first one that is very easy to dispense with is the one that was presented in the petition. It's easy to dispense with because that's already been rejected as unduly broad by the Board in the institution decision, and Petitioner seems to have completely abandoned that construction.

Turn to Slide 5. What's curious, however, is that ever since cross-examination, while Dr. Janoff was very specific and very adamant about his position on how the claim terms could -- should be construed, there's been virtually no comment on that position by Petitioner in their briefing or even here today. They've essentially ignored that. And it's

not something that can be ignored. It's -- again, Dr. Janoff was very specific about that. He testified during cross-examination that -- and repeatedly and consistently, that he interpreted the claimed nucleic acid lipid particles as reasonably being defined as SNALPS, and he testified that interpretation was -- supported both by the patent specification, as well as the content and the context of the relevant prior art. And that's shown on some of the testimony on the slide here, on Slide 5.

Let's turn to Slide 6. Not only was Dr. Janoff clear in his position, but he was specific as to the basis of his opinion. As he previously stated, he indicated a support both by the specification as well as the relevant context in the art, and he also pointed to specific content in the specification. Now, he's pointing to the '127 Patent, but the provisions he was pointing to in the '127 Patent, as we point out in our briefing are identically recited in the specification of the '435 Patent.

The answer from Petitioner as to why -- you know, why Dr. Janoff said this and what their response is, I don't know because I haven't heard it at this point.

JUDGE SMITH: Counsel, could you address the issue of this extrinsic evidence from Dr. Janoff and our role -- these -- the extrinsic evidence and the intrinsic evidence that we're looking at is ultimately, it's a question of law that we're going to be deciding, and you know, I want to know

whether it's proper to consider this Janoff testimony or not.

MR. ROSATO: Well, that's a good question.

Of course, it's appropriate to consider it when the moving party's expert and that party who bears the responsibility of setting forth the scope of their challenge, one of those responsibilities being defining how the claims are to be construed, has offered a construction, and we're asking what the basis of the challenge is. So the -- of course that has to be considered on multiple levels.

And you know, I guess, if you were to reject that construction, then I would ask how does that not carry over to the basis of the Petitioner's challenge and ultimate burden of proof to begin with?

JUDGE SMITH: Well, does this extrinsic evidence trump the intrinsic record?

MR. ROSATO: I think there's an assumption there that there's a difference, and I'm not sure that there is.

So if there's some particular difference that's contradicted, I can address that, but I don't -- to be honest, I don't think -- and we'll get to this. We address in our briefing, but I don't think there's any meaningful difference between the construction that Dr. Thompson advanced, which is extremely well-grounded and unassailable in view of the specification and what Dr. Janoff is -- is proposing.

JUDDGE SMITH: Well, I'm just -- I'm a little -- you know, what -- we've already come out with a construction or

proposed construction. And I think it would be helpful to explain why that's wrong if you believe it's wrong, and, you know, relying on -- you know, it'd be more helpful to point to the specification or some of the intrinsic record, if you have that, than just relying on what either expert says.

MR. ROSATO: Well, I mean --

JUDGE SMITH: Like, for me --

MR. ROSATO: I agree, we need to talk about the specification. I would have to say we cannot ignore what the moving party's expert is stating. That cannot be ignored for many reasons.

JUDGE SMITH: Okay.

MR. ROSATO: Okay?

JUDGE SMITH: Thank you.

MR. ROSATO: But turning to -- why don't we turn Slide 7. Okay.

So this -- let me get to maybe some of the -- what you're more interested in, Judge Smith, and that is looking at the Board's preliminary construction versus the construction that was proposed by Dr. Thompson and -- and how that's supported in the specification.

Now, what's shown here on Slide 7 is reflective of Dr. Thompson's construction, rather than the Board's, but what -- the difference -- the key difference is with regard to the encapsulation issue. And with -- what comes out in the Board's construction is an indication that a nucleic acid

lipid particle may permissively include the nucleic acid encapsulated in the particle, so as to protect that nucleic acid from enzymatic degradation. That's where Dr. Thompson took issue as that can -- that construction -- that preliminary construction by the Board as being unduly broad, and not supported by the specification, and overlooking some other pertinent disclosure.

And, in particular, what Dr. Thompson explains is that the construction that was proposed was very focused on disclosure and the specification around a different term, not the term nucleic acid lipid particle, but disclosure about a definition of the more -- the broader term, lipid particle. Okay? So that matters because the claim term is nucleic acid lipid particle, not just lipid particle. And as shown here on Slide 7, there's pertinent disclosure in the specification that requires yet further refinement of the construction that the Board had proposed.

And, in particular, I would point to Column 11, Lines 51 through 54, where the specification states, in no unambiguous terms, that nucleic acids when present in the lipid particles of the present invention are resistant to a -- in aqueous solution to degradation with a nuclease. And you see other areas of the specification. Again, this is addressed in the briefing where stability encapsulation -- I'm sorry -- encapsulation is defined as a -- testable measure based on resistance to enzymatic degradation. That is precisely --

JUDGE SMITH: So how -- counsel, right. Counsel, how does -- so just how does nucleic acid lipid particle, how is that different than a SNALP as defined?

MR. ROSATO: You'd have to ask Dr. Janoff that question. This is the construction that Dr. Thompson proposed. Dr. Janoff was very adamant in his position that, no, it is a SNALP. At the end of the day -- and, again, this is something we addressed in the briefing, as well as Dr. Thompson's testimony that, you know, it's less -- I guess I would answer that as saying, what's explained as, there's not -- it's hard to find any meaningful daylight between what Dr. Janoff is saying about SNALP and the construction that requires encapsulation because encapsulation is -- what's described in the specification as a characteristic that's conferring the stability or instability of the particles.

So to the extent, you know, that's what Dr. Janoff had in mind, well, that makes some sense and is well supported by the specification. But you know, I would say that -- I would pose that question to Petitioner. This is why it's somewhat curious that they've never addressed the position of their expert, and, you know, and that's just a difficult position to put the non-moving party in, when the moving party's expert is proposing a construction, and then I'm the one being asked to defend that position.

We've proposed economic --

JUDGE SMITH: No, I meant -- I'm actually just

asking a simple question. Is it Patent Owner's position that the term nucleic acid lipid particle as used in the claims should be construed in the same manner that we would construe the term SNALP, that those terms are interchangeable or if -- and if not, what is the distinction that Patent Owner views from their patent?

MR. ROSATO: Our position is the term nucleic acid lipid particle must include a nucleic acid encapsulated in the particle so as to protect the nucleic acid from enzymatic degradation, and that's a position that's well-supported and, quite frankly, unassailable in view of the specification.

Now, beyond that, as far as Dr. Janoff's position, if that is the position that is adopted, that's what they're advancing, then our position is we wouldn't oppose it.

As far as the difference that he had in mind, I have no idea. I honestly would like to hear from Petitioner on this point. I don't know.

JUDGE SMITH: Okay. Thank you.

JUDGE SNEDDEN: Now, when we look at claim -- substitute Claim 21, we see the word serum-stable and in reference to a nuclease test, but in the Claim 1 here, there is no -- there's -- you haven't used the word stable or serum-stable. It only -- in the preamble, it states nucleic acid lipid particle, and then there's no indication that the claims cover something that's nuclease resistant.

So how do we get to encapsulation and nuclease

resistance using the words in Claim 1?

MR. ROSATO: So for the original claim, you know, I would direct your attention to the proposed construction where, again, the specification states that nucleic acids, when present in the lipid particles, they are resistant in aqueous solution to degradation with a nuclease. And when you look at the definition of serum-stable, its defining serum stability as resistance to enzymatic degradation. And when you look at description of how to test for encapsulation, it's defined by resistance to nuclease degradation.

This is what I mean by there's -- it's hard to find any meaningful difference between that, and it's also why in our contingent motion, we specifically pointed out that, honestly, there were aspects of putting in that additional terminology, that would seem to be superfluous in view of some aspects of a proper construction.

I would add that there were additional limitations within the body of the claim, the wherein clause that specifically recite a method. The -- basically the standards are -- I know I'm (indiscernible) the claim, but allow me to talk loosely about it, but read -- recite the aspects of nuclease resistance.

JUDGE SNEDDEN: I understand. So are we arguing the motion to amend now or -- because that language is not in Claim 1?

MR. ROSATO: I'm not arguing that. I'm responding to your question.

JUDGE SNEDDEN: Okay, great.

MR. CHU: Yeah.

JUDGE SNEDDEN: So my question though is that I understand this with respect to substitute claim 21, but when I look at Claim 1, the words nucleic acid lipid particle, I understand you, the argument that you're making, there's not much daylight between nucleic acid lipid particle and the SNALP, but that language only appears in the preamble of Claim 1; nowhere else in the claim. So then we have to consider whether or not that's a limitation, even though it appears in the preamble, and then when we get to the body of the claim, there's no -- what is it in the body of the claim that points me to encapsulation or brings me to encapsulation or to an assay that requires a nuclease test?

MR. ROSATO: I would say that the subject there, the language in the claim is what you see here the nucleic acid lipid particles and --

JUDGE SNEDDEN: Which is in the preamble.

MR. ROSATO: Which is in the preamble, and for --

JUDGE SNEDDEN: Then why is that a limitation of this claim?

MR. ROSATO: Because it's hard to say that doesn't breathe life into the claim when it is defined in the specification as the invention. And that is actually where Dr. Janoff's testimony is also quite pertinent, if we're looking at aspects of what it -- how would someone understand

the invention here. His testimony in -- is certainly pertinent in that regard, if he's doing the invention as being these -- as including serum stability, the very aspects that from this construction, I think are very -- it's a very reasonable position to say that this is -- you know, this is included. It's hard to say that what also is reflected in the specification as critical aspects of the invention are not required by the claim or breathe life into the claim.

JUDGE SNEDDEN: Understood. Thank you.

MR. ROSATO: Thank you. Thank you for the question.

If I may, I would like to turn to a discussion of -- let's turn to Slide 8 and the discussion of this theory of obviousness that's advanced for claims -- excuse me -- for Grounds 1 and 3.

So both of those grounds advance an obviousness theory based on these -- identification of these ranges in the prior art. Now, albeit the two grounds are referring to different references, but I'd like to address the theory in general and the theory as presented in the context of both grounds.

But in each of those cases, in each of those instances Grounds 1 and 3, Petitioner's whole case relies on this mere identification of ranges for individual lipid components in the art. And that's essentially the entirety of the argument. Petitioner essentially drops the microphone once they've identified those ranges and concludes that

obviousness must be found. And in doing so, they're pointing to cases like in *In re Peterson*, and now, more recently *DuPont*. It's an important discussion to be had here as to that theory of obviousness.

Before we get, you know, to those cases in that aspect, it is worth pointing out that what is missing from the petition materials, and we've addressed this throughout our briefing, what's missing are these critical aspects of an obviousness inquiry, like analysis as to the subject matter as a whole. There's no analysis as to the individual lipid components, and how those components interact, or how ratios might affect the properties of the particle both physical and functional, and what negative impacts changing aspects of particles might bring about. There's no discussion of any of that, and there is absolutely no discussion as to motivation to combine or reasonable expectation of success.

And this is important, of course, because every obviousness case requires a motivation to combine and every obviousness case requires reasonable expectation of success. And this is stated and supported throughout the case law. We point to the case of *In re Stepan* from the Federal Circuit in our briefing. There are many others, but in *In re Stepan*, they're specifically dealing with the issue of obviousness in view of overlapping ranges and stated expressly that there are no exceptions to the rule; every obviousness case requires motivation, every obviousness case requires

reasonable expectation of success.

And the cases I've read -- overlapping range cases like *Peterson* and *DuPont* are no exception to that. None of those cases obviate the need for a motivation to combine. And instead, as we point out in our briefing, it's not that they obviate a need for motivation. It's that those cases are grounded in a specific motivation or specific rationale, and that is one of routine optimization.

The very important point in this case because in this case routine optimization, it simply doesn't apply.

This is not a case of routine optimization. The evidence is unambiguous and unanimous on this point, and there's no dispute on this. In fact, Petitioner has not even made at any point here, the assertion that formulating lipid particles that these claims would have been a matter of routine optimization. They actually argue just the opposite. What you see throughout their petition materials and the testimony of their expert, as well as the citation to literature that they provide, is the story that the technology is incredibly complex, it's highly unpredictable, and you don't know what's going to happen. And we even heard some of that today when we're talking about the unexpected results.

So there's no dispute that this is not an instance of routine optimization. They agree with that.

Now, that doesn't mean they don't misapply that analysis; I think they do. They misapply that analysis only

to the -- sort of what we refer to as back end of the analysis when they're talking about unexpected results. But when we're talking about, Why are we even getting to unexpected result to begin with? There is no discussion of routine optimization and no assertion, not even the assertion of routine optimization in any of their materials.

And if we look at the evidence, we can understand why. There's simply no evidence to support the notion, that developing the claim subject matter would have been a matter of routine optimization. What we see is description in the evidence that these are multi-component systems. The interactions are unpredictable. They were poorly understood at the time, and there's an expressed recognition in the field that the industry struggled for decades trying to figure out how to provide viable delivery solutions for the -- in this technology.

Again, none of this is in dispute, and that's a very important point to emphasize because, for obvious reasons, but certainly, for the reason that one cannot reach a finding of obviousness under a theory of routine optimization when routine optimization is simply not a viable strategy. And that is precisely this scenario here, and it should be case-dispositive.

I do want to briefly walk through some of this evidence. And I'll turn to Slide 9. Again, as mentioned, this is an area were experts from both sides are in agreement,

that this was not a simple matter of routine optimization. Dr. Thompson was asked this question directly, addressed at both cross-examination and throughout his deposition, but he had stated directly and unequivocally that during the 2008 timeframe, developing nucleic acid lipid particles would not be considered a routine matter of optimizing variables.

Dr. Janoff agreed with this. Again, as I mentioned, he's routinely emphasizing the complexity, unpredictability, and the difficulty in this area. That is not a picture of routine optimization, and this position is echoed throughout the petition materials.

Let's turn briefly to Slide 10. This is addressed in the briefing again. I would direct your attention to the sur-reply, Pages 14 through 17. But the Petitioner is very clearly embracing this notion of complexity and unpredictability. It describes, for example, starting at Page 8 of their petition, the right -- they're pointing to references like the Gao reference and Ahmad reference in describing the field as -- and the subject matter as being influenced by a whole host of different parameters and a whole host of different parameters whose interactions were poorly understood at the time, with a limited guidance in the art.

That is not a picture of routine optimization. And it's -- and this is further supported by various -- throughout the literature and various pieces of evidence that are submitted and discussed in the briefing. But there is

widespread industry recognition and express discussion that this was precisely the opposite of the situation of routine optimization. The industry in the field struggled for decades to try to figure out solutions to this. The technology and the solutions were described as troubling, difficult barriers, highly complex, barriers to the field. When solutions were finally provided like in the nature article, Exhibit 2023 describing the Patisiran product and the development approval, there are multiple points of discussion. Again, this is a nature peer -- one of the most respected peer reviewed articles -- sorry -- journals, but specifically crediting delivery as the key to success of this significant breakthrough.

So as far as obviousness is concerned, again if we're looking in overlapping ranges, if we're looking at an obviousness case based on the theory of routine optimization, that obviousness theory fails because this is simply not a matter of routine optimization, and there's no dispute that it is.

So I want to turn to the unexpected results, so turn to Slide 11. So is -- again, a little surprised by one of the representations of the experimental data. There was a comment that there were only three data points provided. That's not true. We can talk about this in more detail, but most -- this is most readily apparent from Exhibit 2046, which provides a listing of all the various different formulations that were

tested. There are dozens upon dozens of formulations that were tested involved in the scope of the claim.

And they come from two sources: one is the testing that's reported in the '435 Patent itself, the other source is there are various post-filing date publications that have tested formulations within the scope of the claim and showed them to be highly efficacious and have low toxicity, and we'll go through those as well. Both sources as -- obviously as a matter of law are available to support a case of unexpected results and both were presented by Patent Owner and do support that outcome.

So, now, do we need to get here? Well, that's a good question. So to the extent there is ever any sort of presumption of obviousness as was argued in the petition materials, as we already discussed, that presumption would be overcome by answering the question directly as to whether this is a matter of routine optimization to begin with, and the answer is no. That any remaining or any obviousness case -- or any obviousness case that remains would be further overcome by this showing of unexpected results throughout the briefing. And the general reference to the briefing, if it helps, is the Patent Owner response Pages 22 to 27 and 59 to 61 and also the sur-reply Pages 18 and 27.

But let's be clear on what the -- we were talking about unexpected results. We need to understand what the expectations were at the time. And the expectation at the

time was that increasing cationic lipid in a formulation would be expected to decrease the in vivo efficacy and increase the toxicity to the subject. There are a number of reasons for that. Those were discussed throughout the literature and those that -- I have not seen or heard any meaningful rebuttal to any of that. So the expectation is that it's -- again, as you raise the cationic lipid, you expect in vivo efficacy or efficiency to decrease and toxicity to increase. These were recognized as toxic components that caused problems and there some reasons why some had to be included, but there were great downsides that went with that, and those downsides would be expected to manifest as you increase the level of this component.

JUDGE MITCHELL: Will these downsides be considered to increase when you're talking about the particle itself, where you're adding a non-cationic lipid, conjugated lipid? I mean, don't you have to consider the full formulation to really say, Hey, if I increase the cationic lipid, I'm going to have a problem.

MR. ROSATO: That --

JUDGE MITCHELL: I mean, there's an overall charge that you really have to look at in the particle to really see if there's a toxic effect.

MR. ROSATO: Well, let's talk about the charge thing in a moment as that is an important issue.

Let's talk about the threshold question you raised

there, which is, Don't you have to look at the interaction of components? I would say, Yes, you certainly do. Now, where did the petition materials look at the interaction of individual components? The answer is they don't. There's that -- this -- again, because this goes to my earlier comments that the entire case is essentially an identification of ranges and then the end to the inquiry.

That's not sufficient to establish obviousness, and that's one of -- and that's a point that we argue is, you know, we should -- you know, the inquiry, as far as we're concerned, the obviousness inquiry should essentially stop there when we're asking if they met their burden of proof, but, yes, of course, the different components interact, and at the time, that was very poorly understood, and complicated, and unpredictable.

So, yes, they do. Now, how does that -- does that defeat an obviousness assertion? I would say that it does. In terms of looking at the toxicity, at the time, it wasn't really understood. But what was known, and what was unexpected, and what's unchallenged here is that the conventional thinking was you wanted to minimize the component of that ingredient.

There were other components, and we talked about this in the briefing, that could help mask some aspects of that, like charge differences. I think you're referring to the conjugated lipid. So we -- you know, that is an argument

we point out too which is, well, if you are hypothetically going to increase the cationic lipid component, would it logically make sense to decrease the content of this masking or this other component that has some benefit masking that? But that also factors into the inquiry too because what we're looking at are particles that have very high cationic lipid component, very low conjugated lipid component.

We've asked that question, Why would one be motivated to increase the cationic lipid component, yet have a very low conjugated lipid? And that's a question we don't have an answer to. I don't think it does make sense. Dr. Thompson testified that it wouldn't make sense, as to why that's -- you know, how we get to a rationale, we don't have any answer that because there is none.

JUDGE SNEDDEN: Maybe I need to backup a little bit.

So what is your position in terms of -- explain to me the differences between the prior art and Claim 1, and the elements of Claim 1? Are we talking about simply overlapping ranges or are there other differences?

MR. ROSATO: Yes. Before I get to that, can I finish answering --

JUDGE SNEDDEN: Sure.

MR. ROSATO: -- a question, just so I don't lose it.

I want to be clear too. There isn't a -- you know -- that you raised a question about charge, right? Just to be clear, charge on a particle is not the end-all-be-all, the

sole inquiry when it comes to toxicity. The cationic lipids themselves are toxic molecules, and they're toxic for a number of reasons. Both -- some things have to do with charge indirectly. That matters more for aggregation of particles as their -- and a reason why -- one of the reasons why there's difficulty in systemic administration as the charged particles tend to get cleared out before they reach their target site. But as far as toxicity is concerned, that is not dependent solely on charge or really even on charge. The cationic lipid molecules themselves are toxic molecules, as they're immunogenic, they're cytotoxic, they have bioaccumulation problems. The Ahmad and Lin references actually talk about metabolic burden and as the main concerns with toxicity of those molecules.

But just be very clear, you'll see some interchange of toxicity in charge in Petitioner's briefing, and I think they tried to maybe leverage off some languages in the institution decision, but charge is not the issue. There -- it's not interchangeable toxicity. It -- don't fall for that that being switched.

I'm sorry, Your Honor, your question?

JUDGE SNEDDEN: Just look for -- just a highlight of the differences -- what you're describing as a difference between the prior art and Claim 1. And I thought it was just a matter of just overlapping ranges, which means now, we have to establish a criticality within the range, and, therefore,

we moved on expected results. I mean, is that how I understand?

MR. ROSATO: Well, I mean, I don't think so, and that's why I talk about the issue of routine optimization. Right? I mean, there's a tendency to look -- I mean, if you look at the overlapping range, case law -- and this is the point I want to make sure is made because I think it's very important. When we're talking of this overlapping range paradigm, we tend to think of it as, you know, these enumerated or typical options for overcoming that case, and those do include things like establishing criticality by unexpected results, which is what -- why we're talking about expected results here.

But my point in routine optimization is, that's not the only way you overcome an obviousness case in overlapping ranges. Why is that the case? Because every obviousness case requires a motivation for doing something, a rationale, a reasonable expectation of success. The overlapping range cases, if you go through and read the -- I'm sure you do, I'm just saying this figuratively. When you go through and read those cases, you find the explanation of this whole theory, the whole basis of this case law is grounded in the theory of routine optimization. Right? Ranges that are not especially broad invite routine optimization as is the typical mantra, and those cases also go back to the *KSR* case to ground the routine optimization rational back to this sort of inquiry.

So if the fundamental basis for obviousness in an overlapping range case is routine optimization, you cannot reach obviousness on that theory, that theory being routine optimization, if it simply doesn't apply in a given context.

Now, there are various tools for indirectly, as well directly getting to that issue, like unpredictability and so forth, but there are also indirect ways of conducting that inquiry.

Here, we have somewhat of the luxury of going right to the heart of the question and asking whether this is a matter of routine optimization. It's simply not. And there's never been an assertion that it is. Right? That's why I make that point.

So in terms of the differences, well, as you see, what we see in the claim mapping in the petition is really just in pointing to different disclosure where there are general paragraphs or discussions about things that one component at a time, and the art gives some broad ranges, thus, it's talking about the entire universe of various different things.

So the obviousness cases, as I understand it, is that if you go through on an individual ingredient-by-ingredient basis, you see some limited overlap in what's disclosed versus what's claimed. I would say the differences are in part going to Judge Mitchell's question which is, Don't these different components interact in certain ways and don't

some compensate for others, or there are reasons for doing this? The answer is, yes. So, why, you know this gets the ratio issue.

JUDGE SNEDDEN: There's the combination of these ranges that lead to the unexpected results, but there is -- like some criticality in the ranges.

MR. ROSATO: There's criticality in the sense that it's not routine optimization. Yes, I would agree with that.

JUDGE SNEDDEN: Right.

MR. ROSATO: I always found that criticality question -- or description -- anyway, yes, I would say it's supportive. And you see that concept in various aspects of the overlapping range cases as well.

I mean, if you go back to the result effective variable case, the Antoinette (ph) or *Antonie*, that's probably one of the key areas where result effective variable differentiation, you know, still very viable when you're talking about ratios of different components and how those interact and whether there was a recognition in the art of, you know, some predictable outcome from different ratios.

That's an issue here too. But this go -- there are many issues here. This is why, you know, I want to make sure I point out, you know, I'm sure that this is part of a Patent Owner's job as well, but part of the burden.

But part of the job is to point out the deficiencies in the state of the case or respond to what is stated. But

it's one of the challenges here as non-moving party, looking at a petition where there is no explanation as to why this is all being advanced.

I don't know the theory. I've seen case law citations to overlapping range cases, but I've never heard an assertion that this is a matter of routine optimization. I don't know if that's their theory, and I would encourage posing that question to them. I'd love to hear it.

JUDGE MITCHELL: So let me ask you. So how do you respond to -- in the 554 Publication, the L054 formulation, that does show everything, as I understand it or within the ranges, it has everything in the claim within the ranges; is that correct?

MR. ROSATO: It did -- it's not correct.

JUDGE MITCHELL: Okay.

MR. ROSATO: It doesn't. So I think you're referring to the table, Table 4. So, again, those are starting ingredients. We're claiming particles here. Most of those -- actually, I think virtually all, except maybe the one they pointed to, if we're just looking at the numbers for starting ingredients, they point to one that seems to barely touch with the claimed ranges. And that's the one that they're refer -- reciting -- sorry, relying on for the anticipation case.

And for that anticipation case, you know, their argument is you're pointing to a starting mixture, it's barely

touching on the range, and if in the context of this particular application you're expecting various different efficiencies of incorporation into the particle, then this is essentially an unsubstantiated inherency case with the anticipation charge. Right? Making assumptions about what -- there's no disclosure what the particle composition looks like.

So if we're assuming that it meets the claims, that is -- that's why I described it as an unsubstantiated and failed inherency case. There's no -- the probabilities and possibilities tests is not met there. It's pure speculation.

JUDGE MITCHELL: But doesn't that get them closer on obviousness case? That here, there's -- in the art, at least with the starting formulation, they're within the ranges.

MR. ROSATO: I mean, closer than what?

JUDGE MITCHELL: In terms of the rationale to combine. It's already done. Somebody's done it.

MR. ROSATO: Somebody has not done it. There's not a single embodiment that falls within the scope of the claim. So --

JUDGE MITCHEL: Because it's starting? That's your argument? Because it's the starting formulation and not a particle?

MR. ROSATO: They are absolutely not particles.

JUDGE MITCHEL: Okay.

MR. ROSATO: Yes. They are absolutely not

particles, and there's no dispute on that, other than what we've heard here today, which is the first time that we heard that.

So those are absolutely not particles. There is no particle that meets -- that falls within the scope of the claim. All of them are outside.

Now, if we're looking at the numbers in the table, I think you asked, Are they closer? I don't know. I mean, I don't know how to answer that, and they're the closest thing they've pointed to. I guess this is my answer to that.

So I see I'm down to five -- about six-and-a-half minutes. I do want to get through a couple other points. I want to, obviously, that whatever's most important to the Panel is what I'd like to address, but I had a couple other things that I wanted to go through, if I may.

JUDGE MITCHELL: Sure.

MR. ROSATO: Okay. In terms of the -- I'll just say a couple things on the -- couple things further on the unexpected results.

Again, I pointed to the exhibit and then some other briefing material at Exhibit 2046 and the briefing material. But there are dozens and dozens and dozens of formulations that are falling within the scope of the claim. There's no dispute that any of those formulations fall within the scope of the claim. There's no dispute that those formulations are showing potent silencing or potent activity in vivo and low

toxicity. None of that is disputed. And there are, again, dozens and dozens of formulations spanning their range. Even -- what slide is that even? I think it was mentioned here today, but one of Petitioner's demonstratives show the range spanning, I think counsel mentioned, Yeah, but that only -- you know, the coverage only goes up to 70 percent.

So there's that tail end of the range that there's -- where there's not -- we don't have data points. Otherwise, it's spanning the entire range, many different formulations, many different combinations of lipids, different lipid constituents, many different cationic lipids, many different conjugated lipids, many different non-cationic lipids, many different gene targets. Not only siRNA targets, but mRNA targets. And one of those is illustrated on Slide 14.

But again, I mean, if we go through the various pieces of literature, again, there are multiple gene targets, many different gene targets targeted. But one of the arguments that was advanced by the Petitioner was to criticize or question whether these would work for mRNA, which it was a surprising argument, considering that they've published extensively that these formulations work fabulously on mRNA, including the acetic reference shown here on Slide 14. And I think this is Exhibit 2048, if I'm getting that correct.

But here, again, this is Petitioner's own publication but what they did is in trying to deliver mRNA, they literally took the Patisiran formulation off the shelf

and replaced the siRNA with mRNA payloads and then recorded how well it worked, and it does work well.

They've asked our experts about -- so excuse me. They asked Dr. Heyes, Is it completely irrelevant. I don't know why they were asking him this, but they did ask him if Patent Owner had been using their formulations in mRNA. And Dr. Heyes, who works for Arbutus, which is Aldoner Protiva (ph). But Dr. Heyes explained that, Yeah, of course we've been using these for years. So it was surprising to see some of this argument.

As far as unexpected results, there are various -- various embodiments covered far more. If we're talking about relevant case law, this is actually a good point of comparison, maybe answers your question, Your Honor, about how many points -- how many data points are needed. And what we know, or what we can look at as a basis of comparison are the cases where the Federal Circuit has rejected unexpected results or experimental data for not being in commensurate in the scope of the claims. And in each of those instances, like the *Peterson* case, like the *DuPont* case, what we're look at is, literally, like, one or two data points, and that's clearly not the case here. The unexpected results look absolutely nothing like any of those cases where data was -- experiment results were rejected as not being commensurate in scope.

I do want to talk about this toxicity issue as well,

so let's turn to Slide 15. So, again, what has been pointed out in the briefing and supported with evidence is the fact that cationic lipids were known to be toxic and that the conventional thinking at the time was that their content in lipid particle formulations should be minimized. There are various pieces of evidence. And there's actually not a dispute on that point. The response that Petitioner has advanced is something different.

Let's turn to Slide 16. What they've argued is, Well, that might all be true, but there's an exception to that rule. And that exception is this very convenient, but unfortunately, false, narrative that certain types of cationic lipid weren't toxic and that was well known. They argue that ionized cationic lipids, such as DLinDMA, specifically, which they identify as their argument goes, were well-known at the time to be non-toxic.

As far as the evidence is concerned, there is not a shred of evidence to support this argument. In fact, as we point out in our sur-reply briefing, Petitioner has multiple publications that, you know, are within the last couple years, far pre-dating -- sorry, post-dating the '435 Patent, where they're still specifically identifying toxicity concerns with ionizable cationic lipids and specifically identifying DLinDMA, the one specific example that Petitioner has identified. And that can be seen in Exhibit 2051. The quote provided here on Slide 16, as well as 2052, and as -- and

quite frankly, numerous other publications that Petitioner has put out.

So this is simply not a credible argument as far as the toxicity concern and notion that the general thinking at the time was to reduce the content of this component. The conventional thinking was that -- sorry, the decision of Petitioner, I have not heard any opposition to that.

If I can -- if I may, Your Honor, I want to make a few quick points on Ground 2, and then finally, on the encapsulation issue. I didn't mention it, but I think it's apparent that it's an additional basis as to why Ground 3, the anticipation challenge fails. And I would direct -- this is addressed on Slide 22, but also in our sur-reply briefing.

Dr. Janoff was very adamant in his position that encapsulation was a misused term or improperly used in the art at the time. He thinks it means it could be very different things, and he's even published on the topic, criticizing people for using the term encapsulation when they haven't tested for nuclease degradation and criticizing that it is not real encapsulation. That's addressed in our briefing and provided here on the slide. But that's pertinent for the '554 Publication because there is no nuclease degradation test performed in '554 and not even a claim that LO54 encapsulates.

In terms of Ground 2. And I really appreciate the extra time, let's turn to Slide 18. There are a couple of points, and the fundamental distinction here is Lin and Ahmad

are directed to these different types of particles that are referred to and which they call knowing the artist, lipoplexes. Lipoplexes are a fundament different type of particle. They're essentially lipid aggregates that have nucleic acid adherers stuck to them. And they differentiate, obviously, from the type of particles that we are talking about that are encapsulated nucleic acids within the particle.

And Dr. Janoff's publication says, as well as testimony during cross examination, identified those differences and agreed with them. He also testified that -- and this is another reason why his claim construction is pertinent, we asked him if he thought lipoplexes would be within the scope of the invention, the '435, and he indicated that he didn't think it would. So it begs the question, why are you even looking at these references to begin with? And that is not something that's addressed.

Which brings me to Slide 19. Obviously, the Panel's going to be very familiar with case law, whether assertions and speculation about whether somebody could or may have an impact as a basis for obviousness assertion. We know as a matter of law that those types of assertions are insufficient. They've never been sufficient to establish motivation and that's well supported in the case law.

And then, finally, this really will be my final comment, is on Slide 20. We can't discount the fact if we're still considering Lin and Ahmad, we can't discount the fact

that the whole point of those references is how to decrease cationic lipid. It's a point that seems to get lost in some of the Petitioner's argument. This is explained by Dr. Thompson. That's the whole point of those references. This is actually explained by Dr. Janoff in his reply declaration and confirmed in cross-examination. He explained what those references are doing is you're using multivalent cationic lipids in order to have multiple charges on one molecule for the benefit of reducing the amount of the cationic lipid.

Why are they doing that? Well, they tell us exactly why they're doing it. There are multiple benefits, including reducing cost and toxicity concerns. So they're pointing to references that are fundamentally directed to the concept of reducing cationic lipid and pointing to those references for the notion that you demotivated or that you could increase the cationic lipid, and that doesn't make sense.

Thank you.

JUDGE MITCHELL: Thank you. And I'll just add time to Petitioner's time and give you your rebuttal time.

Whenever you're ready.

MR. FLEMING: I'm ready, Your Honor.

JUDGE MITCHELL: Okay.

MR. FLEMING: Your Honor, I would like to address your question about whether or not LO54 is a particle.

First off all, the Patent Owner, as counsel has represented, that there was numerous times that we haven't --

that there's not a dispute. We would like to categorize what he said. Those things are just not true.

As far as the particle, if you look to the reply on Pages 13, we clearly dispute that issue that they raised that it's not a particle.

One very important thing to point out is the '435 Patent. That's how they tell you whether it's a particle is by telling you what is the formulation of the composite. All we're talking about is a composite. We're not talking about a chemical compound. It is a composite. So what -- how do you describe a composite? With the components that make up the composite.

The other important claim is if what he -- the Patent Owner's counsel is arguing is true, then the '435 Patent is not reduced to practice because there's not one aspect of that patent that actually provides you somehow the structure of what the particle looks like. In fact, that's not the way the industry works. Instead, it refers to the components that make up the particle.

The other point I would like to address is the claim construction. And Judge Smith, I want to address your question about whether the intrinsic record is what you should go to first. That is clear case law that the Federal Circuit has instructed the Board that entrance of cations is the first item that you looked through, and if there is and only do you look to the extrinsic evidence, if there's nothing necessary.

Now, I also want to point out that the Patent Owner's counsel is misleading you on what he was saying is the definition of nucleic acid. These terms are defined in the '535 (sic) Patent and nucleic acid -- '435, sorry -- '435 Patent on Column 10, starting on Line 26, defines the terms nucleic acid.

Going over to Column 11. Starting at Line 14, you have a definition of lipid particles. And if you go down to Line 23 of Column 11, you have a definition, a SNALP. What they pointed to for the definition of nucleic acid is part of the definition of the SNALP because the definition goes all the way down to, it looks like, Line 58. And where he was pulling that definition out was simply talking about what the definition of a SNALP is as far as how it is encapsulated to prevent degradation.

JUDGE SNEDDEN: So I take it that your position is that the Claim 1 is not covering a SNALP; it's something different?

MR. FLEMING: That's right, Your Honor, it does not require encapsulation for the definition of nucleic acid lipid particle. And that is clear from the specification of the '435 Patent.

I'd also like to point out in the claim construction, which is really a minor point, and you don't really need to get to it, but they point to Dr. Janoff's cross-examination testimony. And I want to point out that

that's really all taken out of context on what happened there.

The -- Dr. Janoff is answering the question regarding the level of skill of the person of ordinary skill in the art. And the questions aren't in regard to Paragraph 32 of his '127 Patent declaration, and there he is saying that a person of ordinary skill in the art for the field of the '127 Patent but has specific experience with lipid particles.

During that same deposition, when asked what it -- you rely on -- and may I have Slide 17, please? What did you rely on in formulating your definition for nucleic acid lipid particles? Dr. Janoff answered by pointing to the same definition found in '425.

Also, in Dr. Janoff's reply declaration, if you look at Paragraph 13, he agrees with the board's construction of nucleic acid lipid particles. And Patent Owner's counsel chose not to depose Dr. Janoff in questioning on that answer. That testimony in Paragraph 18 in the second deposition, which is -- they could have challenged him then, and they chose not to.

So I'd like to go to routine optimization, if I can. In regard to Patent Owner's Slides 8 through 10, they're arguing in routine opposition is not applicable. I think we need to look to the scope of the claim. And it only, again, requires a composite of nucleic acid and the cationic, non-cationic, and conjugate lipids.

So the question is, when you look to the publication

of the '544 -- maybe we could pull up Slide 33 or did I lose my slides? The '554 teaches that all this is in routine optimization. They specifically point out that all the things that they've set forth in all these ranges could be modified and optimized. And it's all within the skill of the art. And I think that when you --

JUDGE SNEDDEN: I have a question here. I just want to clarify one thing. Are you arguing routine optimization in your petition, and, if so, what variable are we optimizing?

MR. FLEMING: We are -- yes, we did argue routine optimization. You know, what we're talking about is, would you be able to optimize for the overlapping ranges to obtain the range that's being claimed? And, again, all we're talking about is a particle that is a composite. And if we look to Table 4 of the '554 Patent, you can see how they did go about the very thing that they're referring to about, Well, can it easily be able to put -- adjust the cationic lipid?

If you raise the cationic lipid, then you're going to have to lower the other components, and that's exactly what Table 4 does, methodically. So that's well within the skill of the art to create these particles to obtain --

JUDGE SNEDDEN: Where does the art disclose doing that?

MR. FLEMING: What's that?

JUDGE SNEDDEN: Where does the art disclose doing that?

MR. FLEMING: In the '554 Patent. It is --

JUDGE SNEDDEN: Oh, right, okay.

MR. FLEMING: It is talking about that very thing.

JUDGE SNEDDEN: Got it, okay.

MR. FLEMING: And what I was trying to explain to you is that if you look to the specification in Table 4, as well some of the other tables, that's exactly what they did, is it all has to add up to 100 percent mole. So you're going to be able to adjust this to obtain the particle.

JUDGE SNEDDEN: Okay.

MR. FLEMING: I also want to point out, their routine optimization is assuming that it has to be in vivo, and the claim does not require in vivo. We're just talking about a particle of a certain composition. This claim is extremely broad. They wanted to limit the claim to in vivo or -- in that sense, they could have. But all we're talking about is being able to create a composite where you can have the nucleic acid be part of that particle. It doesn't even require it to be inside the particle. It could be attached to the outside of the particle. That's clear from the definition of reciting the specification.

I'd like to also address the unexpected results. And, Your Honors, it's well-settled case law, and I'm sure you're very well aware of it, that the Federal Circuit looks to unexpected results to determine whether or not what we're talking about is a degree of a known property or whether it's

a known property. And where it's a degree of a known property, then they're expecting a much higher surprising result.

If I could point you to the case law, Bristol-Myers Squibb versus Teva Pharmaceuticals, if you look at that set, 752 F.3D 967, it's 2014, and you look at Page 977, again, that's a well-settled case law. And there's nothing here about -- they did not discover a new property. All they're discovering is that -- their alleged discovery is a matter of degree as far as whether it's better than the prior art.

So let's look at the other figure that they've put up and that was on Patent Owner's Slide 11. And the Patent Owner has -- their Figure 3 is an illustration -- and I don't think we'll be able to pull it up. You can't pull yours up? Yeah, Slide 11. While he's pulling it up, Figure 3 is illustrating that they had a demonstrating activity of the 1:57 SNALP, and that's Example 4 and the compared to the data demonstrating the activity of the 2:30 SNALP.

So first problem, 2:30 is not the closest prior art. The closest prior art is 2:40. So we're comparing to oranges here.

The other aspect is that 2:30 is non-cationic lipid is DSPC, and the 1:57 non-cationic lipid is DPPC. So, again, you're not really comparing apples and oranges with that either because you have different composite.

And the other point is this is just one more data

point, but at best, it's one data point.

And then if I could talk about the post-filing data, that's in Exhibits 2017 through 2019, 2021, and then 2047 through 2050. And the problem here is this is -- these are showing -- that's to see how effective the drug is, you know, for the claim formulation, but it's not a comparison to the prior art.

And, again, I don't know if you can pull up Exhibit 2046? This Exhibit 2046 is a summary of all the post-filing data. And, Your Honors, when you look through that, most of the data involves the formulation of 50 mole percent for cationic lipid. There's no test data for the cationic lipids in the higher range, which is problematic because that's what their alleged invention; is the higher the cationic lipids, the better. So we would expect them to be able to show unexpected results in the higher ranges.

Again, I just want to conclude with this, is that if I could have Slide 67 again? Maybe not.

The claim scope is quite broad. And, again, even if they had showing of unexpected results, which I don't believe they do, and, certainly, it's not surprising at the higher level that the Federal Circuit is requiring, but even if you didn't look to that, what's the answer for why they don't have unexpected results for the entire scope of the claim for being able to carry out for all the nucleic acid lipids?

And if you look to Column 10, Lines 26 onward,

there's a huge list of what they define as nucleic acid lipids -- I mean, sorry, nucleic acids. And so that's the payload. So they haven't shown for that type of scope. So they might have a point, maybe if they had limited the claims to siRNA, but they did not. They chose to be very broad.

And, again, so their unexpected result arguments all failed simply because they're covering -- it's not commensurate in scope with all the payloads that they're talking about.

Okay. I want to talk a little bit about toxicity. And just for a minute, I want to point out that the question is, What is the scope of the claim? The scope of the claim does not require an in vivo. The scope of the claim is broader than that. So when you're talking about toxicity, all their arguments have to go for in vivo. So the question is, would this be so toxic that you wouldn't be able to put it in a Petri dish to see if it could deliver it to a cell? That's not -- they have no showing of that as unexpected. In fact, their own -- again, the '554, the LO54, again, is being used and created.

Now, I'm not arguing it's for in vivo, but it's solely good enough to be able to be put into a Petri dish.

So toxicity is kind of a tough term. What -- sure, all of these things have certain amount of toxicity. The real question is, is whether or not it is tolerable for the intended use. And, clearly, for a Petri dish, is certainly

tolerable for its intended use.

They touched briefly on other secondary considerations, kind of trying to bring it into unexpected results, but I want to point out that they were talking about particular drugs that are on the market.

I want to point out though that the Patent Owner has failed to show a nexus to the scope of the claim. And what's interesting about what their information is about is all of that is directed to a particular payload and how effective it is. And there's not anything that shows in the data that those lipid particles is the cat's meow. You know, and certainly, there's not a nexus to this entire scope of the claim.

So if there's not any -- is there a question?

If there's not any other questions, I'd like to turn it over to my colleague, Morgan Chu.

MR. CHU: Let me start first with an answer to Judge Snedden's question.

If you go to the '435 Patent, Column 12, beginning at Line 65, it reads, quote, A number of cationic lipids and related analogs which are also useful in the present invention have been described in, and then there a number of references, including the '554 Patent, continuing with, quote, The disclosures of which are hearing incorporated by reference in their entirety for all purposes.

So, now, let's go to the '554 Patent. And the '554

Patent at Paragraph 0268 goes on with quite some detail, technical detail, for about a column, but I'll just read the last sentence of that paragraph. Quote, As such, chemically modified nucleotides present in the single stranded siRNA molecules of the invention are preferably resistant to nuclease degradation, while at the same time maintaining the capacity to mediate RNAi.

Going to some other issues that were raised, one by opposing counsel. I think it was their Slide 11. And he said, Well, there were a lot of other experiments. And he was making that argument to try and argue unexpected results. But the law is quite clear according to the Federal Circuit *In re Baxter-Travenol Laboratories*, that, quote, Results must be shown to be unexpected compared with the closest prior art. The full citation of the *Baxter-Travenol* case is on Page 9 of the Petitioner's sur-reply to the motion to amend. And it goes on to describe where some other formulations that the Patent Owner wants to hold onto are not being compared to the closest prior art.

There was another question raised by Your Honors, actually, I think it was Judge Snedden again, in reference to criticality. And I think one of the leading cases on that is the Federal Circuit decision in *ClearValue*.

In that case, there was a claimed range. I think it had to do with the amount of alkalinity being 50 parts per million or less, and then there was prior art that overlapped

with that. And the Federal Circuit held that the Patent Owner did not show that there was criticality, and D, there was no allegation of criticality. And that is exactly the situation we have here. No place in the '435 Patent is pointed to by the Patent Owner to show criticality, even with a paid expert, Dr. Thompson. He doesn't say one wit in his declaration or otherwise about criticality.

In terms to the closest prior art, we've already discussed the three data points. And we said, Well, maybe one data point may or may not be slightly better. And I said -- Dr. Jannof said, he thinks it's likely that it's not statistically significant; that one data point cannot be commensurate with the range, the entire range of the narrowed range in Claim 21. And in fact, the other two data points demonstrate that because the other two data points are points that are worse than, or perhaps one of them either worse than or no better than the prior art.

So it cannot be that surprising and unexpected results can be shown or pointed to by the Patent Owner when two of the data points rebut the claim of surprising and unexpected results. And this is the Patent Owner's own data.

Now, I want to go back -- let me start with Slide 98. There was some discussion about various terms. We see it's nucleic acid. It's not one of the other alternative terms. We've already discussed the fact SNALP could have been there. We discussed the fact that the body of the claim could

have said something else. It could have had the word encapsulated.

So let's go to the Section 112 problem that they have, and this depicts in Slide 100. siRNA is 20 to 23 bases. mRNA, there is, in the record, testimony about it being at least several hundred bases, and elsewhere, a thousand or more. Increased size, it's a lot of complexity.

And here's a big picture bases. It's not just a question of size. Let's keep in mind what RNAi interfering or siRNA small interfering RNA is trying to do. It's trying to act like a red light. It's trying to stop or silence gene expression.

What is mRNA trying to do? It's trying to act like a green light. It's trying to enhance gene expression. The functions not only are different, but they're completely opposite. So you've got big differences in complexity by size and otherwise. You've got two completely different functions.

And we see in Slide 104, the payload can impact the performance. Slide 105, that mRNA is typically larger than siRNA and they are expected to affect the physical properties of a particle. Both 104, 105, and now Slide 106, are testimony by the Patent Owner's expert, Dr. Thompson. And 106, he's addressing the question whether one could start with siRNA variables and then use that to optimize for a new mRNA cargo. And he answers by saying, quote, That's speculation. I couldn't -- I can't go there.

So let's go then to enabling. So I think written descriptions requirements are not met, and enablement law on Slide 113 is not just an invitation to go and conduct a bunch of experiments, but Dr. Thompson, again, the Patent Owner's expert in Slide 118, admits that more testing is required.

So too in Slide 119. The Patent Owner's expert is admitting, you don't know what you're going to get inside.

In sum, these items on Slide 120 were the ways in which the Patent Owner tried to argue the validity of the new proposed Claim 21. He pointed to serum-stable as requiring in vivo or systemic use. We've discussed that. It's quite to the contrary. Other definitions could have been used that are in the patent, as well as the words systemic or in vivo, if that's what was intended.

They tried to use the wherein clause and that didn't add anything. It didn't separate it from the prior art. The prior art was showed on an earlier slide in each of the three primary references; discussed nuclease, degradation, resistance.

Then they tried to say, here, we have some different ranges, but the new ranges still overlap with the prior art. There's still anticipation under '554. And if we had to drop in to an obviousness argument with respect to the other references, it's still the case; that the Patent Owner has not shown surprising and unexpected results. If anything, from two out of the three data points, the Patent Owner

demonstrated the exact opposite.

Thank you very much, Your Honors.

MR. ROSATO: We can start while she's taking a minute. And I appreciate the extra time I was allocated. I'll try to not use time, if necessary.

Your Honor, I want to first address this issue of routine optimization again. And the response was that they were arguing or they did argue routine optimization in the petition. I don't see that and I don't think anyone will see that. It's just not there.

There was one comment about optimizing the cationic lipid; not routine optimizing, but a comment about optimizing just the cationic lipid. There's a mention of that in the specification. That's one component. That's not optimizing a formulation. And even with that one component, there's no -- I mean, it's a one-sentence thing. There's no discussions surrounding it, so we don't know whether they believe that is a -- whether optimizing is routine or something else. I have no idea. You won't find the term routine optimization in the petition materials.

And then beyond that, I have to admit, I'm still a bit confused as to the position on this for a number of reasons. Again, we're asking if on the front end of this, if this is -- if the theory is one of routine optimization, we'd like to know that. If the position is that this is also well known as a matter of routine optimization, then I have

difficulty understanding how that's consistent with arguments about undo experimentation that were just discussed when it comes to using other lipid payloads, as well as the arguments as when they get to the experimental results about how unpredictable and difficult it would have been to have any other data points. So, you know, I think they're trying to have it both ways, and it, you know again, you have to start with an identifiable rationale and this emphasizes the importance of that.

Sticking with the rationale theme, I heard some comments about how you can make formulations for use in a Petri dish. Again, this emphasizes the importance of identifying a motivation to combine or a motivation that's underlying this whole theory. If the argument -- and, again, this is a new argument, so it's hard to respond to that, but if the argument that was being advanced in the petition is that a person would be motivated to make these types of formulations solely for the purposes of using it in a Petri dish or in vivo, that just doesn't reflect reality in the art. These are formulations that are made for therapeutic purposes. They are screened in vitro. We would be very happy to have the discussion about whether there'd be motivation to invest in this technology and make developments strictly for the purposes of in vitro Petri dish.

JUDGE SNEDDEN: There's one argument that the Petitioner is advancing, is that your evidence of unexpected

result when compared to a closest prior art is not unexpected. Could you address that?

MR. ROSATO: I do want to address that.

JUDGE SNEDDEN: Okay.

MR. ROSATO: Let's -- and two points on that.

Go to Slide 11, please.

When I first addressed this argument about differences being a matter of degree and not differences in kind, that is not true. And we point out that these are differences in kind, not merely degree, and that's, you know, one of the reasons why we're talking in vivo potency, right? And they were criticized for focusing on vivo, but that is a difference in kind, right, is they surprisingly efficacious result in vivo, combined with low toxicity.

So it's not just one thing, you've got two things that are doing in the complete opposite direction of what would have been expected at the time.

This figure here, which I think is Figure 3, if I'm getting that correctly, from -- not confusing the example versus the figure, but what's shown here and why this is the fairly pertinent, and it goes to a couple points, one of which is this issue, the closest prior art, it's hard to know what that is. I mean, I don't know what they believe to be the closest prior art. They've latched onto this 2:40 formulation as the closest, I guess, for numerical purposes. The comparison was to 2:30 because that was actually one of Patent

Owner's formulations that was believed their -- that was their -- identified as their lead compound.

But the comparison here is quite compelling or the results here is quite compelling because what you see is a -- what's reported as a huge increase in the silencing ability of the -- this is the '157 or the formulation in the scope of the claim. You're seeing a dramatic increase in the potency, and you're seeing that dramatic increase despite a ten-fold lower dose, right?

So it's not just that it was -- you saw difference in degree of in vivo silencing, you saw a huge difference at a ten-fold lower dose, and virtually no toxicity.

So it's the combination of all that. And this is an illustration. The potency and low toxicity is across the entire range of tested formulations. The -- if you're comparing -- if you're looking at toxicity and you're comparing that to 2:30 and seeing much less -- virtually no toxicity compared to lower cationic lipid component when you're expecting higher toxicity, that's a perfectly appropriate comparison.

If their -- with regard to the 2:40, and, again, they're just calling this prior art because they -- you know, it's a convenient argument to be honest, but if there is a comparison of that, it is compared.

They did test 2:40, and this underscores a point where we're talking about unexpected results. And there seems

to be this assumption that you only get -- what they're talking about are superior results, right? The test is unexpected results. Their point of criticism is, Well, it wasn't superior, therefore, it wasn't expected. But we have to ask what was expected and this is why I raised this point earlier. You have to understand what was expected at the time, and the expectation is you're going to see a decrease in potency and an increase in toxicity, and the opposite was observed. Those are unexpected. And they're differences in kind, not degree for the various reasons we talked about.

I want to point briefly, if I can, to Slide 13. This reference was submitted -- sorry, in -- partially in response to this criticism of the closest, all right? So this is Figure 2, I believe, from the Akinc reference, that's Exhibit 2047.

But if we want close comparison, you can't get any closer than this -- the comparison that was recorded here. A whole panel of formulations were tested. Only three of those formulations tested were within the scope of the claim, and the rest -- those three are shown in the red box. The rest not in the red box are outside the scope, but they're only outside the scope of the claim by virtue of the conjugated lipid component. It's only barely outside the scope of the claim.

So here's a whole bunch of formulations outside the scope that are extremely close to those end, and the three

formulations within the scope were superior to what was -- the other formulations tested.

So there are all types of different formulations tested. They're all types of different comparisons that were done. This is one we saw one in the '435 Patent against the 2:30 formulation, which was, again, the lead product at the time. If for performances were drastically better, and then the results of testing of the 240 reported, and the expectation is -- and, again, we're asking what's expected, not what's superior -- or what was unexpected, not what was superior. So there's a difference there. I want to make sure we observed.

And that I'll just --

JUDGE MITCHELL: Yeah, if you could wrap it up.

MR. ROSATO: Yeah, let me just -- final point, which is this nexus issue.

Really, I mean, at times, I feel like we're talking over each other, but I would turn to Slide 27, please, quickly. Again, there is this argument that the drug is -- the success of the drug is due all to the nucleic acid. And I would just point to the nature article on the next slide. That specifically -- this is again, the nature article that goes on and on about the delivery solving the problem and allowing the success of this very commercial product. So it's hard to see how this is singing the praises of the drug rather than the delivery.

Thank you.

JUDGE MITCHELL: Thank you both.

So the case IPR2018-00739 is submitted, and we'll take a ten-minute break, and then reconvene here for the next case, about -- at 25 til if we could reconvene for the second case. Thank you.

(Break was taken.)

JUDGE MITCHELL: You may be seated. So now we are going to have argument in IPR2018-00680.

And, Petitioner, would you like to reserve any time?

MR. WELLS: Yes, Your Honor. I'd like to reserve half of my time, please.

JUDGE MITCHELL: Okay.

MR. WELLS: If we could go to Slide 121, please?

So now I'm going to talk about the '127 Patent. And a lot of the terms and a lot of the substance of what we're going to discuss is going to overlap with what we've already heard regarding the '435 Patent, but it's important to realize that the '127 Patent is a separate patent family from the '435 Patent family. And so the '069 Patent, which is referenced in the briefing, what we're going to talk about here today, is in the same family as the parent of the '435 Patent. It's unrelated to the '127 Patent and this prior art.

JUDGE MITCHELL: Sorry, let me interrupt you --

MR. WELLS: Yes.

JUDGE MITCHELL: To make sure Judge Smith is on.

I'm sorry. I just don't see him on, and I'm wondering --

JUDGE SMITH: Yes, I'm on.

JUDGE MITCHELL: Okay, sorry.

JUDGE SMITH: I'm here.

JUDGE MITCHELL: Thank you. Go ahead. Sorry to interrupt.

MR. WELLS: Okay.

If we can go to Slide 122. So, here, we have the '127 Patent. Again, Protiva and Arbutus are the owners, but again, unrelated.

If you go to Slide 123, please. And this is the independent claim to the '127 Patent, and it's directed to a particle population, and -- but we have the same basic components that we've been discussing with regard to the '435. We have nucleic acid payload, we have the three lipid components throughout the outline that's any cationic lipid in any percentage, any non-cationic lipid in any percentage, and a conjugated lipid in any percentage.

Now, if you go to Slide 124, please. This is the '069 Patent, which is one of the primary references relied upon in the petition for invalidity. It's the parent to the '435 Patent. It has the same substance disclosures regarding -- as the '435 Patent.

Go to the next, Slide 125. And this discloses the same particles. Again, we have a nucleic acid, a cationic lipid, a non-cationic lipid, and a conjugated lipid in certain

percentages in the '069 Patent, but they're the same basic particles.

So go to the next slide. So what did the '127 Patent add? Well, they argued that they added this additional limitation regarding 95 percent of the particles in the given population having a non-lamellar morphology. And so what did they do to get that?

And if we go to the next slide, they looked at the prior art particles that they had previously disclosed in the '069 Patent and in the '435 Patent in that patent family, and they took a picture of them. And then they looked at that picture of the prior TEM image and then said, Okay, well these are dark, and that looks like a dense center, so we're going to associate that with non-lamellar. And then we're going to count them.

And if you can go to the next slide, Slide 128. And so they counted the particles that had this dark center, this non-lamellar morphology, and you can see the particles that were tested were the 2:30 now, the 2:40 now, the 1:57, and the 1:62 now. And you'll recall hearing about those formulations earlier today regarding the '435 Patent.

Now, if you go to Slide 131, this non-lamellar morphology, it's admitted this is a physical characteristic of the particles. That's not in dispute.

And if you can go to the next slide, it's also --

the '127 Patent itself says that by controlling the SNALP formulation and the formation process of the particles, you get this non-lamellar morphology. It's inherent for a given formulation and a given formation process.

If we can go to the next slide, Slide 133. We have their expert. Dr. Thompson admitted that if you have the same formulation and you have the same formation process, you should get the same three-dimensional structure. It's -- you can -- reproducible. It's an inherent property associated with those particles.

If we can go to Slide 134. But the law is clear. Claiming an inherent property of a prior art composition, even if they didn't know it was non-lamellar at the time, it's insufficient as a manner of law to confer patentability.

If we can go to Slide 135. Now, this is their expert, Dr. Thompson, being questioned at deposition about the '435 Patent particles, but you'll recall that's a child of the '069 Patent and has the same specifications. The detail is exactly the same experiments. And he was asked, Would you expect those particles to have this 95 percent non-lamellar structure? And this is their expert saying, Yeah, based upon these experiments, that's their state. That's what I think was happening on the '435 Patent, which, again, is in the same patent family as the '069.

If we can go to Slide 138. So what was tested in the '127 Patent and what formulations? Well, we had certain

lipid components, we had the conjugated lipid, the peg, we have the cationic lipid, DLinDMA or FOSFA (ph) lipid, DSPC and cholesterol; those together make up the non-cationic lipid. And then we have our concentrations and our mole percentages.

If we can go to Slide 139, please. In the '069 Patent, we have the same tested formulations, the same2:30, the same2:40, the1:57, the1:62. This is all laid out in Tables 3 through 6 in the '069 Patent. These were all tested. And the lipid components, exactly the same lipid components. The only variability is that for two of the formulations, the 2:40 and the1:57, DPPC was used instead of DSPC.

But if you can go to the next slide, 140, there, expert admits that that type of small change wouldn't be expected to have any impact on the result in three-dimensional structure.

So we have the same formulations. Now, we have to go to the four formation process and what's disclosed regarding the formation processes.

So if we can go to Slide 141, please. What does the '127 Patent say about the formation processes? Well, it says that you can use any method known in the art to produce these particles and get particles with this non-lamellar morphology. Does that mean that every method known in the art results in these? No. What it means is that a person of skill in the art would know how to use the prior art known methods of

production to achieve this non-lamellar morphology. That's what the '127 Patent says about this. And it goes further. It gives us some examples.

So if we can go to Slide 142, please. It gives two examples. It points to a step-wise dilution method, and it references US Patent publication 2004-0142025, which I believe is Exhibit 1018, and a direct dilution method, and it references there, Patent publication 2007-0042031. And it says -- these are two examples of publications that detail known methods of producing these particles that you can use to get this non-lamellar structure.

If we can go to Slide 143. The '069 Patent references exactly the same publications. Here's two example publications in the '069 Patent that also detail how you can get the particles disclosed in the '069 Patent. And, again, the '025, talking about the step-wise dilution method and the '031 talking about the direct dilution method.

If you go to Slide 144. Now -- actually, go to Slide 145, please. The '127 Patent does discuss formation process parameters, and it provides the formation process parameters used to produce the non-lamellar particles that it says result from the testing in the '127 Patent. And those are produced in Table 1, that's in Column 104, and you can see the DDM there, stands for direct dilution method. And we have six variables, one of them, arguably, the batch size probably has no impact, but several variables.

If you go to Slide 146. But the law is clear. The claims don't have anything about the formation process that has to be used. The claims --

JUDGE SMITH: Counsel, can we go -- just for a second.

MR. WELLS: Yes.

JUDGE SMITH: To your Slide 145, Table 1.

MR. WELLS: Yes.

JUDGE SMITH: Now, under this, the DDM column, is it correct that these were the particular parameters used in the '127 to do some testing or is it your position or to your knowledge -- or your position that to practice the DDM method, you got to use exactly these parameters?

MR. WELLS: Thank you for the question.

So this was -- were the parameters that were used in the testing for the '127 Patent for the direct dilution method. The '127 Patent does not discuss these parameters as having any impact on the non-lamellar morphology, does not state anywhere that these have anything to do with the non-lamellar structure resulting. But Patent Owner pointed to these parameters in the course of the briefing and said, Hey, these parameters are important. That's how we got the non-lamellar structure. And our response there -- well, our first response is obviously, Where does it say that in the '127 Patent? And the answer is, it doesn't. But the law also addresses this fact. The law is very clear.

If we go to Slide 146, the law says, When there's not a limitation in the claims, you can't rely on that limitation to try to defeat inherency. Patent Owner is asking you to read into these claims, limitations that say, Oh, using these DDM method with these specific parameters. And the claim simply don't say that. There's no limitation there, and what we have is the specification of the '127 Patent saying that you can use the opposite. Any method known in the art and a person of skill in the art would know how to make these non-lamellar particles.

If we can go to Slide 147. Now, the '069 Patent is silent -- I'm sorry. If we go to Slide 148. So the '069 Patent is silent on the specific parameters used and the testing for the direct dilution method or the stepwise dilution method, but the '069 Patent references the '031 and the '025publications.

And, again, these parameters are not actually in the claims, but even if they were, the test for anticipation isn't whether it was actually reduced to practice and testing. The question is, do the '031 Patent -- Publication -- I'm sorry -- and the '025 Publication disclose to one of skill in the art using those parameters to produce particles? And the answer there is absolutely. They have to. The '127 Patent references these publications as disclosing exactly that.

And if you go to these publications, they talk about the different parameters that you can use. They talk about

the ranges of the mixing speeds, they talk about the equipment that can be used. It's all in there. And it's actually not disputed that it's in there.

If you can go to Slide 149. Their expert says that the '031 Patent defines the larger set of possibilities and the '127 Patent on Table 1 is simply identifying one of those possibilities, one of the embodiments in the '031 Patent that the '127 Patent acknowledges, result in this inherent three-dimensional structure.

In other words, nothing is missing from the disclosure in the '031 to enable one of skill in the art to produce particles using the formation process that's disclosed therein to result in a non-lamellar structure.

So what do we have now? We have one, the same formulations, basically the same lipid components, the same numbers, the same percentages, and then we also now have the same formulation process to result in those particles. And that's what the '127 Patent says, defines whether or not a specific embodiment has this inherent non-lamellar structure.

Now, Patent Owner also puts forth some evidence of a test that they had one of their employees run. If we can go to Slide 152. This is -- their test is legally irrelevant, first of all. It doesn't matter that an embodiments exists out there in the '031 Publication or the '025 Publication. That might not result in the non-lamellar structure. The law only requires one embodiment that has this inherent property.

Second, if we can go to Slide 154. These tests were designed by counsel for the Patent Owner to fail. They were -- he instructed the employee of the Patent Owner to use manual syringes and did not even attempt to recreate the production methods actually used in the '069 Patent.

If you can go to Slide 155. During this testing, the employee actually held two syringes in his hand and counted one 1,000, two 1,000 to approximate a steady flow rate.

If you can go to Slide 156. And he admits that this is going to add fluctuations to the test results. If you don't have good mixing, you're not going to have a full homogeneous particle population. This testing was -- again, he was instructed to do so. The testing was designed to fail.

If you go to Slide 157. If you looked at the results associated with this testing, these were bad particles. These are badly run tests. The particles had high background that made it difficult to judge the structural features. The particles were far larger than the size called for in the '069 Patent, and large amounts of the particles couldn't be evaluated one way or the other, fully, 22.7 percent for one of the samples. It's hard to address 95 percent non-lamellarity in a particle population when 22 percent of the particles, you can't figure out one way or the other what they are.

In addition, even if the claim non-lamellar

structure was determined not to be an inherent property of the disclosed particles in the '069 Patent, it's obvious. '069 Patent discloses the same formulations. There's no dispute there. The '069 Patent discloses the same formulation processes that were given as examples, specific examples in the '127 Patent regarding how you can make these particles.

The '069 Patent actually identifies having a non-lamellar structure as one of the goals. If you go to Slide 161, please. This is a quote from the '069 Patent, Wherein the therapeutic agent is fully encapsulated within the lipid portion.

What does that mean, within the lipid portion? It doesn't mean simply within a biliary in a liposomal structure. It means it's actually encapsulated in the lipid portion of the particle. Now, that's a three-dimensional structure that results when you had a non-lamellar structure. You either have an inverse hexagonal structure or a cubic structure, according to the '127 Patent.

JUDGE MITHCELL: Can I ask you? Do you have expert testimony that says that the prior art formulations would necessarily result in the non-lamellar particles?

MR. WELLS: We have testimony from both experts that the prior art formulations using the formulation processes disclosed in the '031 Patent will result in the non-lamellar structures. Both experts agree on that. The dispute is whether all of the formulation processes, formation processes

in the '031 Patent must result in the non-lamellar structure. And that's a legal issue that the Federal Circuit has clearly said. It's not required. You need one embodiment. And nobody disputes that that embodiment is disclosed in the '031 Patent. The '127 Patent says it.

JUDGE MITCHELL: Okay.

MR. WELLS: I have no more at this point, Your Honor.

JUDGE MITCHELL: Would you like to reserve five minutes?

MR. ROSATO: Yes, thank you.

JUDGE MITCHELL: Sure.

MR. ROSATO: So we're looking first at Slide 3 here. And this is just the listing of the grounds that were presented in the petition, and I just want to -- worth the clarification that very little remains of the challenge, in the sense that most of the grounds, 2, 3, and 4 have already been deemed insufficient to meet the institution standard, although, of course, the entire petition was instituted, as it should be. The deficiencies of Ground 2 through4, of course, also are incurable, and they have, in fact, not been cured.

So we'll be talking about Ground 1, and Ground 1 really focuses around this limitation of the claim, I'll refer to as the morphology limitation or the at least 95 percent non-lamellar limitation.

Let's turn to Slide 4. And in going through that, I

know that these are very well-known legal principles listed on Slide 4, but they bear repeating in the context of this case. The first is with regard to inherency, the main argument with regard to Ground 1.

It is very well-established that, as we all know, that inherency may not be established by mere probabilities and possibilities. That's not enough for an inherency case, and it's a very high bar. It's not one that is the burden of the Patent Owner to demonstrate.

Patent Owner does not bear the burden of proving no inherency. Proving inherency is the burden of the moving party.

The second principle listed here is the idea that picking and choosing amongst different disclosures and different embodiments is not sufficient to support an anticipation case of any kind, and that includes an inherent anticipation case. This latter principle -- and distinguishing both of them is pretty important here because what seems to be going on in a number of instances is an invitation to pick various different aspects from various different embodiments, and put those together, and then claim that the result would be one of inherent anticipation, but that is not an approach that can substantiate an inherency case. You can't start by going from one place in the specification and looking at it in an embodiment for a formulation, looking at -- picking ingredients or lipid

constituents for that formulation, going somewhere else, looking at different options for formulation methods, picking a method, going within that method, picking various different parameters. That's picking and choosing, and that's what we see going on here quite a bit.

So let's look at the argument that was actually advanced in the petition with regard to inherency. And let's turn to Slide 5.

So the inherency theory is, as one seem to exist, was actually fairly clear. I think it was reiterated here, to the extent that there was reference to the same exact same formulations, lipids, and methods being used. But looking at what was advanced in the petition materials, Petitioner pointed to some very specific lipid formulations in the '069, those listed in Tables 3 through 6, and the petition asserts that the exact same method was used to make those particles as compared to -- identified particles in the '127 Patent, right? So there's specific identification here of particles or embodiments of Tables 3 through 6, and the assertion that everything is the same in terms of composition of those, and everything is the same in terms of the method that was utilized.

There are a number -- oh, and then of course, it draws the conclusion. Because that all was the same, while '069 didn't test morphology or doesn't say anything about morphology, due to the identity between all of these aspects,

the morphology result must -- has no choice but to be exactly the same as well.

So that was the theory that was advanced, and there are a number of problems with that, starting with the fact that the entire case rests on a faulty and unsubstantiated premise, that is, Petitioner fails to establish that everything is in fact exactly the same as they charge. And this is particularly apparent with regard to the formulation method used for the embodiments listed in Tables 3 through 6 of the '069 Patent that are specifically being identified or relied upon.

The '069 Patent provides multiple different formulation methods, and Petitioner never establishes which of those methods was used for the embodiments that are listed in Tables 3 through 6. There is no evidence to support that point, that the exact same formulation method was used. We have no idea what method was used according to the Petitioner, and are different embodiments and a -- simply have not been identified or established which was used.

That alone is sufficient to defeat Petitioner's inherency case. Again, you've got a case that is premised on very specific factual assertions. We've just identified one of them that is completely unsubstantiated and lacks any support in the record. That is an unsubstantiated and faulty premise to the argument. The argument fails at least for that reason.

Let's turn to Slide 6. There's an additional reasons why the inherency theory fails, and that is based on Petitioner's assertion that the formulation method used, and insofar as they go in making assertions, their assertion only goes so far as to assert that the method used was the direct dilution method. They don't say what direct dilution method or anything about the direct dilution method. They just assert that the direct dilution method was used.

We asked Dr. Janoff about this during cross-examination, and he actually recoiled that the notion of using the term, the direct dilution method, explaining that there is no such thing as the direct dilution method. Direct dilution is a class of methodologies. So if he's going to be asked what method we're talking about, you know, it would have to be specified. We were very clear on this. I specifically asked him, if someone walked into his office and said they used the direct dilution method, he indicate he'd have no idea what they're talking about because you would have to specify precisely what direct dilution method you're talking about.

So we're talking about a class of methodologies, and that's really what they're pointing to in the petition, that they say the same method. They haven't substantiated that a direct dilution method was used, but even the assertion of the direct dilution method is referring to a class of methods.

And then just to go along with Dr. Janoff's testimony during cross, they've identified this '031

Publication as being the direct dilution method. If we look at that publication, it's pretty clear that it's not describing one single solitary method. You can see that from Figures 3A and 3B, which are outlined in different apparatuses. And then if you go through the disclosure, what we're seeing are various different parameters being identified and various different options all along the way.

So Dr. Janoff is correct. There is no direct dilution method. We're talking about a class of methods, and the reference we're looking at substantiates that.

By the way, there's not a single citation. I want to be careful with how far we go with '031 because there's not a single citation to anything specific in the petition materials. There's only general reference to the '031 Publication as a broad matter.

JUDGE MITCHELL: If you can hold just a minute. I think we've lost Judge Smith, so I just want to make sure he is reconnected.

MR. ROSATO: Sure. I hope he can't hold that still in real life.

JUDGE MITCHELL: Can you tell if Judge Smith is connected? We lost Judge Smith. Sorry.

Sorry to interrupt you.

MR. ROSATO: No problem.

(Off the record discussion.)

JUDGE SMITH: Hello.

JUDGE MITCHELL: Oh, great. So can you hear and see us?

JUDGE SMITH: I can, yes.

JUDGE MITCHELL: All right. Well, we will resume, Judge Smith.

So when you're ready, Mr. Rosato.

MR. ROSATO: Okay.

JUDGE MITCHELL: Sorry about that.

MR. ROSATO: No problem. Okay.

So I think we were going through the inherency case and trying to take this in a dual burden of proof, one step at a time. And starting with the fact that the issue of the unsubstantiated premise is that everything was the same and focusing first on this method issue.

We pointed out first that the particles that they were -- that they identified, they hadn't established what method or even what class of method they were generated using. Next, looking at their assertion that they were all generated the direct dilution method, we looked at why that isn't good enough, even if accepted as true because we're talking about a class of methods when we say the direct dilution method. But it doesn't specify which direct dilution method and, in particular, which sets of parameters are being contemplated or they think are being used. And there's --

JUDGE SMITH: Counsel, can I stop you there?

So the '127 Patent uses the word, The direct

dilution method, whenever it's referenced. So what is, The direct dilution method?

MR. ROSATO: The direct dilution method is a class of methodologies.

JUDGE SMITH: But why does it say, The? I mean, what's the significance of the word, The?

MR. ROSATO: Well, perhaps, it should say the direct dilution method referring to the class of methodologies. But it's clearly referring to a class of methods as illustrated in the '031 publication, which lists --

JUDGE SMITH: But any of those -- based on your -- the '127 spec, it says any of those then would be acceptable to actually make the particles that you're claiming, the composition that you're claiming.

MR. ROSATO: Well, okay. Let's -- I'm starting with the '069 Patent, not the '127, right? And then it's another issue in -- with the asserted challenge. I mean, we're taking the '127 Patent and trying to use that as a road map to find something. I'm starting with the case that's set forth in the petition materials, and there's specific materials that are identified in the '069 Patent that are allegedly producing inherent -- these particles that are accused of inherently meeting the claimed properties.

So I'm trying to approach the assertion that was made and respond to that. So I -- no, I don't think it'd be appropriate to start -- and the Petitioner does this quite a

bit, but I don't think it's appropriate to then try to backfill the deficiencies in that stated case by reverting back to the '127 Patent and then trying to map things up and see if we can find something here.

Again, this is why -- in part why I started out by saying let's remember that there are two important principles of law that are guiding us here. They're the principles of what constitute a case of inherency and what's required by that. And then there's the principle of law that reminds us all what we know, and that is picking and choosing amongst various different options and different disclosures, embodiments, and so forth is not any type of anticipation case. It's really an assertion of obviousness.

So we're talking about, you know, this assertion again trying to understand what Petitioner means by using the same direct dilution method, and we asked their expert and he said there's no such thing. You have to know more than that, and we looked at the '031 Publication that was cited, and indeed there are a fair amount of details.

Why does this matter? Let's -- can we turn to Slide 7? It matters because knowing what process was used, in particular, some details about that processes, it matters because if you alter aspects of the process of forming particles, what happens is that alters the physical properties of the resulting particles. That is substantiated, supported by testimony from both witnesses. Both witnesses agree that

that's the case.

If you start altering parameters of a formation process, you expect differences in the physical properties of the resulting particles. And that's particularly true, even with using a direct dilution method as -- and Dr. Janoff supported this during cross examination, indicating that if you start changing parameters such as -- he identified three parameters; speed, mixing rate, and temperature, that that is sufficient affect the physical properties of the particles enough or you might not even get the claimed particles.

So we're starting with inherency, and we're asking whether inherency requires more than probabilities and possibilities, which we all know that it does. It's hard to see how this type of evidence and testimony does anything other than demonstrate they failed inherency here.

Okay. Let's turn to Slide 8. So there's no reason -- we have identified several reasons why the inherency theory that's been advanced fails. It also involves a lot of speculation, but there's no reason to speculate as to whether the particles that are being identified would have the same physical properties or not.

We can -- if we're going to do this comparison between the subject matter that's being identified and the respective disclosures, '069 and '127, we can look at that and see that they actually tested and reported physical characterization of those particles to different degrees.

'069 didn't characterize the particle morphology, but it did characterize other physical properties of those particles such as encapsulation, percentage -- sorry, I almost said morphology, I didn't mean that -- size, polydispersity, and various different properties. Similar -- some of those same properties were characterized in '127.

So what's being identified is the exact same particles. We can look at the reported physical characteristics of those, and we see that shown in Tables 5 of '069 next to Table 5 of '127, and what you're seeing by that comparison is a difference in physical properties. So --

JUDGE SMITH: But not necessarily a difference in the morphology.

MR. ROSATO: Morphology is not listed in there, but just to be clear, what we're talking about, no. '069 doesn't characterize morphology. But if we're going to be making assumptions about the physical property of morphology, it's a reasonable assumption that particles having different physical properties, as shown by the data, may not necessarily have the same common morphology, with morphology being also -- another different physical property. So --

JUDGE SMITH: Isn't the -- counsel, isn't the issue not the particles but the disclosure?

MR. ROSATO: I'm not sure what you mean by that, Your Honor. I would say that given the stated case of inherency that's presented in the petition, that there are

specific particles identified, and the assertion is those specific embodiments were made by a very specific process, and, therefore, the logic that's being advanced is you must assume the same outcome. I would say it does matter which particles we're talking about.

Okay. Let's turn to Slide 9. So, I mean again, we're -- non-moving party, we're doing our best to respond to the argument that's made. If they thought there was something other, some other embodiment that they're pointing to, then you know we would be happy to address that. But they're pointing to very specific things; we're addressing those.

Now, if they really wanted to argue is that there would've been some reason why someone would want non-Lamellar particles at a high degree, they could have -- and that somebody would then be motivated to go pick all these different options, pick a particular class of formulations, pick different lipid constituents, pick a method, pick various different parameters, that there'd be sufficient guidance to do that, and there'd be reasonable expectation of success, they could have put that all together in an obviousness challenge, and we would have addressed that. But they didn't do that.

So we can't back into -- present an inherency theory, and then sort of back into what we might really want to address as Petitioner, you know, some sort of shorthanded obviousness theory, and then sort of cut corners and call it

all good.

Inherency theory is on the table, we'll address the inherency theory, and we can move to what was presented in terms of obviousness when we get there.

But continuing along to address the inherency theory. So we're looking at Slide 9 here, and I want to talk about the experimental testing that was performed by Dr. Heyes. There was a comment earlier that the -- that stated that testing was specifically designed by counsel. That's correct, it was designed by counsel.

But what opposing counsel, perhaps, fails to appreciate is that Petitioner's counsel was the one that designed this experiment. They designed it by virtue of what they were providing in terms of their -- what was being asserted as being providing the inherency. And they cited specifically to Column 73, Lines 13 to 39 in their petition, and this was the instance where they had a particular formulation that they were identifying with some content about what type of process was used to prepare it. And Dr. Heyes attempted to reproduce this process by following the formulation guidance, following the syringe press guidance, and then assuming that the accusation of the direct dilution method according to the '031 Publication was true, generating particles using a process according to the '031 Publication. Right?

So all of the detail that can be discerned from what

was presented was followed, and that was precisely what defined the confines of the experiment performed. So if the Petitioner has any complaint as to the type of experiment that was run, they can look to the petition materials as a source of that guidance.

Let's turn to Slide 10. And this is just Dr. Heyes' declaration explaining precisely why he chose what he did.

Turn to slide 11.

JUDGE SMITH: Could you respond to -- I believe before I lost contact, the issue of the Heyes test data not being relevant or not necessary.

MR. ROSATO: I completely agree. It's not --

JUDGE SMITH: Something like that. I forget exactly the way they phrased it, but the fact that they -- their essential point, as I understood it, was the fact that Dr. Heyes failed to come up with a non-lamellar morphology --

MR. ROSATO: I see.

JUDGE SMITH: It doesn't really --

MR. ROSATO: Yeah, I see.

JUDGE SMITH: Factor in --

MR. ROSATO: I understand the question, Your Honor. I would say we're in agreement to the extent that the data is irrelevant because we should never get to the data to begin with. This is a Patent Owner putting forth evidence to disprove a stated inherency case.

So we shouldn't need to get there. There is no

substantiated inherency case to begin with. We can dispense of the inherency case simply by virtue of unsupported unsubstantiated premise on which it's based.

So, in that sense, we in fact never need to get to Dr. Heyes' declaration testimony. I think what they were arguing, and this is a point that we will want to address, is this idea that, well, he may have demonstrated an embodiment or a situation where you follow all the guidance in '069, and it doesn't give you the claim particles. I think the point of criticism was, we should have kept going and kept exploring and varying parameters. That there's got to be something out there somewhere that would meet the claimed limitations. I think that's the suggestion, is that --

JUDGE SMITH: But you would -- yes. But you would agree that if there is a composition that the -- that Claim 1, in this case because Claim 1 is broad, there's a composition in the prior art that Claim 1 reads on, regardless of whether anyone appreciated what the morphology would be, that would be anticipatory; not composition.

MR. ROSATO: Yeah, I guess, I would just -- I don't think Claim 1 is that broad. I mean, it has a very specific limitation.

JUDGE SMITH: I understand. I mean, I -- it can't be as it reads on a composition the prior art -- one composition.

MR. ROSATO: So --

JUDGE SMITH: Inherency isn't -- you don't have to prove that every possible combination or composition has that result.

MR. ROSATO: Sure. I think we can agree on a point of law. I mean, I guess where I struggle with this case is what composition are we talking about?

JUDGE SMITH: Well, my understanding --

MR. ROSATO: Petitioner --

JUDGE SMITH: Again, I -- well, go ahead. Go ahead.

MR. ROSATO: No, I'm sorry, Your Honor. I didn't mean to interrupt you.

JUDGE SMITH: Well, my understanding, part of their argument is what you're stating as the '127 Patent. That's where I wanted to talk about that. A person reading the '127 Patent is going to believe what it says that the -- if you want to practice the invention, you go to the '031 Patent and it tells you exactly the process that you would use because it says, It's described in detail. The direct dilution method is described in detail. And that's what I'm trying to ask you; what -- you know, that's what I'm asking. I mean --

MR. ROSATO: I think I understand the question.

Look, I think the reality is this. What we're really talking about -- and again this is sort of what I wanted to distinguish between the two legal principles up front. What we really seem to want to know is if you go through the '069 disclosure, and you make all the right

choices in terms of the general class of formulations you're using, the right choices in terms of lipid compositions, and then you get to a method, and you make the right choices along the way of the different types of parameters that you're going to be using, if you make all those right choices, will you get the claimed particles?

I set this out upfront as a point of -- a distinction between a point -- two different points of law because what I just described is an obviousness challenge, right? It's picking and choosing amongst a host of different choices and options to try to arrive at -- to --

Now, whether you're trying or you do arrive at the claimed subject matter. So, it's really important to bifurcate the inherency charge from what would be an obviousness charge.

So if we're looking at inherency, we have to find some embodiment -- this is where we all agree, it's a one-embodiment thing. But we have to find that embodiment and a reason to believe without -- about -- above mere probabilities and possibilities, that that meets the limitations. So that hasn't been done.

Separately, there's this inclination -- maybe it's just, you know, the human mind of wanting to go, well, there must be something. But, you know, in an obviousness inquiry, you know, again we're trying to put ourselves in the position of not having the '127 Patent in front of us. Right? We're

trying to avoid this improper hindsight construction, and we're trying to start with the '069 Patent and say, Why would I want particles that are highly non-lamellar? Right? Particles that were believed to be highly unstable and nobody even knew you could get from these types of processes. Certainly, nobody knew how you would get them.

So, if you're starting with '069, and you don't have a reason why you would want this. You wouldn't -- you don't have a reason to believe you could get it even if you did want it, and you don't have any guidance on how you would do it, then that's an unsubstantiated obviousness case as well.

JUDGE SMITH: So are you saying that a person who took the same components, person skilled in the art reading the '031 Patent, with the same components that you -- you know, basically overlap the '127 and the '069. You're saying a person skilled in the art would not be able to make a composition that Claim 1 reads on? I mean, anticipation is directed to a person skilled in the art.

MR. ROSATO: I'm not sure I understand the question.

JUDGE SMITH: Well, I'm not sure I know how to say it differently. I mean, the question is again, the '127 Patent says that the direct dilution method as disclosed in the '031 Patent will get you there for the same -- for Claim 1, again, assuming you have the same components, which the '069 discloses the same components.

And my question is, so a person of ordinary skill in

the art looking at the '069 Patent and says, Okay, I'm going to look at the '031, and I'm going to practice what it tells me to practice on. I'm going to come up with a composition. It doesn't matter whether I know, or whether I'm even looking for the non-lamellar morphology.

MR. ROSATO: Well --

JUDGE SMITH: I'm going to make acomposition, and you're saying -- it sounds like you're saying there's no way you can get there.

MR. ROSATO: I'm not saying -- that's not what I'm saying. I'm saying the standard for inherency is not a -- it asks a specific question. It asks the question in reverse. Would you necessarily, and without variation, get there? Not, Do you have a possibility of getting there, do you have a probability of getting there? It's, Have you necessarily arrived there? That's the question --

JUDGE SMITH: Okay, so --

MR. ROSATO: Right? That's the question we're asking. If we want to --

JUDGE SMITH: Okay, let me -- question -- I guess the question I was trying to ask before. Where in the '127 does it tell you what those parameters are? I mean, you can't have it both ways.

MR. ROSATO: I guess I don't see it as both ways. We're conducting a non-hindsight based analysis, so they're two separate questions. Right? I mean, if we're starting

with -- we're starting with 069. We're looking for a sort of a linear path or an embodiment that gets you to a result that you can substantiate as inherent of the properties we're talking about.

JUDGE SMITH: Let me -- let me break it down.

So I -- and I'm just trying to understand here.

MR. ROSATO: Uh-huh.

JUDGE SMITH: There's been a discussion about this Table 1, and I asked Petitioner's counsel about that, and I don't know if your client's position is that this is the secret sauce that you got to use in those particular parameters and the correct dilution method to get the composition. So that somehow, your claim is limited to those particular parameters.

MR. ROSATO: Yeah. That was -- honestly, that's a straw man argument that was presented in the Petitioner's reply materials, that we're trying to read in some specific table to our claim, and then attack that as not making sense. We didn't make that argument; I mean, we're not arguing that a table be read into our claims.

What we did do, just to differentiate our actual argument versus the one that was attacked, the argument's we've made are consistent with what I'm presenting here. This is the inherency case as we understand it; this is what they're pointing to. This is what they're asserting. Is this premise factually supported? No. Are these particles they're

pointing to, and saying, These inherently possess this property, is there evidence to that? No. We ran testing on some of them to reproduce it, to demonstrate. They don't have the properties.

So the arguments that were presented are directly responsive to what was addressed in the petition materials. I have no idea what they're talking about in terms of tables being read into the claim, because that's not an argument we advanced.

If you're asking me, does the -- a different question of, Does the '127 Patent provide sufficient guidance to make these, and is Table 1 and the corresponding parameters an example of that? I would say it is because it's describing an experiment that has corresponding data that specifically demonstrates that it produced 95 percent non-lamellar particles.

So, yes, it's an experiment that was run and demonstrated to produce the resulting particles. So, yes, that -- of course, I believe that data.

JUDGE SNEDDEN: Can I -- let me just see if I can understand the argument.

MR. ROSATO: Uh-huh.

JUDGE SNEDDEN: So prior -- if we look in the prior art document, you can find a nucleic acid, cationic lipid, and non-cationic lipid, you can find each of the elements in the claim. But what you're saying is there's not one

(indiscernible) presented in that prior art reference, the '069 I believe, that necessarily produces this morphology that's recited in the claim.

Is that the argument, Judge Smith?

MR. ROSATO: I mean --

JUDGE SNEDDEN: Maybe that's too simplified, but --

MR. ROSATO: No, it's not too simplified. Again, like -- sorry. I -- maybe I take too seriously the non-moving party role so look at the very specific things that were identified as being the embodiments, and I'm trying to address whether there's a reason you believe with certainty that they have this. And I don't think that there is. I don't think that, you know, there's a logically cohesive argument in terms of supported premises and so forth, ones that would support the conclusion drawn, in what they've provided.

Now, if you want to ask me --

JUDGE SNEDDEN: That conclusion is, Is there no embodiment in the '069 Patent that necessarily has this non-lamellar morphology.

MR. ROSATO: I'm sorry. I didn't hear the first part, Your Honor.

JUDGE SNEDDEN: That the conclusion is that there's -- no one has identified an embodiment in the '069 Patent that necessarily has this morphology, that displays this -- a composition that displays this morphology.

MR. ROSATO: I think that's true, that they have not

identified an embodiment.

JUDGE SNEDDEN: Right. So without that, how do we -- we're left with picking and choosing amongst the -- everything that has been disclosed. Nucleic acids are disclosed, but which combination will get you to the morphology? That's the question. So --

MR. ROSATO: That's the question.

JUDGE SNEDDEN: Right? So maybe certain combinations will lead to the morphology, certain other ones won't. But that's where we are in terms of probabilities, and there's nothing that necessitates this morphology.

MR. ROSATO: I would agree with that, and I think --

JUDGE SNEDDEN: I'm just trying to rephrase your argument, make sure I understand it.

MR. ROSATO: Yeah, and I think that's what stated in -- if we want to again go back to the '127, and I really -- my nature makes me resist doing that and not -- in addressing a patentability challenge because of the hindsight guard. But if we look at what's described there, and I think there's a slide I'll put this up on the screen, there's some ham-handed description to be honest in how things are written in the specification.

But one of the things that's stated is, the discovery is by controlling these components and controlling the process parameters, we were able to achieve this stuff. And I think that actually does capture some of the essence of

what we're talking about here. That's a matter of make -- you know, making the right choices and controlling the right parameters, and some choices will get you what you want or get you the 95 percent non-lamellarity, and some will not.

In terms of the challenge, we do have this vague assertion that there -- from Petitioner that there must have been some embodiment. I don't know how to respond to that because I don't know what they're -- what embodiment they're talking about, other than the ones that are identified in the petition materials.

JUDGE MITCHELL: But does the '127 tell you which particular formulations are going to get or which particular dilution processes can get you to the claimed invention?

MR. ROSATO: It gives some guidance. I mean, it doesn't lay out a, you know, a matrix to, you know, say, Under these conditions you will get, under these conditions you won't. I mean, it lays out, you know, the categories of methodologies you can work with. And I think what Judge Smith was asking was, Are there experiments that demonstrate how you get this? Yes. You know, and list some parameters that will get you that. But is -- it doesn't have some specific, you know, sort of matrix on how to -- anything like that. But I mean, there's --

JUDGE SMITH: Is there -- as a follow up to that, is there anything in the '127 in terms of the process that you couldn't find or there is not disclosed in the '031?

MR. ROSATO: Yeah, there is some things. I mean, just as an example, they list on Table 1 -- and, again, this is not reading in Table 1 to a claim or anything like that, but because it was up on the screen, and it's fresh in my mind there's a listing of a robotic lipobot press that is something that is not a mixing apparatus that's listed. I know that's true. I think there was some -- maybe some other things that I don't recall at this moment, but -- I mean, that's at least -- you said, Is there anything? And that's one I can think of.

So we were talking about experiment -- Dr. Heyes' experiment and why this was, you know, an attempt to actually follow the direction that was given. There was criticism about using handheld syringe presses. We actually asked Dr. Janoff about this during cross-examination, and he specifically commented on that. But I think we can -- I don't need to run through the results of the experimentation. We all know -- we all know that they demonstrated that it -- the particles didn't meet the morphology. The Petitioner doesn't like the experimentation, but it is evidence of record in the Board and evaluate how much weight to attribute to that.

Let's turn to slide 15. We addressed this in the briefing, and there's a motion to strike on this point too. But there's this issue of whether the '069 Patent can be used for an obviousness challenge. To begin with, and the answer is no, the '069 Patent was issued in November of 2011. That's

after the June, 2010 filing date of the '127 patent. And because '069 is a commonly owned one and to be referenced, it's disqualified under 103(c).

Beyond that, we don't think there's really any obviousness inquiry to be had, beyond that point. If the Board is inclined to review any of the obviousness challenges, it will find -- to be brief, it will find those challenges are conclusory in nature and lacking really any coherent explanation.

And I'll just refer direct -- generally to the obviousness argument that's at page -- and it's in the petition, Page 32 through 33. This is shown on Slide 17. But this is what we're talking about in terms of the types of obviousness challenges that are -- that are met.

There's no -- you know, this is a couple sentences that mention that non-lamellar particles are mentioned elsewhere, and it jumps to the conclusion of obviousness. There are no -- none of the critical aspects of an obviousness inquiry that would be necessary here, and I don't need to enumerate what those are, but they're missing. And I won't waste the amount of time.

JUDGE MITCHELL: Thank you.

MR. CHU: Your Honor, may I be excused because of where I need to get to by the end of the evening for the rest of the hearing?

JUDGE MITCHELL: Sure.

MR. CHU: And you're in good hands with Mr. Wells and Mr. Fleming.

JUDGE MITCHELL: Sure. Thank you.

When you're ready.

MR. WELLS: Thank you, Your Honor.

So I'd like to start with going to the reply brief, at Page 5, and I don't need this pulled up.

There's a discussion of the Federal Circuit's holding in the King matter. And the full citation is 616 F.3d at 1274. And the discussions about what's disclosed in the patent that's being challenged on the anticipation basis. And, here, the Patentee argued that the prior art's disclosure of taking a certain drug with food reduced gastric discomfort. And -- but it was too vague as to the conditions under which the food was actually supplied, and the patent being challenged in that case had discussions of what conditions the food needed to be supplied in order for the drug to be effective and avoid the discomfort. And the claims in that case though, in the patent that was being challenged, were silent on how the food needed to be taken.

And the Federal Circuit said, Look, we're going to look at what you're claiming when we're evaluating anticipation by inherency. And if you're relying on stuff that's not in the claim to differentiate yourself from the prior art, we're not going to listen to it. That's not what the claim covers. And in that case it was an actual

discussion in the specification regarding what the specific parameters you needed to take the food with.

Here, we don't even have that. We have the '127 Patent claims that are completely silent, completely, on the formation process that needs to be used. And there's no discussion in the specification of '127 Patent, no experts pointed to anything where there's a discussion as to how the parameters used in the formulation process influence this claimed non-lamellar morphology. The only thing we have is a reference to the '031 reference as an example of the direct dilution method that can be used, and the stepwise dilution method described in the '025 publication. Both of those exact references are referenced in the '069 Patent that's the prior art.

And then we have the general statement in the '127 Patent that any process known in the art could be used by persons skilled in the art, and they would know how to manipulate the variables to get these particles. So the argument that we should ignore the '127 Patent's disclosures and not engage in hindsight analysis? We're not engaged in hindsight analysis. We're allowed to look at the challenged patent to understand how it treats the claimed inherent property.

JUDGE SNEDDEN: I think the problem identified by Mr. Rosato is that you have, in this claim here, recitation broad classes of components, so a nucleic acid, cationic

lipid, and non-cationic lipid. But the claim narrows when -- in the Wherein clause, which is those components need to come together and produce something with particular morphology, and in the '069 Patent, we have similar starting materials. We have similarly disclosed methods of mixing, but how -- but where's the certainty that every time you do this with these broad classes of components will you get this morphology? Not necessarily. We do not necessarily get that.

MR. WELLS: Sure, and I'm going to take --

JUDGE SNEDDEN: Okay.

MR. WELLS: Your question in two parts as I think I understand it.

JUDGE SNEDDEN: All right.

MR. WELLS: And tell me if I miss any part of it here.

JUDGE SNEDDEN: Okay.

MR. WELLS: So first we have to start with, What are we talking about here?

So we have a property, this non-lamellar structure, and we agree that it's a physical property. And we agree that the '127 Patent says that this physical property is the result of a formulation and a formation process. And for a given formulation and for a given formation process, this should be a reproducible property. It should always arise. It's not speculation. It's not uncertainty. If you have the same formulation and same formation process, all the experts agree

that you should have this physical property. So --

JUDGE SNEDDEN: Can I interrupt?

MR. WELLS: Yes.

JUDGE SNEDDEN: I think I -- I hope I know where you're going. So is there an embodiment in the '127 Patent that you can find in the '069 Patent?

MR. WELLS: Yes. Every embodiment in the '127 Patent is disclosed in the '069 Patent.

JUDGE SNEDDEN: Because I think that's what we're looking for. We're looking for an embodiment that is alleged to have the same properties as what's disclosed as an embodiment in the '127 Patent that's stated to have these properties.

MR. WELLS: So let me start -- the answer is two-fold.

JUDGE SNEDDEN: Okay.

MR. WELLS: The first answer is the broad answer, and then the second answer is looking at the specific, reduced, practiced testing the '069 had, which I -- whereas I think you're going, but we need to start with the broad disclosure.

And your first question was, Was there any embodiment in the '127 Patent that's disclosed as having the non-lamellar structure that's also disclosed in the '069 Patent? And if there's every single one? Why? Because the '069, you don't have to reduce to practice to anticipate

inherency. It's what would be disclosed to a person of skill in the art regarding the formulation and formation process.

And that person doesn't need to know whether it was going to be non-lamellar or not, that's not a requirement. The question is whether a person of skill in the art, based upon the disclosures in the '069 Patent, would have known a formulation and a formation process that's used in the '127 Patent to result in the non-lamellar structures.

So broadly speaking, the exact same disclosures are in the '069 Patent. The '127 Patent says, Oh, you can use nucleic acids, and this is how we define them. It's a verbatim disclosure in the '069 Patent.

If you go through the cationic lipid, the non-cationic lipid, the conjugated lipid, that's all the same too.

And so the actual disclosures to a person of skill in the art are completely encompassed in the disclosures to what an ordinary skill in the art in the '069 had.

Now, your question I believe is going to, Well can you point to a specific embodiment, that was reduced to practice in the '069 Patent, that results in the non-lamellar structure in the '127 Patent? Do I have the second part of your question there correct?

And so the answer there is, yes, as well. So, one, it's not legally required. Reduction to practice is not a requirement for anticipation by inherency. But, even if it were, we already have the formulations that we've been talking

about. We're talking about the same payload, the exact same siRNA payload, being used in the '069 Patent testing as was used in the '127 Patent testing. Nobody disputes that those are the same.

We have the same lipid components. We have the same cationic lipid being used, DLinDMA, which was known to be fusogenic and known to promote a non-lamellar structure. We have the non-cationic lipids, either DSPC or DPPC, and some of the formulations in the '069 Patent do use DPPC instead of DSPC, but their expert admitted that wouldn't be expected to impact the non-lamellar structure. Those are very closely -- very close in structure and -- as a phosphor lipid. We have the same cholesterol, and we have the same conjugated lipid.

So the formulations -- and we have the same concentrations. The2:30, the2:40, the1:57, and the1:62. So the formulations actually tested, we have -- again, complete overlap. The only question is the formation process.

And so in the '127 Patent, we have only one guiding principle for the formation process. Table 4, column 104, for the actual testing that they did. Those parameters. That's the only thing we can divine from the '127 Patent regarding how you get these non-lamellar particles; what the secret sauce is. And there's no discussion whatsoever regarding varying these parameters, what ranges would be acceptable, anything like that. That's just not in there. And that's

also true with regard to the stepwise dilution method.

So then we say, Okay, are those specific parameters disclosed in the '069 Patent? The '069 Patent is silent on the parameters used, but we know that those parameters are encompassed in the '031 disclosures that are referenced in the 127 patent. Again, the experts don't dispute that. They say that these -- the '031 Publication is enabling of the disclosures in the '127 Patent on how to make these particles.

The only difference identified by counsel just now is that, Oh, a Lipobot could be used in the '127 Patent direct dilution method. But there's no discussion in the '127 Patent of using a Lipobot, which is an automated syringe press to get constant flowrate. Is any difference -- different than the stuff that is disclosed in the '069 Patent? And Lipobot's automated syringe presses were known in the art at the time of the invention. That's not an argument that's put forth in the papers that that's any kind of novel piece of equipment.

And so we know that the '031 Patent discloses multiple embodiments, and one of those embodiments has to be the one in the '127 Patent. By definition, the '127 Patent says it, you have to believe the patent. So that is absolutely an embodiment that is one, the formulations overlap or -- are the same. We have no arguments there. The formation process, well, we know from the '031 patent that it's got to be embodiment A, B, or C. And one that's skilled in the art knows from the '031 Patent that A, B, C are enabled

and there's no argument there.

So, yes, an embodiment is disclosed.

JUDGE SNEDDEN: There was one -- that was the formulation processes, they described not one but a class of processes.

MR. WELLS: So --

JUDGE SNEDDEN: That's what --

MR. WELLS: I don't know what a class of processes refers to.

JUDGE SNEDDEN: Or category then.

MR. WELLS: I can tell you that the '031 Patent, the direct dilution method in the context of the '435 Patent and the direct dilution method in the context of the '127 Patent is the direct dilution method as disclosed in the '031 Publication. That's what they're talking about.

And they say, Go to that publication. You're one of skilled in the art, you'll be able to identify the different ways of making these things, embodiments A, B, and C. And as long as one of those embodiments would have been -- clear to one of skill reading that reference, and that embodiment results in a non-lamellar structure, it's end of story as far as the inherency. And it has to have -- include that -- one of those embodiments, including the embodiment specifically listed on Table 4 of the '127 Patent with those specific parameters.

So if we even got to this argument, and again, these

aren't limitations in the claims, but if we got to this argument it has to be in that disclosure. The '127 Patent relies on it for it.

Does that answer your question?

JUDGE SNEDDEN: It does, thank you.

MR. WELLS: Now, just before counsel went off, he put up some testimony from Dr. Janoff. And if we could call up Exhibit 2028, Page 185.

Now, it's the last answer on this page, and they cut it off at line 22. They conveniently left out the rest of the quote, and it's telling. Oh, there's reference to T-2 connectors, so might not necessarily be holding these in your hands. They're apparatuses to push the -- and if you can go to the next page -- the syringe.

So Dr. Janoff didn't say, Oh, stand there with two syringes and press them counting to five, so you get a bad flowrate. That's just a complete mischaracterization of his actual testimony.

If you actually go to the patent, if we can go to Exhibit 1001, and go to Column 104, Line 33 through 43. I'm sorry, yes, go ahead. 104, Lines 33 through 43, if we could blow that up?

And so here, they talked about a syringe press. It's just an automated syringe press as opposed to somebody sitting there pressing a stopper with their hands. And you can imagine how pressing a stopper with their hands -- you

don't get consistent fluid mixing rates, and you get non-homogeneous particles such that some of them are lamellar and some of them are non-lamellar.

So, again, an automated syringe press was not a point of novelty for this patent. No one's alleged that that was new. No one's alleged that having an automated syringe press as opposed to a peristaltic pump or some other mechanism, as described in the '031 Patent, would make any difference.

Now, again, one consistent theme that came up from counsel was it's not the exact same particles that were tested in '069 Patent. That's not the standard. Reduction to practice is not required for anticipation by inherency. It's whether the '069 Patent discloses to one ordinarily skilled in the art particles with the same formation -- formulation and particles used in the same formation processes. That's the standard.

JUDGE SNEDDEN: I understand that the reduction of practice is not required, but what is -- what I need is an identification of some formulation that necessarily has the properties in the claim.

MR. WELLS: Yes, and you need a combination of a formulation and a formation process to get that property. That's what the '127 Patent tells us. We need to believe that if we're going to do any analysis.

And so, as we've already discussed, we have the

formulations. We can look in the '127 Patent and say, Which ones work for the '127 Patent? Right?

We know for the direct dilution method, the 2:30 formulation did, the 2:40 formulation did, the 1:57 formulation did, and the 1:62 formulation -- it might be 2:40 -- did as well. And that was with using a direct dilution method as put forth in Table1, Column 104, right? So we know that. So then we say, Well, what's disclosed in the '069 Patent?

And so I'll skip over the fact that the disclosures broadly encompass all those, and a person skilled in the art would have recognized those disclosures and been able to make particles with those formulations and processes, and move on to the narrower question which is, is there a physical embodiment that we can point to? And so, yes.

We have exactly the same formulations, right? We have the2:30, 2:40, 1:57,1:62. Those numbers are the same. There's some rounding differences, but there's no dispute that those same numeric concentrations are disclosed.

Then we look at the payload. The payloads are exactly the same, exactly the same siRNA. Exactly the same target for silencing. And then we look at the lipid components, and we have exactly the same cationic lipid, exactly the same conjugated lipid, exactly the same non-cationic lipids, except in two instances, DPPC is used instead

of DSPC.

So formulation-wise, we've identified exactly that, right? Are we on the same page, thus far?

JUDGE SNEDDEN: Yeah.

MR. WELLS. Okay. So then we go, Okay, well, what formulation process was used? Was exactly the formulation process used, disclosed in Table 4 of -- on -- Table 1 on Column 104 of Exhibit 1001, the '127 Patent? And we'd say, Oh, well, the '069 Patent doesn't say what specific parameters were used, and it doesn't. Instead, it references the '031 Publication. And we know the '031 Publication discloses all of those parameters on Table1.

Why do we know that? Well, the experts all admit it, and the '127 Patent itself says you can rely on the '031 Publication for how you do the direct dilution method.

So we know it's disclosed in there. And I think your question is, Well, is there anything correlating those specific -- the embodiment -- those specific parameters to what was actually tested in the '069 Patent? And there is evidence that those specific parameters or some other set of parameters that result in non-lamellar particles was used in the '069 Patent.

But I want to stress that's not a requirement for inherency. Inherency doesn't require every embodiment to result in non-lamellar morphology. It's simply saying, Oh, well, some embodiments don't, so then it's -- you know, then

we're talking about picking and choosing and we're talking about --

No, we're not. We're talking about there's multiple embodiments in the '031 Patent. And one of those embodiments by definition, by the -- terms of the '127 Patent itself, has to result in the claimed non-lamellar structure.

Now, if you go through the '031 Patent -- or Publication, I'm sorry. I keep calling it a patent. It's a publication. And you say, Okay, well, where are the disclosures of the ranges of the different parameters and whatnot? They're all disclosed in there. And Example 2 of the '031 Patent sets out a lot of these. But there's a section of the '031 Publication that says, This is how you make the particles, and it spans Paragraph 0039 through 0087, and it gives you all the encompassing ranges. And this is what a person of skill in the art would reference and say, Okay. Using this as the embodiment in Table 1 on Column 104 of the '127 Patent, one of the embodiments that fall within this broader grouping of embodiments. And, yeah, it is. And how do we know that? Well, the experts testify to it. And how do we know that? The '127 Patent says it.

JUDGE SNEDDEN: I understand, thank you.

MR. WELLS: Now, regarding the evidence that a formulation was actually used, which results in non-lamellar particles in the '069 Patent, again, this isn't a requirement for the inherency argument but would relate to an obviousness

argument.

We have the statement that we brought up earlier that one of the goals in the preferred embodiment was to have the nucleic acid in the lipid portion. And in the lipid portion refers to inside, encased within the lipid superstructure that you find in these non-lamellar structures.

In addition, could we go to Slide 161? So this is the reference to being encapsulated within the lipid portion of the particle. In addition, we have the '069 Patent incorporates by reference -- reference the 613 reference, which is Exhibit 1017, and this is incorporated at Column 11, Line 64 of Exhibit 1002 in its entirety. And the '613 Patent talks about the benefits of having a non-lamellar structure, and that it can increase your fusogenicity, and in fact, discloses embodiments where all of the particles -- it's a homogenous particle population of non-lamellar particles, and those are at Columns 7, Lines 22 through 26, and 763 through 84 of the 613 patent.

We also have expert testimony. Their expert specifically testified that if a particle is showing poor encapsulation, it's probably lamellar. And if it has high encapsulation, you would expect it to have a non-lamellar morphology. And he did this at Exhibit1023, Page 126, Lines 4 through 11. And so we have plenty of evidence that the '069 particles that were actually formulated were indeed non-lamellar. But, again, not a requirement for anticipation by

inherency.

Very briefly, regarding the obviousness challenges; the obviousness challenges still do exist. The '069 Patent has a publication date on its face. The Board is entitled to rely on the publication date for determining whether it is 102(a)(2) art. It says it was published. The Patent Owner says, Oh, there could be differences, different claims. It's a continuation application, the claims had to be supported by the original specification. So the scope of the disclosures is the same.

In addition, the 817 reference, which is the basis for Grounds 2 and 4, now this reference has very similar disclosures to the '069 Patent. They claim the same -- priority to the same provisional application. In the original PCT -- oh, I'm sorry -- in the original petition, we identified where in the provisional application the corresponding disclosures could be found for '817 patent because it has the same disclosures as the '069 Patent. So that made it seem to make sense. I understand that the Board didn't like that approach and didn't want to have to go looking through the '817 patent for the specific correlation. That correlation was divided in the reply brief. So that is before the Board.

The 817 reference, there's no dispute that that can qualify as an obviousness reference for the purposes of the analysis under 102(a)(2), so that the -- obviates any problem with

regard to that issue.

And it looks like I'm over, so with that, I will thank you, unless you have any other questions.

JUDGE MITCHELL: Okay. Thank you.

MR. ROSATO: A few brief comments.

So on Slide 7, I'm not going to bring up the demonstratives again here, but I'll note it for the record. On Slide 7, we point to content of record that talks about this notion that the parameters, the specific parameters of a formulation process are important because they affect the physical properties of the resulting particles. So if you change process parameters, that changes the physical properties of the resulting particles. And that there are a wide range of parameters that can be varied in a process used to formulate particles.

We also pointed to Dr. Janoff's deposition testimony or during cross-examination, where he identified three specific parameters that would affect the output or the outcome such that, as he described, you might not get the claimed particles.

I point that out again because I think I understood counsel to state several times that the '069 Patent is silent on the parameters used in their formulation processes. So putting two and two together there, it sounds like we're talking about probabilities and possibilities.

Second, there's a -- Judge Smith had posed a

question to me, and I identified the Lipobot syringe press as one of the things I could think of that wasn't found in the '069 Patent. The response that I heard was that is in the prior art there's no documentation or any evidence to -- in this record to support that, but it's in the prior art.

I don't know how to respond to those types of arguments. I haven't seen any prior art to substantiate that. We can't make assertions that -- or hearing about what is or is not known at the time, and we can't dismiss those types of things by merely returning argument.

And, finally, there was an argument or an assertion that Dr. Thompson admitted that particles with a high encapsulation percentage would be understood to be non-lamellar particles. That actually was a position taken by Dr. Janoff in his declaration. Dr. Thompson addressed that in his declaration, Exhibit 2009, Paragraphs 67 and 68, and explained why that actually makes no sense.

With that, I will thank the Panel for the time and the extra time in particular. Thank you.

JUDGE MITCHELL: Thank you, all. The arguments were very helpful and thank you for your patience with our snafu with the equipment.

And so with that, IPR 2018-00680 is submitted. Thank you so much and we are adjourned.

(Proceedings concluded at 5:19 p.m.)

PETITIONER:

Michael Fleming
Crawford Wells
IRELL & MANELLA LLP
mfleming@irell.com
mwells@irell.com

PATENT OWNER:

Michael Rosato
Steven Parmelee
Sonja Gerrard
WILSOM SONSINI GOODRICH
& ROSATI
mrosato@wsgr.com
sparmelee@wsgr.com
sgerrard@wsgr.com