

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00003 (Patent 11,952,600)
PGR2025-00004 (Patent 12,018,298)
PGR2025-00006 (Patent 12,152,262)
PGR2025-00009 (Patent 12,123,035)

Held: March 2, 2026

BEFORE: JEFFREY N. FREDMAN, SUSAN L. C.
MITCHELL, and CYNTHIA M. HARDMAN, Administrative
Patent Judges.

The above-entitled matter came on for hearing on March 2,
2026, commencing at 1:38 p.m.

PGR2025-00003 (Patent 11,952,600), PGR2025-00004 (Patent 12,018,298),
PGR2025-00006 (Patent 12,152,262), PGR2025-00009 (Patent 12,123,035)

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P R O C E E D I N G S

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JUDGE FREDMAN: And we're ready to move on to the main event. Oh, and we can open up the public. So I'll let you reserve three minutes of -- or no. Three? Everyone's here. The public line is open.

MR. KUSHAN: Thank you, Your Honors. Jeff Kushan again for Petitioner Merck. Each of the --

JUDGE HARDMAN: Well, Counsel, before you go on, I just wanted to -- note for the record that Judge Valek has left the hearing for this portion of the presentation.

MR. KUSHAN: Thank you, Your Honor. So Your Honor, each of Halozyme's patents has claims that are not supported by Halozyme 731 application that was filed in 2012. And that makes each of them PGR eligible. It also means those claims are unpatentable under section 112. Halozyme's original '429 Patent from 2003 also makes obvious hundreds of single amino acid substitutions into the PH20 protein, five of those land within the scope of these claims and render those claims unpatenable for 103.

If we go to Slide 5, just to get oriented, we have two experts who've addressed the 112 issues on the protein science side, Dr. Hecht and Dr. Naismith. Dr. Park is also a protein scientist. He's never seen the patents in suit or any of their claims.

1 He's just worked from the prior art. And Dr. Kelsoe is an
2 immunologist who's taken a very narrow role in this case looking
3 at the contraceptive utility issue.

4 So if we go to Slide 7. All of the claims of these patents
5 have kind of a similar formula. They require one amino acid
6 substitution at one position. And then they may have optionally
7 additional changes.

8 If we go to Slide 16. An important point is that the claim
9 language imposes no constraints on where in the protein or what
10 kinds of changes are made in the protein. Changes could be
11 substitutions to any of 19 other amino acids. They can be at any
12 position. They can include deletions and additions of amino acids.
13 They can also be randomly distributed throughout the protein.
14 They can be localized into groups.

15 JUDGE FREDMAN: So Patent Owner is basically
16 arguing the claim of construction. Can you sort of address that a
17 little bit?

18 MR. KUSHAN: Sure. So they've argued that the claims
19 define the genus in a structural term. And we think that doesn't
20 really help them on the questions of patentability that we're
21 addressing. First, if you look at Slide 62, defining a chemical
22 genus in purely structural terms does not exempt it from
23 complying with the written description requirement under the
24 Ariad standards.

25 In the University of Minnesota case, you see the

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1 definition of the claim was structural. It's a structurally defined
2 genus of compounds. The panel here and then the Federal Circuit
3 addressed and assessed that using the two possession tests used in
4 Ariad. It failed under the common structural features prong of
5 that, but they were applying the Ariad law to that chemically
6 defined genus.

7 In Slide 14, another point is that the structural claim issue
8 is kind of orthogonal to the actual question is have they
9 demonstrated possession of the entire genus? They're claiming
10 there's no dispute that genus includes both, as under their
11 construction, that it would include all the enzymatically active
12 PH20s. Along with them, they would also have to include all the
13 inactive forms of PH20.

14 To demonstrate written description and enablement of
15 the full scope, they have to describe the actives as well as the
16 inactives. And under enablement, the same test is applied. So if
17 they don't meet the requirements for the active subpart of this
18 broader scope they're portraying, they have the same problem with
19 not enabling or describing the full scope of the claims. In fact --

20 JUDGE FREDMAN: The argument that their expert
21 makes, right, is well, we have this 95 percent, we have the
22 sequence -- I mean, I was going to say with enough time, but that's
23 a little bit of a misnomer. I think it would take -- but one could
24 print them all.

25 MR. KUSHAN: So the 95 percent identity --

1 JUDGE FREDMAN: It might take all the paper in the
2 universe.

3 MR. KUSHAN: Well, the 95 percent identity
4 requirements isn't really a description of the genus of molecules
5 that are being claimed. If you look at the Ariad decision, what the
6 court is looking for is evidence to show they possess the genus of
7 -- which is reflected by the possession of the various species that
8 reflect that. And the 95 percent identity is -- let's be very clear, it's
9 not a structural characteristic of any molecule, it's just basically the
10 boundary of the molecule.

11 If you could put up the Ariad decision from Slide 61. So
12 you see in many of these cases, the court saying to demonstrate
13 possession of a genus of chemical compounds, you just can't draw
14 a box around all the ones you want. You have to demonstrate the
15 possession of the different things that make up the genus, the
16 molecules. So if there's a difficulty of defining it by a common
17 structure, function, relationship, then you have to provide
18 representative species that reflect the diversity --

19 JUDGE FREDMAN: We do have structure. And we
20 can argue, though, there is a common structure.

21 MR. KUSHAN: Yeah. Well, I would like to devote a
22 fair amount of my time to that question because I don't think it
23 does have the common structure features -- common structural
24 features identified as a genus in the patent. But I want to make
25 sure we start with the foundational point that when they look at

1 that 95 percent identity requirement, it is the epitome of the type of
2 boundary drawing language that the courts have found insufficient
3 to demonstrate possession of a genus of chemical compounds.

4 So we look at this as either you can focus on the active
5 ones, and I think that's a proper focus. But if you look at the
6 broader collection of the inactives, all that does is add more
7 problems under 112 and also 103. For 112, it adds a question of
8 what is the use -- what is the practical use of so many of these
9 inactive mutant set that many can't be made. We don't know the
10 form of them. They don't have contraceptive utility. We'll address
11 that.

12 But then the obviousness question also becomes what is
13 -- if there's no requirement for any properties of these sequences,
14 how does that become not obvious over the '429 Patent, which
15 specifically, it says to make at least one change to the PH20
16 sequence. So it just constantly -- it makes the challenges greater
17 for them if they broaden their claims out.

18 Now, if you look at Slide 8, you found in your
19 construction that the claims, at a minimum, encompass
20 polypeptides with some hyaluronidase activity. We believe that's
21 the right way to look at this. In Slide 22, that's also what we took
22 -- as our position, we said as -- the claims, as a whole, are directed
23 to enzymatically active PH20s.

24 JUDGE FREDMAN: We did do that. But there are
25 statements in the specification, like in column 75, for example, just

1 also provided -- or modified PH25 peptides that are inactive. And
2 they can be used, for example, at the end of the contraception
3 vaccines. So they kind of pull.

4 MR. KUSHAN: So there's two points we flagged about
5 this, one is there's a TIP case that looks at whether the claims as a
6 whole have limited the invention of -- the claim invention to one of
7 two alternative embodiments. There's no dispute in this case.
8 These are two alternative embodiments. The second is the
9 language of the claim itself.

10 And I think here, what I'd like to do is focus on Slide 10.
11 When you were addressing the question of whether the claims
12 defined the genus in structural terms, you flagged and you found
13 that it did not because there was more context. And I think the
14 critical thing here is the word PH20. The claims define modified
15 PH20 polypeptides. So there's one definition that defines modified
16 PH20 polypeptide.

17 There's another definition in the patent for PH20 as well.
18 And we think the record that's been formed since institution
19 demonstrates that that has to be considered and given weight.
20 Their construction gives PH20 zero weight. They see the same set
21 of amino acid sequences if you strike the word PH20 out of the
22 claim. And I think that's pretty clearly incorrect as a standard.

23 If you could put up Slide 9. It's also important to look at
24 how they are portraying their claims. They portray their claims as
25 being the D320 variants. And then they have a derivative set of

1 variants they call the subvariants, which are the 95 percent
2 identical ones.

3 And then you look at the passage you cited in the
4 institution decision that explains what a modified PH20 is. You
5 have one modification that's required, and then there's the optional
6 modifications that are allowed after that. And this aligns with that
7 kind of logic that the first change is made. It kind of defines the
8 fate, they're all active. And the additional modifications are then
9 selected or done to preserve that activity as the explanation is
10 providing in the spec.

11 But as far as PH20, PH20 is a word that their expert
12 described as meaning a folded protein. If you look in the
13 definition -- and this is at Slide 24 -- we pointed out that their
14 expert called it -- used that phrase, (INDISCERNIBLE) PH20 as a
15 folded protein. It's important to note that he was referring to the
16 95 percent version of the protein, not the one that just is found in
17 nature.

18 That's also important because in the next slide, on Slide
19 25, we have testimony from their expert -- their other expert
20 looking at that definition of PH20 in the patent and seeing that that
21 signaling is supposed to be a folded protein -- a properly folded
22 protein. And properly folded proteins typically have activity.

23 But at the end of the day, we also have the language in
24 the claim --

25 JUDGE FREDMAN: I'm --

1 MR. KUSHAN: Yes, sir?

2 JUDGE FREDMAN: I'm not sure of properly folded
3 proteins, that's the way of activity. It was one of the questions
4 about folding is just whether you check sort of disruption of 5
5 percent to prevent it from functioning as a contraceptive. In the
6 context of the immune system, right, approaching to present it to
7 the macrophages or whatever immune cells are being chewed up,
8 essentially, macrophages (INDISCERNIBLE).

9 And that's how the antibodies are generated in the
10 immune system. Presumptively, that's how contraceptive activity
11 in the vaccine is happening. So the three-dimensional structure
12 doesn't seem to matter as much in that context.

13 MR. KUSHAN: Well, the three-dimensional structure
14 does matter. But if we want to dig into the contraceptive issue, I'm
15 happy to do that. Let's make sure we understand what the
16 evidence is on the table. First one -- if I could go to Slide 118. So
17 the actual content in the patent is very limited as to what is
18 addressed.

19 This is the sum total of the guidance in the patent on
20 contraceptive utility. So it's just two short paragraphs. It doesn't
21 really give any guidance as to what has to be on these proteins.

22 Second point -- Slide 119 -- let's be clear, there is no
23 evidence before 2012 that a modified PH20 protein had ever been
24 used or even tested for contraceptive effects. So there's no
25 evidence that it has that ability. It's also never been tested whether

1 an aggregated or a misfolded protein has that effect either because
2 there's just no evidence at all on modified forms of protein.

3 But it's also important to look at what was in the
4 literature looking at the one experiment that did work against the
5 rest of them that didn't. And if you could go to Slide 120. This is
6 a quote from a paper in 2006, Dr. Martin Leon -- DeLeon surveyed
7 the evidence that we're looking at today and wrote in this 2006
8 paper that taking together all that evidence from non-primate and
9 primate models suggest that PH20 is not a useful antigen for
10 inclusion in immunocontraceptive vaccines.

11 This is very probative to the question because it's
12 contemporaneous evidence that validates and confirms our expert's
13 perspective. But it's also reflecting the view of someone of skill in
14 the art in the time frame that's relevant. And it's signaling that
15 there's not a credible belief that you could use that modified PH20,
16 or even the regular one, as an immunocontraceptive vaccine.

17 JUDGE FREDMAN: So let me ask a question on that.
18 This is probably more on your side. As in the context of the
19 guinea pig, there also seems to be some indication that the way it's
20 functioning as it comes up is by causing essentially inflammatory
21 responses, damages the guinea pig reproductive system, sort of a
22 foreshadowing for that.

23 That seems to be something that at least would not be
24 quite desirable in other contraceptive vaccines. I mean, at least if
25 there (INDISCERNIBLE) permanent, that might not be so good.

1 MR. KUSHAN: Right. You think of sterility at that
2 point, right?

3 JUDGE FREDMAN: Sterility and --

4 MR. KUSHAN: But I think it is correct, you know, the
5 -- that the best way to think about that guinea pig experiment is to
6 look at it through the lens of somebody looking at it in 2006 and
7 looking at this array of other experimental investigations and
8 finding that it was not indicative that this is a viable antigen. I also
9 want to flag that on Slide 128, this part -- what you raised about
10 immune tolerance does come into play and it does -- it's one of the
11 mechanisms that would suppress targeting of epitopes.

12 There are a lot of variables that go into the question of
13 whether you can induce an effective contraceptive response
14 through the immune system. Again, the most probative evidence
15 we think is from the time back before the patent.

16 So you asked us in our call to address some of the
17 questions that are relevant to enablement and the description for
18 multiply modified proteins. So I'd like to get into that.

19 If you could put up Slide 38. Let's start with some
20 basics. Proteins are inherently unstable molecules. They have to
21 balance, basically, all these negative and positive energetic effects
22 of the protein. And if the net balance of that energetic set of
23 interactions is positive, it stays folded. If it becomes negative, it
24 becomes unfolded in physiological conditions.

25 So when you're looking at a protein and you put changes

1 into the protein, it's important to note what Dr. Hecht pointed out.
2 The amount of energy that can make it flip from folded to unfolded
3 is associated with the -- can be as little as a single hydrogen bond.
4 So you could put a bunch of changes in, even one change, and you
5 can shift it from a stable protein to something that just falls apart.

6 And that's actually reflected in the data in the patent. If
7 you look at Slide 40, it looks like about 80 percent of the tested
8 mutants, you know, had something bad happen to them by
9 introducing a single amino acid change. And that's reflecting this
10 kind of effect that it has energetically.

11 Look at 47. Now, multiply modified proteins introduce
12 complexities that single mutants don't. Most of the structures on a
13 protein derive from patterns of amino acids in the protein
14 sequence. And those patterns form the alpha helices and the beta
15 sheets. But they also form the broader, bigger motifs.

16 So if you look at Slide 95, one of those motifs you've
17 seen in the briefing is something called the HyalEGF domain.
18 That is associated with a pattern of residues that has to be present.
19 And so if you disrupt the pattern, you can start to change the
20 protein. You can make new shapes of the protein. It's not just
21 disrupting it like a single mutant can. So these are impactful
22 things in sets.

23 If you look at, for example Slide 49, Dr. Hecht addressed
24 a number of these scenarios in his declaration. I'll also just refer
25 you to paragraphs 40 to 46 and 54 to 61, where he kind of goes

1 through some of these implications of multiple changes versus one.

2 But I also want to bring out one other point. Go to Slide
3 51. In settings where you're putting multiple changes into a
4 protein, there's an effect -- a long distance effect that can happen.
5 And what that means is instead of just colliding within their same
6 neighborhood, now you have mutations in different parts of the
7 protein contributing to -- in the aggregate, cause a negative effect
8 on protein.

9 JUDGE FREDMAN: These are directly or indirectly?
10 Because obviously, occasionally things that are far away, primary
11 structure, are adjacent to each other in the tertiary structure.

12 MR. KUSHAN: Yes. So when you're doing modeling,
13 you can kind of see the ones that are local and adjacent. You kind
14 of see if there's an interaction. It's harder to find the ones that are
15 what we call epistatic or long-range effects. These are the ones
16 which cause an impact on the overall protein structure. You can
17 imagine it like rippling through the protein. And then if more than
18 one change are happening, you're now causing all these very
19 unpredictable consequential events on the shape of the protein.

20 If you look at Slide 54, we cite this because it's Dr.
21 Petsko, their expert, revealing that he's very familiar with this
22 phenomenon of long-range effects. And what he points out -- I'd
23 like the quote on the bottom of the middle -- he says, these long-
24 range effects are common, complicated, and subtle. And that's
25 right. They can be caused by electrostatic interactions.

1 They can be caused by van der Waals forces. They can
2 be caused by steric. So these are all very complicated things that
3 are happening. What that means is they're very unpredictable,
4 especially when you're putting multiple 5, 10, 15 changes into the
5 same protein.

6 Look at Slide 89, please. Dr. Hecht -- I'm sorry, Dr.
7 Petsko also recognized that this is not a stable protein. He said that
8 normally, proteins with the alpha/beta barrel structure have a
9 robust tertiary structure, but not this one based on the mutation
10 data that is in the patent.

11 Go to Slide 55. Now, this phenomenon we refer to as
12 epistasis or non-additivity is another word you see. It is something
13 that was well-known to protein scientists. This is just a paper
14 demonstrating that the awareness in 2010, 2011 of the effect of
15 epistasis as a complicating factor when you put more than one
16 change into one protein.

17 If you could go to Slide 41. Dr. Naismith, our expert,
18 has pointed out that the thing that's interesting about this graph
19 shows all of the activities of the active mutants is that there are
20 very few, very few of them actually stayed unchanged. Those are
21 the ones around the 100 percent mark.

22 Most of them had some detrimental effect. But the bulk
23 of them are not unaffected by a single mutation. And these
24 changes are all over the protein. They're not near the active site.

25 If you go to Slide 42. Another point that's very

1 important, there's a lot of data in this patent and another patent
2 that's incorporated. I referenced '457 publication measuring the
3 activity of the truncation mutants. These are all changes away
4 from the active site at the end of the protein. You see, there's just
5 widely varying activity of these one amino acid, different
6 truncation mutants.

7 The two that I flagged here have a difference of 135
8 percent based on one difference in how long they are. So these are
9 long-distance effects happening in the protein caused by this
10 terminal sequence.

11 I also want to point out that all of the proteins that were
12 tested with single mutants were in one seq, 447. There are no
13 species tested that have more than 447 amino acids in it. So that's
14 that portion to the right of the 100 percent bar, which there is no
15 mutagenesis data either.

16 JUDGE FREDMAN: Does the claim encompass --

17 MR. KUSHAN: They do. So the claims used have that
18 95 percent identity applied to 35 different sequences. They are
19 roughly the ones scattered across this histogram. Any one of those
20 is a reference of PH20. Some of the dependent claims limit it to
21 particular ones.

22 But that is the array of proteins that are being the point of
23 reference for that 95 percent identity. So they can even be longer
24 because they permit additions to these sequences. The 465 is the
25 longest one in that set.

1 So two other points on predictability that I want to touch
2 on quickly, one is -- go to Slide 43. Their expert prepared this
3 tolerance table. And the dark green entries are the ones he labeled
4 100 percent tolerant to change. That means you could put any
5 amino acid in that position, and you would --

6 JUDGE FREDMAN: What slide number --

7 MR. KUSHAN: Sorry, this is Slide 43. Slide 43, Dr.
8 Petsko's image, or an excerpt of it, is on the right. And you see
9 these are positions 100 percent tolerated. So you would expect
10 you put any amino acid there without impact. The data shows
11 that's not correct. What it shows is that every different amino acid
12 had a big impact, often a very big impact, on the activity that was
13 seen.

14 And they're all over the protein causing these impacts.
15 Dr. Naismith says, that's another sign this thing is going to be
16 susceptible to epistasis.

17 And then the last thing I wanted to touch on is there was
18 a paper we introduced, this Ochena Lavia (PHONETIC) paper.
19 This is Slide 44. This is an experiment that was done before 2011.
20 And it is a protein that has an alpha-beta barrel motif and it's an
21 enzyme.

22 And what the scientists here did was design a very
23 constrained experiment that then kind of tilt the odds in favor of
24 folding, right? They chose loops that were found in homologous
25 similar proteins. And they put them in places that they thought

1 would be least impactful.

2 It's important to note they, the spectrum of things that
3 were being tested here, introduced between 4 and 19 amino acid
4 changes. They also introduced additions and deletions. At the
5 bottom of the chart, you see the lengths -- the change in length of
6 the loops at each of these positions.

7 And what the punch line here is that 40 to -- 30 to 70
8 percent of these proteins did not fold. So this is a constrained
9 experiment and most of the things went poorly.

10 What that does is it tells us that against this claim -- this
11 claim, remember, has no restrictions on where the changes are
12 made, no restrictions on the nature of changes, any kind of
13 addition, deletion, et cetera, so that's kind of what we're dealing
14 with in terms of complexity and unpredictability.

15 If you could also -- let's just finish out on -- there are two
16 points I want to make. Go to Slide 109, please. So the patent has
17 one concrete example of attempting to make multiply modified
18 proteins. And what it has in it is an iterative mutagenesis process
19 where you make a library of mutants. You screen them for
20 activity. Then you introduce changes into that set of actives. And
21 you repeat that iteratively. That's what the patent says.

22 Dr. Petsko said, no one would ever do that. And I think
23 the reasons are clear. It's impossible.

24 If you go to Slide 110. All these techniques require use
25 of screening assays. The screening assays that were available in

1 2010, 2011, 2012, they capped -- they have a limit of about 10 to 9
2 species in a library that you can practically screen.

3 You can see in our graph, you hit that limit after about
4 three mutations, you know. Now, we're dealing with a very tiny
5 fraction of this huge universe of possibilities, and you can't get
6 past it. So you really can't use this technique to sample even more
7 than a tiny fraction of this very large space.

8 Now, Halozyme points out that this -- they say in their
9 surreply that -- go to 148, that this passage only related to
10 evaluating proteins for stability. Look at the first quote on the top.
11 This methodology -- this iterative methodology is used to identify,
12 modify, or further modify to increase or optimize the activity of
13 the proteins. So it's the only technique they've got.

14 What they also put into play is a new thing that's not in
15 the disclosure. It involves picking sets of residues, amino acids
16 that were tested from the data set and combining them, not with
17 any direction, just combining them. And then putting them in a
18 homology model and inspecting that homology model one by one.
19 So that -- again, there's no homology model described in the
20 patent, there's no described use of it in this process.

21 JUDGE FREDMAN: And then there's the structure of
22 the related protein was not right the bee venom hyaluronidase?

23 MR. KUSHAN: So there was no experimental structure
24 of the human PH20 protein.

25 JUDGE FREDMAN: Right. That was created later.

1 MR. KUSHAN: Right. So the closest thing was the
2 Hyal-1 protein. And I want to touch on that in a minute. But there
3 are very significant limits about using that homology model to do
4 this type of work.

5 The point I want to kind of end with on this is that this
6 methodology -- if you go to Slide 111 -- just -- let's make sure we
7 see the scale of this. Even if you restrict it to five changes, avoid
8 all of the highly-conserved positions that you don't want to change,
9 you're talking about trillions of combinations of amino acids that
10 you're selecting out of the set.

11 That translates even if you've spent, like, one minute on
12 each protein in the homology model, you're talking about billions
13 of years of labor. We don't need to do that.

14 JUDGE FREDMAN: Having a computer like
15 (INDISCERNIBLE) at your house.

16 MR. KUSHAN: Well, in 2011, what they're actually
17 describing is doing -- creating the structure and then you have to
18 inspect the structure to see what happened. That's the
19 methodology they're describing. So it's -- we're being very
20 generous. You could think about -- you could do that in a minute.

21 But the point of it is that this is a very, you know,
22 individualized assessment that they're speaking of. And the scale
23 is just -- you can't even touch this -- you know, scratch the surface
24 of that.

25 So I want to talk about homology models because there

1 are important limitations that we had identified in our petition in
2 our experts' declarations. If you can go to Slide 102. First, they
3 say in their surreply, all parties agree that an accurate homology
4 model of PH20 structure showing the alpha/beta code and location
5 of each amino acid in the structure was available to a POSA. That
6 is incorrect.

7 I mentioned before, the homology model is built using a
8 template. The template is a protein that has been experimentally
9 determined as to its structure. The template here is Hyal-1. Hyal-
10 1 is much shorter than PH20. So our expert, Dr. Park explained in
11 his declaration that you can't use the portion of the sequence past
12 position 403 of PH20 in the model. It's actually not even in the
13 model because it's not reliable.

14 And that translates to that stretch of amino acids that I've
15 highlighted in yellow, which shows a significant portion of this
16 molecule cannot be modeled with this template. That's particularly
17 relevant because that has part of the highly conserved EGF domain
18 which is essential to activity.

19 And if you go back to Slide 42, it has all of these. This
20 whole region is in that portion that cannot be modeled. So you
21 have a lot of unpredictability and activity derived from truncation
22 mutants. And there's no way to model this portion of the protein.

23 JUDGE FREDMAN: (INDISCERNIBLE) C-terminal?

24 MR. KUSHAN: This is all the C-terminal truncations.

25 Now, another point to keep in mind about this is very timely. The

1 Nobel Award was granted last year. That was a very helpful
2 insight. Go to 101, please. In that background or on the Nobel
3 Prize it gave us a nice survey of where the technology was in 2011
4 and 2012.

5 And what this is showing is that the computational tools
6 did not have the quality and reliability that allowed one to predict a
7 structure just from the sequence alone in 2011. That only became
8 possible in the 2019 time frame.

9 JUDGE FREDMAN: But here, we don't really have just
10 a sequence. We also have the Hyal-1 structure. So it's additional
11 information. Maybe they're really talking about situations where
12 there was essentially no structure that was known. And here, we're
13 a little bit (INDISCERNIBLE) from that.

14 MR. KUSHAN: This is also reflecting inputs from
15 structural -- I mean all these computer models use the structural
16 information in order to design their algorithms.

17 JUDGE FREDMAN: Right, of course.

18 MR. KUSHAN: So they're all based on real structures.
19 Otherwise, they wouldn't have any legitimate context.

20 JUDGE FREDMAN: They're all crystal structures,
21 originally, and I guess I'm saying that I think that prior to 2011,
22 people were using known crystal structures to model other related
23 proteins.

24 MR. KUSHAN: Correct. And that goes to a couple of
25 other problems with doing that. If you look at Slide 100, you see

1 in our experts' declarations from Dr. Hecht and Dr. Park that they
2 say you can't really model in a homology model something that's
3 more than a few residues different from reality. Reality, in this
4 case, comes from -- you have a sequence which has been found in
5 nature. It's folding. It's active.

6 On the other hand, you have a template of an
7 experimentally-determined structure. So those are the two things
8 that give the model its legitimacy.

9 When you start to change the sequence, you're now
10 moving away from nature. You're also moving away from the
11 model that is the base -- the structure that's the basis of the model.

12 JUDGE FREDMAN: So how many changes would they
13 say you can make?

14 MR. KUSHAN: Our experts kind of see three to five as
15 what you can -- realistically, that's where the limit is at.

16 JUDGE FREDMAN: Does it matter which changes are
17 made? I mean, obviously, a proline change is a more significant
18 change than leucine to isoleucine or something.

19 MR. KUSHAN: It's --

20 JUDGE FREDMAN: Maybe.

21 MR. KUSHAN: I think in speaking with these protein
22 experts for a while, I feel like most of them want to say one, but
23 they have to be reasonable. And so they're trying to find some flex
24 around one. The reality is that you can't detect epistatic changes.
25 You can't detect electrostatic changes. You can detect local impact

1 changes. And that's a small universe. That's why they're so
2 hesitant about drawing a sharp line. But they all kind of land
3 around this.

4 JUDGE FREDMAN: (CROSSTALK) electrostatic
5 (INDISCERNIBLE).

6 MR. KUSHAN: Well, these are long-distance
7 electrostatic effects.

8 JUDGE FREDMAN: (INDISCERNIBLE).

9 MR. KUSHAN: Yeah. And again, this -- I'd love to
10 give you a better answer, but the reality is that these experts have
11 told us that there's only -- you can only, really, realistically model
12 a few at a time. And they put at --

13 JUDGE FREDMAN: At least that's 2011.

14 MR. KUSHAN: Yeah. In 2011, 2012, that's where they
15 were. You're nowhere close to where the claims are in this case,
16 15, 20 changes. It's well beyond the boundaries.

17 So well if I could is I'd like to shift over to written
18 description. And let's start with some basics. Slide 61. Again, we
19 talked about this a minute ago. For written description you have to
20 demonstrate possession of the claimed invention. You have to
21 -- for a chemical genus, you need a very precise definition of the
22 chemical structures. You have to be able to visualize and
23 recognize the members of the genus. And drawing a fence around
24 the outer limits is not enough.

25 If you go to Slide 77, kind of just very basic level. Those

1 two tests of representative species and common structural features
2 are designed to inform whether the disclosure has demonstrated
3 possession. Both experts have recognized it's literally impossible
4 to identify the set of proteins, the sequences that turn into
5 enzymatically active proteins in this genus. Dr. Hecht, in his
6 declaration --

7 JUDGE FREDMAN: (INDISCERNIBLE).

8 MR. KUSHAN: And that --

9 JUDGE FREDMAN: Assuming that contraceptive
10 (INDISCERNIBLE).

11 MR. KUSHAN: So what we would need to know is
12 which ones are inactive because that's the part that is not
13 overlapping with the active ones. We can't tell which ones are
14 inactive, which ones are going to fold, which ones are going to be
15 stable. You can't determine that from the sequences alone.

16 And the problem at the root of this is that it's impossible
17 to just even approximate the portion of the genus that would be in
18 that set. If you look at Slide 78, their expert recognizes as well,
19 Dr. Petsko, he testified that it was not possible for a POSA to
20 calculate or experimentally determine which sequences would
21 properly fold and be enzymatically active. So he's telling us you
22 can't see within the set of sequences in the 95 percent number
23 which sequences actually are going to turn into proteins, which he
24 also means you can't tell which ones won't.

25 So that's the threshold point just at a very high level. If

1 you can't even approximate which of this huge set of sequences is
2 going to be the active one, you can't really possess it.

3 Now, they also can't -- they can't visualize the inactive
4 forms of PH20. Halozyme really never describes what that
5 universe of 95 percent identity proteins is in the inactive set.
6 We've asked our expert to try to provide insights into that. If you
7 go to Slide 36, we asked Dr. Naismith to tell us what's in that
8 sequence space.

9 Certainly, there are the enzymatically active ones, which
10 are in that green-shaded box. But there are a lot of other forms of
11 PH20 sequences that are structurally distinct. There's a number
12 that cannot even be produced. Some cells will not produce certain
13 sequences. There are some that can't be secreted, so they get
14 broken down before they leave the cell. Some are improperly
15 formed. They are misfolded or they're partially folded.

16 And they can sometimes be secreted. And there's a set
17 that do get folded. But they get out and they fall apart because
18 they're unstable. So all of the ones that are not stable, not
19 completely folded, typically will aggregate because they're just
20 now in that form.

21 JUDGE FREDMAN: This protein, is it from the surface
22 of cells, right? Is that where it's located.

23 MR. KUSHAN: Yes.

24 JUDGE FREDMAN: And so is it coupled? It has a -- is
25 the C-terminal basically linking it into the plasma membrane?

1 MR. KUSHAN: Yes. So it's a GPI-anchored protein, so
2 it's -- it attaches to the membrane that way. But it also exists in a
3 cleaved form.

4 JUDGE FREDMAN: The question, I guess, is sort of
5 does it matter? In other words, to some extent, the part that's going
6 to be antigenic would be presumably not part of the GPI anchor.

7 MR. KUSHAN: Right. It would be the remainder of the
8 protein, this -- the -- and all those mutants we were looking at
9 before the C-terminal truncated ones, all removed the GPI anchor
10 sequence.

11 JUDGE FREDMAN: Right.

12 MR. KUSHAN: So the point of this slide is -- just to
13 make clear, if you read the claims broadly to cover inactives,
14 there's a whole bunch of forms of PH20s that are also not
15 described in this patent. So it's not just the active ones are
16 incompletely or not demonstrated possession of it. It's this whole
17 array of different forms of PH20s. It's not homogeneous.

18 I want to touch on a couple of other points. Let's look at
19 Slide 80. So in our petition, we tried to illustrate what they gave
20 us in the form of examples in the patent and what's missing. And
21 what they gave us were single amino acid substitutions in one 447
22 linked protein. All those examples following the red box.

23 JUDGE FREDMAN: That is a fairly large number of
24 examples. You often don't see that.

25 MR. KUSHAN: Yeah. When we were presenting this,

1 we were trying to show that the -- there was not representativeness
2 demonstrated, meaning that they only gave us one type of
3 mutation, one type of length. That's very similar to the Janssen
4 case where you got all the antibody types in one type, right?

5 JUDGE FREDMAN: The Joe-9 case?

6 MR. KUSHAN: Right. And I think what we're trying to
7 show you is that in this array, all those proteins that have varying
8 activities, they're all different. You're going to have different
9 impacts of those. Keep in mind there's only four claimed species
10 actually described. Those are the only four that fall into these
11 claims' scope.

12 You see the growth of the universe of sequences showing
13 -- what we're looking at as a challenge for -- so there's really no
14 -- you don't see much of a fight on representative species. So we
15 see them pivoting over to the common structural feature prong.
16 And here, what they did -- if you can go to Slide 52 --

17 JUDGE FREDMAN: Did you see that you have five
18 minutes left?

19 MR. KUSHAN: Yup. Our experts pointed out there was
20 not any kind of analysis of the mutational data that would
21 demonstrate something looking like common structural features.
22 Let's go to Slide 86. So they come back with the argument that the
23 common structural feature -- they say here in the top left -- the
24 active PH20s share the same characteristic PH20 alpha/beta barrel
25 tertiary structure, including a common active site in the same

1 catalytic residues absent the -- any inactivating changes.

2 So this, again, is very inaccurate. Let's start with the
3 basics. The set of -- in -- by 2012, POSAs would have believed
4 that the enzymatically active proteins had to have several features.
5 They had to have an active site with the correctly positioned
6 residues and also in relation to the substrate binding and have the
7 highly GF that had been shown to be necessary for activity
8 mammalian hyaluronidases. And they would also have to have
9 this unusual alpha/beta barrel motif. It's not a canonical or normal
10 one.

11 So there are several pieces that have to be in this protein
12 in its structure in order to have activity. They haven't identified
13 them all.

14 Go to 93. There's also no mention of anything looking
15 like the alpha/beta barrel motif in their patent disclosure. So
16 they're not identifying this feature as a common structural feature
17 shared by all enzymatically actives. We're not saying they had to
18 use the exact name. There's just nothing in it. There's nothing that
19 can be linked to that region.

20 If you go to Slide 85, they also portray this as something
21 which is, you know, the same tertiary structure as PH20 Hyal-1
22 and bee venom. That is also incorrect. First of all, as Dr. Petsko
23 pointed out, the alpha/beta motif -- barrel motif is only part of the
24 PH20 structure. It's not the whole protein. They're portraying
25 these as tertiary structures. Tertiary structures refer to the whole

1 protein.

2 Next, I mentioned before --

3 JUDGE FREDMAN: They're tertiary structures.

4 They're not all protein.

5 MR. KUSHAN: They're not the whole protein. But
6 generally, the terminology tertiary structure is the whole protein
7 because it's the entire sequence of --

8 JUDGE FREDMAN: The tertiary structure is just now
9 secondary structure, right? The primary structure is the line, the
10 secondary structure the alpha helix or the beta sheets, whatever,
11 the tertiary structure is longer, larger configurations, right?

12 MR. KUSHAN: Generally, the tertiary structure is the
13 structure of the whole protein because it reflects all of the pieces
14 that have folded up in each of the right orientation. You can refer
15 to a fold sometimes informally as being not the whole protein.

16 JUDGE FREDMAN: I see his quaternary structures
17 rather than seeing four proteins together sometimes you're taking
18 just the four parts that actually interact.

19 MR. KUSHAN: Right. So obviously we're --

20 JUDGE FREDMAN: That's multi protein they're saying
21 -- I mean, I don't know that that's unreasonable, but okay go
22 ahead.

23 MR. KUSHAN: The main point is that they're
24 presenting them as the same; and they're not. They're not the same
25 in the whole and they're not the same in the details. That's an

1 important point.

2 If you look at Slide 86. Most importantly, before 2011, it
3 had reported that the active site of these proteins is not in the
4 alpha/beta barrel motif. As I showed you a minute ago, they're
5 portraying it as in the alpha/beta motif. It's not. It's outside of the
6 alpha/beta motif. This is in a paper, Stern, that showed this. And
7 they have not addressed that in their briefing.

8 Another thing that we think is important is that their -- if
9 you go to Slide 89, their experts are using alpha/beta barrel motif
10 at a level of abstraction that is incapable of differentiating the
11 human PH20 version of this thing. And that's important because
12 you have to -- if they're using this as a common structural feature,
13 they have to have enough precision in it.

14 If you look at Slide 63, the Juno case presents something
15 that's directly relevant to this. Juno, the question was, did the
16 phrase scFv provide sufficient written description for the claimed
17 invention? And this is a part of a CAR-T molecule. And the
18 Federal Circuit affirmed a judgment that it was not sufficiently
19 detailed because it couldn't differentiate the scFvs that bound to the
20 CD -- to the target from those that didn't.

21 So it just was a level of use of the term that was too
22 general. And it was incapable of describing the specific structure
23 of those would be claimed.

24 JUDGE FREDMAN: (CROSSTALK).

25 MR. KUSHAN: Right. So that's very similar to what we

1 have here. You have these motifs that are in these different types
2 of proteins. Bee venom is very different. And they're using the
3 word alpha/beta barrel motif to refer to all of them. So it doesn't
4 differentiate the one that's being claimed.

5 JUDGE FREDMAN: You want to go into your rebuttal
6 time or not?

7 MR. KUSHAN: I do. I think I would like just a few
8 minutes of my rebuttal time.

9 JUDGE FREDMAN: All right.

10 MR. KUSHAN: If any of these points, I'm happy to dig
11 into further. As I said before, there's no HyalEGF on their list of
12 common structural features. I want to point out that in their reply
13 -- surrely, they kind of point to the whole protein and say it's an
14 inherent feature, it's in there somewhere. And that's not the level
15 of precision that you have to satisfy to describe a particular motif
16 like this.

17 The reason that's important is that we're talking about
18 amino acid sequences that have to be altered significantly but still
19 preserve this essential structure for activity. And there's no
20 guidance, there's no description of that in the patents.

21 If you could go to Slide 91, you see them pointing to this
22 concept of inherency they say. But it's an inherent feature of the
23 actives that their -- the alpha/beta barrel hold, or they may refer
24 also to the HyalEGF. But it has to be also known in the art.

25 What has to be -- the connection here is that the structure

1 they're referring to that is an inherent feature has to be known in
2 the prior art. It wasn't -- this one, the PH20 alpha/beta barrel motif
3 wasn't solved until 2024 by antigen scientists. So there was no
4 structure that they could say is inherent that gives a connection to
5 this authority they're pointing to. What they're pointing to instead
6 are homology models.

7 So if you go to 103. We talked about this a little while
8 ago. I mentioned before that the homology models don't have the
9 capability of describing accurately what the structure is. There
10 was a PH20 homology model published in Stern. But the Chow
11 paper pointed out it was wrong. And it's because that one was
12 based on the bee venom drug.

13 You can look at, I think, page 820 to 831. They have a
14 description of the homology modeling that's reported in Stern.
15 And the point of this is that in 2006, Chow said, that model, that
16 -- the only one that was known, the only PH20 homology model
17 that was known, was significantly wrong.

18 So if I can just take a couple of minutes to talk about
19 obviousness. Actually, I have a few comments about the
20 tolerability heat map, as I've been calling it Dr. Petsko's map.

21 If you could go to Slide 116. So in fact -- why don't we
22 go to 113? Just so -- this is the thing I keep referring to as the heat
23 map. It's basically a tolerance rating for every position which is
24 built out of the inactive and active mutant classifications in the
25 patent.

1 And the point of this is that they took this model, which
2 is not in the disclosure, and they are portraying it as what the prior
3 art -- what the disclosure would lead somebody to do in -- let's go
4 to 116. What we did was we asked their other expert, Dr.
5 Simpson, that if you took that model, that map that Dr. Petsko
6 created, and you followed it, what changes would you make?

7 We particularly asked about four positions. Would you
8 have tried to change positions 282, 299, 303, and 431 in active
9 proteins? And she said, yes. The problem is that the patent says,
10 do not do that. So what you see is this Petsko map leading a
11 person of skill in the art to move away from what the --

12 JUDGE FREDMAN: If you're reading the patent, you
13 would know not to do that because the patent would tell you don't
14 do those for changes. So that kind of seems a little bit she had not
15 read that portion of the patent to know that.

16 MR. KUSHAN: Right. Our point is that this thing that
17 was -- this heat map, that's not in the patent disclosure. It's his
18 interpretation of it. And relying on interpretation is --

19 JUDGE FREDMAN: But it's sort of implicitly in there
20 right because any of them could generate this based on the data
21 that they gave.

22 MR. KUSHAN: Well, I think what the patent is saying
23 is not as conditional as he's proposing. He's giving kind of these
24 ratings. And that's definitely not in the patent.

25 JUDGE FREDMAN: We're arguing over colors, I

1 guess.

2 MR. KUSHAN: Well, it's kind of getting a qualitative
3 layer on the data that is not in the patent. The patent's pretty
4 absolute with these types of positions. So just very briefly, Rob is
5 -- I want to flag a few points. So the -- 131, please. The '429
6 Patent described and claimed these single amino acid substitutions
7 of the PH20 wild-type protein.

8 So they not only claimed the wild type, they claimed 95
9 percent identical. And they pointed to the single amino acid
10 substitution that said the POSAs would expect they would retain
11 activity if you make the changes in nonessential regions.

12 So we actually went to an expert, Dr. Park, kept him
13 away from the disclosure, said what are those proteins? What are
14 those single amino acid substitutions that are being referenced in
15 this patent? And so he devised a way to figure this out.

16 Go to 134. First, he had to figure out what are the
17 nonessential regions and that simply, he took a -- did a homology
18 model, multiple sequence alignment, found out where the essential
19 positions were. And then he deduced from that the positions that
20 are nonessential. Those are the one -- that's what led him to
21 evaluate those positions.

22 He also used the same model -- 135, please -- to decide
23 which amino acids to consider at these positions. His choices
24 weren't anything other than the MSA telling him, start at the top
25 and go with the most frequently occurring amino acids. So he

1 used this as the reason to look at particular substitutions. It came
2 from his MSA.

3 JUDGE FREDMAN: (INDISCERNIBLE) mutations,
4 you're arguing in your description argument, there are, you know,
5 obviously 19 changes that you could potentially make, but we're
6 looking at every possible alternative, thousands of possibilities in
7 the situation. I mean it seems that you're saying picking 320 or
8 whatever, for the other cases going to be different numbers, but
9 what -- why is this not just the (INDISCERNIBLE) situation?

10 MR. KUSHAN: So by using the MSA to filter choices,
11 it's taking it down from the universe that they're claiming from 19
12 choices at every position to a very small number at every position.
13 And so by -- and he was using this technique --

14 JUDGE FREDMAN: Isn't that from your own data?
15 That's not 100 percent predictable either so --

16 MR. KUSHAN: No, it's not. No. I didn't --

17 JUDGE FREDMAN: So that's just your --

18 MR. KUSHAN: And --

19 JUDGE FREDMAN: -- maybe. Maybe the factor is one
20 of the ones you think wouldn't work, would work.

21 MR. KUSHAN: If you see what Dr. Park explained --

22 JUDGE FREDMAN: You could have it argued both
23 sides.

24 MR. KUSHAN: Well --

25 JUDGE FREDMAN: Your argument is somewhat

1 inconsistent. You can see that I'm sure.

2 MR. KUSHAN: So what we pointed out in the petition
3 was that one amino acid difference can be assessed with some
4 level of an assessment around the local environment. You still
5 don't have that certainty. You're right. That's why none of our
6 experts are saying they predict how much activity will be retained.
7 They just say, I don't see anything going wrong at that position.
8 And that's all he did with his assessments.

9 But I want to make sure you leave us -- I'm going to
10 leave us with this point that -- go to 140, please -- there was no
11 bias or -- this is what he did. He looked at all these positions and
12 evaluated many or several of these MSA-dictated sequences or
13 substitutions at each position.

14 So I'm going to stop there. I'm happy to cover any
15 questions in rebuttal.

16 JUDGE FREDMAN: Thank you very much.

17 MR. HACKMAN: And Your Honor, given that Mr.
18 Kushan went over a little bit, I think I'd like to reduce my rebuttal
19 time to 10 minutes, if that would be okay.

20 JUDGE FREDMAN: Sure.

21 MR. SUMMERS: May it please the Court, we do have
22 physical copies of our slides if that would be helpful to you that
23 we'd be happy to hand up. So I just want to give you a brief
24 roadmap to what I will be talking about today. I want to do a brief
25 introduction to the invention. Petitioner didn't discuss much of the

1 invention here.

2 And then I'll discuss claim construction and cover why
3 under a structural construction Petitioner's 112 arguments fail.
4 Then I want to spend the bulk of my time under the board's claim
5 construction that the claims require enzymatic activity,
6 hyaluronidase activity. I want to address that question. And
7 specifically, I want to address for both written description and
8 enablement. I want to focus on why the full scope of the claims is
9 described, enabled, including for multiple modifications.

10 As part of this, I'll separately address the issue of
11 modified PH20 polypeptides as a contraceptive. And then I'll
12 address why the claims are nonobvious.

13 Throughout the presentation, as we previewed on the call
14 with the Board, I'll largely refer to the '600 Patent. This Petitioner
15 and their argument did not raise separate issues as to those claims.

16 Go ahead and go to Slide 7, please. So Your Honors, I
17 want to talk briefly about the D320 discovery and focus on the
18 invention here. The '600 Patent is limited to modified PH20
19 polypeptides with a substitution at one specific position in the
20 amino acid sequence of PH20, position 320.

21 Now, Petitioner, at the beginning of their argument,
22 focused on the fact that the claims are not restricted. He said, to
23 any position except for one. Well, the one is the invention, the
24 D320 invention. And specifically it's one of four amino acids that
25 must be substituted there, H, K, R, or S.

1 So you heard a lot of talk about the 95 percent identity
2 limitation. But you don't get to that limitation, which is really a
3 limitation that requires similarity to that structure that's claimed,
4 unless you're already practicing that D320 mutation.

5 The inventors here did not claim by function. They did
6 not claim, for instance, all hyaluronan-degrading polypeptides.
7 They didn't even claim all modified PH20s that are within 95
8 percent identity to the sequences recited.

9 The inventors restricted the claims here to the D320
10 mutation at four positions and then required similarity to that
11 structure. We're going to see in Hashimoto that similarity to a
12 common structure, that is a common structural feature. And it
13 does provide a structure function correlation.

14 Hashimoto is very clear about that. It says, we don't
15 require identity to structure. We don't worry about perturbations
16 out in a secondary structure that aren't affecting -- we require
17 correlation. So I want to talk more about that.

18 Now, all four of those are cited amino acid substitutions
19 at position 320 improve the activity with the K mutation that I've
20 highlighted here on the slide, improving it over sixfold. The
21 values in these tables, you see it's 6.42. That's an over 600 percent
22 increase in activity.

23 And this was completely unexpected. Petitioner in their
24 obviousness argument referenced that they're using the '429 Patent
25 as motivation. Well, what it says there is that if you make a

1 conservative substitution, you expect to maintain biological
2 activity. That's not what happened. You got a 600 percent
3 increase here. So I want to say the inventors saw radically better
4 hyaluronidase activity.

5 Now, they discovered the D320 mutation through an
6 unprecedented comprehensive and systematic analysis of PH20
7 structure. What they did -- if you go to Slide 8 -- Petitioner
8 referred to this as the heat map. This is just the patent's
9 mutagenesis data imported into spreadsheet and helpfully color
10 coded.

11 The patent's data is actually much more granular. He
12 referred to it sort of adding a sort of value-based layer. But the
13 patent's data is actually much more granular than what we see here.
14 Because what they did was they mutated at every single position in
15 a mature soluble active PH20 sequence, seq id number three.

16 It's mutated with 18 amino acids at some positions -- they
17 used all 20 -- and then tested for activity compared to wild type.
18 There's a mean of 14 substitutions and a median of 15. That's at
19 Petsko, paragraph 263 and 264.

20 So what you're seeing is that patent's mutagenesis data.
21 And Dr. Petsko color coded it. The dark green there, that -- those
22 are positions that tolerated every single substitution. The ones that
23 are in dark red, they tested no tested substitutions. The ones in
24 light green, greater than 90 percent of the substitutions. And the
25 ones that are in orange, less than 30 percent. Then you see there's

1 a few in the middle between those values.

2 JUDGE FREDMAN: Does that really give you any
3 information about what would happen if you do two mutations? Is
4 --

5 MR. SUMMERS: There are some limited examples of
6 double mutants, but not in this patent mutagenesis data.

7 JUDGE FREDMAN: Right.

8 MR. SUMMERS: So --

9 JUDGE FREDMAN: Well, I'm taking it -- the question
10 I'm asking is, can you just point to the evidence that would show
11 that that matters in terms of whether you have a second mutation
12 or a third mutation, fourth mutation, or fifteenth mutation?

13 MR. SUMMERS: That the patent's mutagenesis data
14 allows you to make its --

15 JUDGE FREDMAN: This will allow you to then say
16 that -- I think a knockout would generally knock it out. Even with
17 more mutations, obviously, you could have (INDISCERNIBLE)
18 mutations, right?

19 MR. SUMMERS: I'm sorry, I'm having a little bit of
20 trouble hearing you, Your Honor.

21 JUDGE FREDMAN: I'm talking about just where you
22 would have -- essentially, your argument is that -- I mean, we have
23 all this data for single mutations. I'm asking how that applies to
24 multiple mutations.

25 MR. SUMMERS: Sure. So I think you heard Petitioner

1 make reference to the fact that in the first instance, there's an
2 agreement among the parties that up to five mutations is
3 predictable here. And that comes from Dr. --

4 JUDGE FREDMAN: I mean, they say that. But
5 personal experience, that wasn't true, both as an examiner and in
6 an actual lab. I mean, I think there's a question, right, of how
7 predictable this is. I mean, I -- do you have any evidence other
8 than statement by experts that it would have been predictable to
9 make a second mutation in any of these conditions?

10 MR. SUMMERS: And maybe I need to discuss with you
11 what you mean by predictable, Your Honor. But we do have
12 evidence that these are, in fact, predictable. And we can talk about
13 some of the evidence that they rely on for unpredictability as well.

14 So for instance, the Powell (PHONETIC) paper that's
15 cited by Petitioner as supposedly showing sort of this
16 unpredictable epistasis. That's Exhibit 1137. The Powell paper
17 that discusses the fact -- actually, a very small protein, 30 amino
18 acids. And they made four -- they identified four beneficial
19 substitutions. And then they went and they additively added those.

20 The first three were additive in actually a predictable
21 way, in an additive sense, that they actually increased by the
22 amount that each one increased. When they got to the fourth, that
23 fourth one just didn't do anything anymore. So when we're talking
24 about unpredictability, what we care about for this patent is
25 retaining enzymatic activity. It doesn't require you to predict a

1 particular level of activity. It just requires you to maintain --

2 JUDGE FREDMAN: (CROSSTALK) contraceptive --

3 MR. SUMMERS: Under the Board's -- I'm already

4 speaking under the Board's construction, Your Honor --

5 JUDGE FREDMAN: We can accept both arguments at

6 least. So would a contraceptive activity also be equally

7 predictable?

8 MR. SUMMERS: Contraceptive activity would be also

9 predictable but for different reasons there. And I'm happy to talk

10 about -- Your Honors made reference to the antigenic

11 determinants. I can talk about that now or I can do that later.

12 JUDGE FREDMAN: Okay. However you want to do it.

13 MR. SUMMERS: Okay. So let me continue on here

14 briefly. So -- if we can go to the next slide. Now, this data from

15 both of our experts have noted that this is virtually unheard of. As

16 Dr. Petsko here testified, I am not aware of a comprehensive

17 mutagenesis study like this for any human protein of comparable

18 size. This is a vast amount of data.

19 So I take Your Honor's point that for some proteins,

20 things appear to be predictable because you don't have

21 mutagenesis data like this. It's just very rare in the art that you

22 would have somebody go across every single position in the amino

23 acid sequence and make substitutions and find out what it's doing.

24 It's teaching you a structure function correlation between each of

25 those positions at the most granular level.

1 So I want to actually hand something up at this point. It's
2 Appendix B11. It's from --

3 JUDGE FREDMAN: Is that on the record?

4 MR. SUMMERS: It is in the record. It's at Exhibit
5 1133. That's the Naismith report. And it's Appendix 11. This is
6 Petitioner's expert.

7 JUDGE FREDMAN: Yeah. But what page is the record
8 --

9 MR. SUMMERS: Yeah. It's PDF pages 355 to 357.
10 And it's cited by Petitioner Reply 33. And then we dealt with
11 these issues. So I just wanted -- I want to show this briefly. So
12 Petitioner's expert, Dr. Naismith, they submitted a 250-page expert
13 declaration on reply.

14 And Petitioner's expert -- in this appendix, what he did is
15 if you see on the left, that's Dr. Petsko's mutagenesis data color
16 coded on the left. And then if you see on the right, you see the
17 prior art confirmed essential residues. And so where you see an X
18 there, that's where something was known in the prior art about one
19 of the residues here.

20 And then when you -- the Petitioner referred to Dr. Park's
21 analysis. When you see that middle column --

22 JUDGE FREDMAN: For my colleagues that's page 23
23 of the (INDISCERNIBLE).

24 MR. SUMMERS: Thank you, Your Honor.

25 JUDGE FREDMAN: Okay.

1 MR. SUMMERS: Apologies if I'm going too quickly.

2 JUDGE FREDMAN: No, that's fine.

3 MR. SUMMERS: So if you look then in the middle
4 column, you see Dr. Park's essential residues. That's identified by
5 Dr. Naismith. These are the ones that Dr. Park identified in the
6 obviousness analysis that Mr. Kushan referred to.

7 And what I want you to focus on here is look back out
8 and look at all of that white, compared to what you actually have
9 here. For most proteins, you might have some essential data here.
10 You have data once you have the patents disclosure at all of the
11 447 positions.

12 So I was surprised to hear Petitioners say that he's now
13 disputing that you could make up to five changes. I just want to
14 direct you to Exhibit 1004. That's the Park declaration at 162,
15 where he said that these models that we're going to get into, they
16 could be used to reliably predict the effects of five or so.

17 Dr. Naismith then said, I agree with Dr. Park and Dr.
18 Hecht that after about five mutations, a POSA could no longer
19 predict enzyme behavior by simple linear combinations of single
20 site mutations. Now, he's putting a little caveat of that. He's
21 saying we can do five. And then the linear part of this gets a little
22 bit hairy. And that's because what they're talking about is really
23 predicting a specific level of activity.

24 There's no evidence in this record that the sort of
25 mutations we're talking about are going to abrogate enzymatic

1 activity. To the extent you construe these claims to require
2 enzymatic activity, that's what they would have to show. They
3 would have to show that the epistasis that Mr. Kushan talked about
4 actually abrogates enzymatic activity, talk about why that's not.

5 If we go to Slide 9. Back to Slide 9. So Dr. Petsko said,
6 this is an unprecedented amount of data. And I want to make one
7 more point. You asked for more evidence on why this is
8 extremely important, these single substitution mutations.

9 Again, I want to use the Dobson paper that was cited
10 throughout Dr. Naismith's. That's Exhibit 1138. And the Dobson
11 paper is a paper where they've cited to it as allegedly evidence of
12 epistasis that would affect folding. It's Exhibit 1138. You're fine,
13 just stay on the PASCO site.

14 So for the Dobson paper, the Dobson paper says -- and
15 this is a paper that's investigating epistasis in relationship to
16 folding. It says the most important experimental strategy in
17 investigating folding and unfolding has been to use site-directed
18 mutagenesis to probe the roles of individual residues in the folding
19 process.

20 And they explain why. So Dobson says, in the art at the
21 time, what was understood is that proteins take a rudimentary
22 shape early on in their process due to a certain set of residues,
23 right? So it goes on, it says, it appears that this topology can result
24 from the acquisition of a native-like environment for a very small
25 number of key residues that constitute the core of the folding

1 nucleus and natural proteins.

2 In essence, these interactions force the chain to adopt
3 rudimentary native-like architecture. And this is the key part.
4 We're talking about identifying just those essential residues to
5 folding. Once this topology has been achieved, the native structure
6 is almost invariably generated when the remainder of the protein
7 coalesces around the nucleus.

8 So if you remember that messy chart that was shown
9 there with all the folding and misfolding, when it comes to
10 distinguishing between actives and inactives and what's going to
11 fold and what's not, single site mutagenesis data is the most
12 valuable thing that you can have. That's from their own paper.

13 JUDGE FREDMAN: I mean, that might be an
14 overstatement. There are proteins like RNase that can certainly
15 fold when they've been denatured. Lots of proteins are very
16 helpful in other proteins like HSPs and things to fold properly.
17 Your protein is embedded in the membrane. So it particularly will
18 require that.

19 MR. SUMMERS: But I think I'm just talking about the
20 value of the mutagenesis data here, Your Honor.

21 JUDGE FREDMAN: Sure.

22 MR. SUMMERS: And the value of knowing -- having a
23 POSA know from that mutagenesis data where those essential
24 residues are in structure, which ones are going to be necessary to
25 getting to that state.

1 Now, I want to move on. I'm going to come back to why
2 that allows you to multiply, mutate and answer your question even
3 more fully about why it's not just experts say so here, why there's
4 actually quite a lot of agreement about the reliability of that model.
5 But let me first go through claim construction, if I may?

6 JUDGE FREDMAN: Yes.

7 MR. SUMMERS: So let's go to Slide 11. We've talked
8 about the fact that these claims define the invention by structure. I
9 want to talk about it for two reasons, one, it's actually a quite
10 critical distinction between the cases that Petitioner relies on. So
11 Petitioner made a reference to AbbVie. AbbVie, those are
12 functionally bounded claims. There isn't a structure there that
13 bounds them. They are bounded by, for instance, binding to IL-12.

14 Similarly, in Ariad, what you had was the discovery of a
15 unique process but no way of actually inhibiting that process as
16 was recited in the claim. It's a functionally bound claim. And
17 because it's functionally bound claim, you don't know what's going
18 to get you there based on the claim. That's true of Amgen as well.
19 We'll get into that when we talk more about enablement.

20 But here, we have structurally defined claims. There's no
21 question about that. There is a structural boundary on these
22 claims. And to the extent Your Honors read function into them,
23 what we're talking about is distinguishing within that structurally
24 defined claim what's active and inactive.

25 That is a substantial difference from this case law. It

1 puts it here on all fours with cases like Hashimoto and Wands
2 rather than AbbVie and Ariad and Amgen.

3 JUDGE FREDMAN: Wands is enablement.

4 MR. SUMMERS: Wait, say that again.

5 JUDGE FREDMAN: Wands is enablement.

6 MR. SUMMERS: Yes, that's -- I -- for enablement. As
7 to Wands, yes.

8 JUDGE FREDMAN: Okay.

9 MR. SUMMERS: I totally agree with you. We're quite
10 fond of Wands for enablement. And quite frankly, we like the
11 language in Amgen. It's quite directed to much of what
12 Petitioner's arguments are here.

13 If we go to Slide 15. Your Honors asked at the
14 prehearing conference what intrinsic evidence was in the record
15 about the claim construction. I think you're probably aware of this
16 already, but Petitioner's construction that would require 40 percent
17 or even requiring some level of activity, it really cannot be squared
18 with this language here. Provided herein are modified PH20
19 polypeptides that contain one or more amino acid replacements in
20 a PH20 polypeptide that are inactive, whereby the polypeptides --

21 JUDGE FREDMAN: It can't be entirely structured,
22 though. Because I mean, essentially, to satisfy, say, one part of
23 enablement, you have to have a use.

24 MR. SUMMERS: You always need to --

25 JUDGE FREDMAN: You just have to be either, right?

1 In your case, unless you're going to come to a third use that I'm
2 unaware, either hyaluronidase activity or contraceptive.

3 MR. SUMMERS: I --

4 JUDGE FREDMAN: There's not a third use, right?
5 Essentially, even to the extent that you want to argue that, well, the
6 claim does require hyaluronidase activity, which I think is a strong
7 argument based on the statements in this patent. There is some
8 requirement, just some --

9 MR. SUMMERS: Your Honor, I agree that there must
10 be articulated a utility in the specification that is consistent with
11 this full scope of the invention. And that is actually present here.

12 If we can go to Slide 28. There is more intrinsic
13 evidence in the record. I'd be happy to address it. For instance,
14 there's a clear statement in the specification that PH20s are
15 different than modified PH20s. Those are in the slides.

16 But I just want to direct you now to your question, Your
17 Honor. What here is the standard? So the parties debated between
18 the Boehringer 1 and the Boehringer 2 case. And if you're familiar
19 with those cases, in the Boehringer 1 line of cases, the claims were
20 interpreted to require an antigenic effect. And that was based on
21 one of the functions recited in the specification.

22 In the second Boehringer case, the claims were not
23 interpreted to have a function. They were structurally defined 10
24 percent to the open reading frame of a porcine circovirus. And
25 there, they didn't have any mutagenesis data actually in that

1 specification. It's a distinction with Boehringer 2.

2 But what was found in Boehringer 2 is Petitioner's
3 section 112 argument improperly focuses on certain functional
4 characteristics disclosed in the specification that are not recited in
5 the challenged claims and therefore lack sufficient merit in the
6 context of the claims. And that's the error at the heart of
7 Petitioner's 112 arguments.

8 If these claims are construed to be structure only if you
9 don't import a function improperly from the claims. Because what
10 you need here is you need to show that you can make the structure
11 and that there is a utility consistent with the full scope of the
12 invention.

13 And for both actives and for contraception, we've shown
14 that. It's scientifically credible, for instance, that contraception is
15 able to do that. That's from *In re Brana*, 51 F.3d 1560 at 1566.

16 JUDGE FREDMAN: Brana's a pretty famous case.
17 You say that -- I guess, the best evidence, really, on contraception
18 is unfortunately for you, I think DeLeon, okay? DeLeon is a paper
19 that says, you know, at the time of invention or before that data
20 from non-primate and primate models with PH20 ineffective for
21 inclusion in immunocontraceptive vaccines. It's an expressed
22 statement in a reference that doesn't work as balanced against any
23 expert who's going to -- you know, I don't want to say motivated
24 reasoning but they're experts --

25 MR. SUMMERS: Your Honor, I don't think it's

1 motivated reasoning that DeLeon --

2 JUDGE FREDMAN: I mean for both sides, not --

3 MR. SUMMERS: Yes. And I understand that, Your
4 Honor. No offense taken whatsoever. We took on all those
5 papers, including DeLeon. And we took on the individual papers
6 in that summary. We submitted a declaration from Dr. Sher.
7 Now, he's an expert in reproductive biology and was in fact
8 working on PH20 at the time. And he was surprised to learn --

9 JUDGE FREDMAN: But the only evidence for it
10 working at the time was the guinea pig. And that does seem to be
11 a sterility type operation where you're causing inflammation that
12 sterilizes animals.

13 MR. SUMMERS: Dr. Sher doesn't believe that that was
14 the ultimate effect from there. So let me first direct you just to
15 where Dr. Sher took on these papers that are in the DeLeon
16 reference. It's from paragraphs 44 to 56. He took on that DeLeon
17 reference and the other references. What happened in those others
18 is that they were looking at serum-based studies.

19 And what we did after institution is a change in the
20 record here is we put in a declaration from Dr. Sher discussing
21 those papers and what they would show to a POSA, which is
22 serum-based routes are not going to work.

23 JUDGE FREDMAN: You're sharing his deposition. I
24 think this is at page 38 of the deposition, Exhibit 1129 is that there
25 was epididymitis -- I'm probably saying that wrong -- and orchitis

1 in the test there was massive inflammation. And that was what
2 was deemed to be responsible for the contraceptive effect rather
3 than the sort of antibody binding cells. So that suggests to me that
4 it was not a reversal of contraceptive effect.

5 MR. SUMMERS: I think that's a summary of the
6 statements in those papers, not how a person of ordinary skill in
7 the art would take that from (INDISCERNIBLE). Let me address
8 actually this -- excuse me, sorry, go ahead.

9 JUDGE FREDMAN: I was just thinking he said that.

10 MR. SUMMERS: Yeah. So let me take on specifically
11 what was shown in these declarations. So first of all, I want to
12 focus on the fact that with 95 percent identity, you expect to
13 preserve most epitopes. I'm aware Your Honors expressed some
14 concern about retaining the antigenic determinants in the
15 institution decision.

16 Dr. Moon shows that POSAs expect antibodies to
17 sufficiently preserve --

18 JUDGE FREDMAN: But that's really not entirely true
19 for 15 amino acid changes, right? Because you could easily have a
20 situation where the epitope is that exact location and that's totally
21 gone because it's an entirely different epitope, right? And so that
22 can't be entirely true at all.

23 MR. SUMMERS: Yup. Yeah, that's true. And we took
24 that on -- so specifically, Dr. Sher talks about what was known
25 about antisperm antibodies. And the issue here and I think the

1 confusion here is that for antisperm antibodies you're not looking
2 for an epitope that's specific to contraception. It's not like a virus
3 where you need to interrupt the mechanism by which it's entering
4 the cell or something.

5 So he talks about the fact that it's well-known with
6 antisperm antibodies that you could allosterically hinder them,
7 right? They have a long journey to make it and actually the most
8 fit must make it up.

9 So Dr. Sher at paragraphs 32 to 34 in Exhibit 2072, he
10 cites Exhibit 2114, that's Franke. And that talks about how
11 antisperm antibodies interfere with agglutination or cause
12 agglutination; Exhibit 2117, Kramer, that it interferes with the
13 Sperm's path through the mucosal membrane. That's also in 2116,
14 that's Changwei (PHONETIC).

15 So what's happening here is you just need to get these
16 polyclonal antibodies onto the sperm. You don't have to get them
17 necessarily in one specific place. And once you've done that --

18 JUDGE FREDMAN: (CROSSTALK) understand how
19 these are being used. Are these being used as like an additional
20 item that you're adding -- you're implanting into the woman,
21 essentially, I'll say?

22 MR. SUMMERS: They would be used for female
23 contraception via a mucosal or out of administration, yes.

24 JUDGE FREDMAN: So these are -- sorry, I didn't quite
25 understand that. So these contraceptives, they're not injecting the

1 male guinea pigs, which is what's happening in the reference.

2 MR. SUMMERS: That's right, Your Honor. That's what
3 distinguishes it from those DeLeon papers is that --

4 JUDGE FREDMAN: So what you're proposing is that
5 they -- if they have a reservoir, the antibody isn't in a person or in
6 an object. And it prevents the sperm from progressing.

7 MR. SUMMERS: That's right.

8 JUDGE FREDMAN: Okay.

9 MR. SUMMERS: Yeah. And there are a number of
10 different contraceptions that actually work in that way, right,
11 sponges or cups, many things that actually just will physically
12 hinder sperm from moving up the canal.

13 JUDGE FREDMAN: Right.

14 MR. SUMMERS: So with that, I want to move back
15 now to our discussion why --

16 JUDGE FREDMAN: Is that in the specification? Is
17 there anything like that in the specification?

18 MR. SUMMERS: There's not a discussion specifically
19 of inhibiting the antisperm antibodies in that way. It's
20 acknowledged that that's in the prior art.

21 JUDGE FREDMAN: The spec is solely contraceptive
22 vaccine I think; is that right?

23 MR. SUMMERS: It refers to is as a contraceptive
24 vaccine. And that is what we're talking about is administering how
25 --

1 JUDGE FREDMAN: But it's not the same thing. A
2 vaccine would be presumably subcutaneous administered to the
3 male, right? I mean, this-- what you're talking about is almost a
4 barrier method. They're different things, I think.

5 MR. SUMMERS: They aren't because what we're
6 talking about here is a mucosal route of administration that
7 generates polyclonal --

8 JUDGE FREDMAN: Do you have any -- in the spec, is
9 there any discussion of the mucosal route?

10 MR. SUMMERS: There is a discussion. I can find that
11 for you, Your Honor.

12 JUDGE FREDMAN: (INDISCERNIBLE)?

13 MR. SUMMERS: Not necessarily for contraception, but
14 it discusses administering PH20 through mucosal administration.

15 JUDGE FREDMAN: But that would be for like an
16 intruder, like an antibody. And I'm talking about, for
17 contraceptive, is there any disclosure of that?

18 MR. SUMMERS: Not specifically to contraception,
19 Your Honor, no.

20 JUDGE FREDMAN: So there's no disclosure of this
21 idea of using the antibody as a barrier method of contraceptive --

22 MR. SUMMERS: It's --

23 JUDGE FREDMAN: It's only touted as a vaccine.

24 MR. SUMMERS: Yeah. It's not a barrier method that
25 we're talking about. It is an immunocontraceptive. That is --

1 JUDGE FREDMAN: That's a problematic argument.

2 I'm going to just -- go ahead.

3 MR. SUMMERS: Okay. And I think Dr. Sher explains
4 why that was an understood antisperm antibodies via --

5 JUDGE FREDMAN: Yeah.

6 MR. SUMMERS: -- mucosal administration were
7 known to sterically hinder them. So let me now turn back to
8 -- under the -- under Your Honor's construction. Why -- if you are
9 to construe the claims to have some hyaluronidase effect, you can
10 make multiple mutations with reliable predictability.

11 Like I say, under your construction, I'm going to talk
12 both to written description and enablement here. But if there are
13 specific questions as to one or the other, we'll break them out.

14 So if you can go to Slide 35. As Your Honors noted, the
15 key dispute between the parties is whether single mutations can
16 reliably be used to predict multiple mutations, such that a person of
17 ordinary skill in the art can distinguish actives from inactives and
18 can reliably practice the invention without undue experimentation.

19 You can go ahead and go to the next slide. So Dr. Petsko
20 was asked about this at deposition. Portion of the genus that is
21 reflected in the dataset is a tiny, tiny fraction of that genus. This
22 is on Slide 36. Apologies, I said next slide. A portion of that
23 genus is a tiny, tiny fraction of that genus, referring to the single
24 mutants because the multiple mutants are larger genes there, he
25 said.

1 The real question is what about the informational
2 content? The informational content of that particular set of
3 substitutions, those single amino acid substitutions is enormous.
4 When combined with the structural information from modeling
5 PH20 structure, it allows you to visualize and make predictions
6 much more the data set than what you see here.

7 We can go to Slide 37, please. So Petitioner frames the
8 question about whether you can predict multiple substitutions from
9 a single substitution. You can see that visually on the slide here.
10 This is the chart that was reproduced in the institution decision
11 showing that all the single mutants are up there in the upper left-
12 hand corner.

13 JUDGE FREDMAN: So indeed, all the data in the slide
14 on the right is in that little red square on the left.

15 MR. SUMMERS: All of the mutations that were made --

16 JUDGE FREDMAN: All the mutation data to the --

17 MR. SUMMERS: All of the mutants that were made are
18 in that left hand square material. On the right, though, what you
19 have is the mutagenesis data for PH20. And that's across the full
20 structure of these. So the idea that you have no information about
21 any of the rest of this view isn't correct because what you have is a
22 rich amount of information for making these substitutions using a
23 rational protein design approach.

24 Petitioner, when they filed their petition, they said,
25 POSAs practice designing proteins in one of two ways. And

1 Petitioner referred to the sort of screening approach. They said
2 and they went on quite at length from 13 to 14 in their petition
3 about why you would take a rational protein design approach.

4 Now, Petitioner made much of that AbbVie warning that
5 a claim can't have functional boundaries specifically in reference
6 to this. We can go to the next slide.

7 JUDGE MITCHELL: Can I ask you a question?

8 MR. SUMMERS: Yes.

9 JUDGE MITCHELL: So can you address Mr. Kushan's
10 statements about the state of the art at the time, like being able to
11 take this information on single substitutions and how one of skill
12 in the art would have then translated that into making enough of
13 the proteins so that it would look -- you would possess what's
14 claimed.

15 MR. SUMMERS: Sure. So if you don't mind, Your
16 Honor, I'm going to hand up a second exhibit from the Naismith
17 appendix. Again, this is Exhibit 1133, Appendix B12. It's PDF
18 pages 358 to 360. And this is a document titled compilation of
19 citation on conventional tools and techniques from the experts.

20 JUDGE FREDMAN: Wait a minute, she --

21 MR. SUMMERS: Again, this is from Petitioner's own
22 materials. So you can see there's a leftmost column that Dr.
23 Naismith, Petitioner's expert, put together here titled POSA
24 knowledge in 2011. And I just want to walk you through some of
25 these as the underlying basis. It's agreed that this is what a POSA

1 would do.

2 He says, sequence alignments and structural information
3 found in the prior art, such as Chow, would guide the identification
4 of residues suitable for modification. And then there's supporting
5 expert testimony cited next to it.

6 So there's no dispute between the parties here that people
7 would use mutagenesis data, things that they can find and say there
8 was a mutation, I think that I can practice it or not if they're an
9 essential residue. If you go to them --

10 JUDGE FREDMAN: The problem is that -- I mean,
11 unless the protein -- unless you have the complete structural
12 information, the tertiary structure, there is some level of
13 unpredictability amount in that. I mean, for example, if you look
14 at polymerases, you can change a DNA polymerase in -- I think it
15 was a virus -- I can't remember which virus I worked on, but with
16 single amino acid change in the main, you know, conserved region
17 from a DNA to RNA polymerase. So changes -- single changes in
18 conserved regions that you think maybe don't matter or do matter,
19 it is still unpredictable.

20 MR. SUMMERS: Right. But you've tested them here.
21 You've gone across the protein --

22 JUDGE FREDMAN: Even whether you tested them to
23 find one mutation change, it doesn't tell you what's going to
24 happen when you make the mutation next to this change.

25 MR. SUMMERS: Let me get to that. And if you'd like,

1 I can just go to how Dr. Petsko walks through a POSA would
2 -- using these techniques here would do that.

3 JUDGE FREDMAN: Sure.

4 MR. SUMMERS: So let me just -- let me finish on the
5 leftmost column because I think this is the basis for what Dr.
6 Petsko is doing. And I was actually quite surprised to hear
7 Petitioners say we don't have a reliable model here. Because the
8 POSA knowledge on that second page includes the crystal
9 structure of Hyal-1 described in Chow.

10 It was the best template to generate a PH20 structure
11 homology model. So the model that you're going to see that Dr.
12 Petsko used -- and actually that Dr. Park used -- to evaluate
13 substitutions, that's based on that model. If you look down at the
14 next one, homology models are important tools for evaluating
15 substitutions. That's, again, something that's agreed on between
16 the parties. As a matter of fact, POSA's expert testified that you
17 would be expected to evaluate that model.

18 And then the next line down, the next entry down,
19 POSAs would be able to generate reliable PH20 homology models
20 using Swiss model. And that's what's been done here. It's exactly
21 what Dr. Park did. It's exactly what Dr. Petsko did. And available
22 sequence alignment information.

23 Now, reliable. They would be able to generate reliable
24 PH20 homology models. I heard Petitioners say, well, maybe this
25 model is actually not so reliable. And I take it that might be -- but

1 I disagree with that. And I think their expert said right here that he
2 disagrees with that.

3 A POSA would examine residue interactions using e.g.
4 PyMOL to evaluate substitutions. That is exactly what Dr. Petsko
5 has done here.

6 Let me walk you through what Dr. Petsko did now to
7 address specifically this question of multiple mutations and how a
8 POSA would go about it. This is based on the scientific evidence
9 in the patent. It's a huge study of the effect of each of those
10 mutations on the structure, how it affected enzymatic function.
11 That is the scientific data we have here.

12 You can go ahead and go to Slide 39. So we talked
13 about that mutagenesis data. All you're seeing here is a
14 visualization of that on the structure. We're not saying that you
15 can generate a homology model reliably putting in 20 changes into
16 the sequence and then putting it into the homology modeling and
17 seeing what you get out. That's not our contention here.

18 What Dr. Petsko did do is use PyMOL, as we just see, to
19 actually just color code where on the structure, the places that
20 tolerated all substitutions are. And then if you look in the interior,
21 that tightly packed hydrophobic core, where those substitutions
22 that didn't tolerate substitution.

23 And for the most part, you see that those that tolerated all
24 substitutions, those are along the surface of the protein. And those
25 red, those -- the ones that didn't tolerate substitution, those are in

1 that tightly-packed hydrophobic core. This is structure function
2 information. Petitioner calls this evidence of epistasis or evidence
3 of unpredictability. This makes making mutations to this protein --

4 JUDGE FREDMAN: This is generated information
5 based on that. This wasn't in the specification, right?

6 MR. SUMMERS: This is an undisputed practice about
7 what a POSA --

8 JUDGE FREDMAN: I'm not arguing it's not a practice.
9 I'm asking, this is -- these images are --

10 MR. SUMMERS: These images are generated.
11 Absolutely, yes, Your Honor.

12 JUDGE FREDMAN: Not from the specification, right?

13 MR. SUMMERS: These are the data from the
14 specification. Visualized as a POSA would visualize them. The
15 figures that you're seeing here are not from the specification. That
16 is absolutely true.

17 JUDGE FREDMAN: (CROSSTALK).

18 MR. SUMMERS: Yes. So what Dr. Petsko did is he
19 showed -- for instance, at those green spheres along the surface of
20 the protein where all tested substitutions were, there were 43 of
21 them. And similarly, all or most substitutions were tolerated at
22 158 of the positions. Actually, it's undisputed between the party
23 over 200 --

24 JUDGE FREDMAN: I'll be honest, visually, it doesn't
25 look like 43 of them are green. It seems like it's much more.

1 MR. SUMMERS: Let's maybe go to the next slide to
2 make sure we don't get off on that. So you see here on the left, this
3 is showing 43 positions that tolerated all tested substitutions. And
4 then what happens here in the middle column, Dr. Petsko just
5 filled in. So now we're looking at positions that tolerated 90
6 percent or greater of the tested substitutions.

7 And you can see, as you would expect, that they start to
8 fill in across the surface of the protein. And then there's 158
9 positions total that tolerated 60 percent of the tested substitutions.
10 And what you're seeing is that green sphere format is just
11 PyMOL's way of visualizing that data.

12 JUDGE FREDMAN: So the green spheres are only the
13 ones that are -- only the 43.

14 MR. SUMMERS: The green spheres on the far left are
15 only the ones -- those are the ones that tolerated all tested
16 substitutions.

17 JUDGE FREDMAN: Right. But as I look at this, for
18 example, we have the alpha helix on the bottom right -- oh, that
19 was in the top left image, right, on the 43. There is an alpha helix
20 on the bottom right. That would have a number of amino acids.
21 But they're not shown because none of them were tolerated. So we
22 really -- I mean, it's interesting because you're showing this in sort
23 of mixed mode, right? Usually, when you see these sort of fill in
24 modes, you see all of the amino acids. And here, you're only
25 showing us a very small fraction of amino acids.

1 MR. SUMMERS: Let me take you to Slide 62. I think
2 that it's useful to look at it in this way, in this mixed mode because
3 -- and that's not something special that was done with the program.
4 It's useful to look in this mixed mode because you can see that
5 interior core and specifically --

6 JUDGE FREDMAN: Sure, but --

7 MR. SUMMERS: -- you can see where they're at. But if
8 I take you to Slide 62 -- you can look at it.

9 JUDGE FREDMAN: Where is --

10 MR. SUMMERS: So this is where it's filled in
11 completely. And you can see based on the crystal structure, they
12 have the HA tetramer there in the active site cleft -- in the active
13 site cleft.

14 JUDGE FREDMAN: And so presumably, there's lots of
15 parts that are also in problems, at least for the 43 side, that are not
16 visible because they're buried in the three-dimensional structure.

17 MR. SUMMERS: Right. So if you were to look -- and
18 Dr. Petsko walks through this in detail in his report. But if you
19 were to look at those ones that we were looking at, you can see the
20 core. And unsurprisingly, they're red. If you look at Slide 62,
21 what you're seeing here is really the surface residues. I actually
22 want to point something out to you about this. What's interesting
23 is this is now filled in completely. You can see that active site
24 cleft. But then you see there's actually somewhat surprisingly two
25 patches on the surface down at the bottom and over to the right,

1 those red patches that were not tolerant on the surface of the
2 protein. And then there's a little orange region as well.

3 And what's interesting about that is that is information
4 that you only have now that you have the patent's mutagenesis
5 data. So a POSA who's going to try to mutate this and make
6 multiple mutations, they might have previously stumbled into
7 some of these positions that don't tolerate substitution.

8 But here now, a POSA knows, those are places that I
9 can't make changes on the surface of the protein. And that's
10 important structure information. Petitioner claims that the
11 inactivating changes is evidence of epistasis based specifically at
12 PH20. They don't have any evidence that these epistatic effects
13 that they're claiming so beset PH20 that you would have to go
14 through an undue amount of experimentation.

15 But here, what you can see is if epistatic effects really
16 were just random like they're saying, you would expect to see not
17 tolerated substitutions across the surface of the protein. Instead,
18 you see these red patches. You're getting structural information
19 from the invalidity data. It doesn't show that it's unpredictable. It
20 actually makes it substantially more predictable.

21 And unlike all of these other protein-based cases where
22 you're saying, well, sometimes we know that if I make a change, it
23 surprises me. Here, you're getting much, much fewer surprises.
24 This isn't evidence of epistasis even if you ask --

25 JUDGE FREDMAN: (CROSSTALK) with a single

1 amino acid change.

2 MR. SUMMERS: So let me take on what Dr. Petsko
3 says about making additional mutations. So this is consistent
4 -- first of all, Petitioner mentioned that he thought there's only one
5 method that's taught in a patent from doing a mutagenesis study for
6 multiple mutations. And it's a screening. I just want to direct you
7 Exhibit 1001, column 79 to 80, and specifically 80, 12 to 19. The
8 patent teaches to do what Dr. Petsko is doing here. So --

9 JUDGE FREDMAN: Can you say that again?

10 MR. SUMMERS: Yeah. It's Exhibit 1001, column 79 to
11 80, and specifically 80, 12 to 19. The patent teaches to look at the
12 active change -- the active positions that have been identified and
13 make changes there to avoid less tolerant positions, to make
14 changes there. Petitioner mentioned this trip up from Melanie
15 alleging -- Dr. Simpson, allegedly, in her deposition about a couple
16 of positions.

17 I just want to direct you to the language in there.
18 Specifically, it says generally are not made there. And that's
19 because a POSA is able to go down into that data and see which
20 positions actually would be tolerated on the -- in the substitution.

21 So if we can go now to Slide 41. So Dr. Petsko talks
22 about how a rational protein designer would go about making
23 multiple modifications. Because I don't think we're talking about
24 just making random mutations across the surface of the protein.
25 Petitioner's own experts said that's not something that any rational

1 protein designer would do.

2 Somebody off the street, they might do that. But a
3 rational protein designer isn't just going to try to make random
4 multiple mutations. They're going to look at the structural data.

5 And Dr. Petsko talks about one way, one very
6 conservative way of making multiple mutations across the surface
7 of the protein. He says a POSA wishing to make multiple
8 modifications but retaining activity can select from those positions
9 the best tolerated substitution.

10 And he goes on, he says, you know, if you're seeking to
11 be conservative, you can just look at those 43 positions and all of
12 the different amino acid changes that were tolerated. And you
13 would expect that those are not going to abrogate activity. We're
14 talking about not abrogating activity. We're talking about
15 distinguishing things that are active from inactive, not a specific
16 level of activity here.

17 Petitioner suggested that Dr. Petsko said that he couldn't
18 identify what would be active or inactive. If you can go to the next
19 slide. Dr. Petsko testified at his deposition -- they were asking,
20 you know, there's this huge number here, 10 to the 49th, this huge
21 unit. He said, can you do -- at the very bottom here, he says, they
22 can do that for any number of modified PH20 polypeptides that
23 approaches the 10 to the 49 different sequences tends to predict the
24 effect of these multiple mutations.

25 He says, they can do that for any member of the 10 to the

1 49 sequences that they wish to examine. And that's actually the
2 test for enablement here. The law is quite clear.

3 If you want to go to Slide 77. Now --

4 JUDGE FREDMAN: Are your claims limited to new
5 positions that can tolerate change?

6 MR. SUMMERS: No. The claims are not limited to
7 positions that tolerate change.

8 JUDGE FREDMAN: So it encompasses ones that
9 (INDISCERNIBLE).

10 MR. SUMMERS: It encompasses --

11 JUDGE FREDMAN: It encompasses ones that abrogate
12 activity.

13 MR. SUMMERS: It potentially encompasses -- I mean,
14 to our point that these cover inactives, it does potentially cover
15 ones that abrogate activity. And as we've shown here, with the
16 knowledge of these positions that didn't tolerate changes, you
17 know how to naturally protein and you know which ones are going
18 to abrogate activity. What we're focused on then is using the ones
19 --

20 JUDGE FREDMAN: You know which ones are the
21 single mutation. Again, you're focusing all this on single mutation
22 data. But part of the problem is that you just -- you have up to 22
23 mutations, right?

24 MR. SUMMERS: That's correct. You can have up to 22
25 mutations here and know it with knowledge of which positions are

1 tolerated --

2 JUDGE FREDMAN: That would be half of the 43.

3 MR. SUMMERS: That would be half of the 43 that
4 tolerated all. That's correct.

5 JUDGE FREDMAN: I'd be interested to see a study of
6 that. I mean, I suspect it would not substantially all function.

7 MR. SUMMERS: That's actually an interesting point,
8 Your Honor, which is that it's Petitioner's burden here. And they
9 have put forward no evidence, none, that there is a single
10 polypeptide within this -- that following the guidance in the patent,
11 following what a POSA would do, doesn't act as if the patent
12 teaches you. And that's a critical --

13 JUDGE FREDMAN: The expectation is for Petitioner's
14 to do experimental data now?

15 MR. SUMMERS: It's their burden to do that. They've
16 relied on things like epistasis. But in view of their --

17 JUDGE FREDMAN: They have expert testimony.

18 MR. SUMMERS: What's that?

19 JUDGE FREDMAN: They have expert testimony
20 supporting their position.

21 MR. SUMMERS: I still didn't hear you.

22 JUDGE FREDMAN: They have expert testimony
23 supporting their position.

24 MR. SUMMERS: That epistasis would --

25 JUDGE FREDMAN: Oh, you know, and that mutations

1 would impact the stability and function of the protein.

2 MR. SUMMERS: Sure. They do. In the same way, we
3 have expert testimony actually following through with the rational
4 protein design.

5 JUDGE FREDMAN: Yes. And so the question we have
6 to resolve is which experts we're more persuaded by.

7 MR. SUMMERS: I don't think that's the only question
8 that you have to resolve.

9 JUDGE FREDMAN: Partly.

10 MR. SUMMERS: I don't think it's a say so only between
11 -- but I do think that that's something that you --

12 JUDGE FREDMAN: It's a parameter.

13 MR. SUMMERS: I agree that it's a parameter, Your
14 Honor. So let me go to Slide 77.

15 JUDGE HARDMAN: Counsel, can I just interject with a
16 question here? It's Judge Hardman. How did Dr. Petsko account
17 for in the homology modeling, that the Hyal-1 protein is shorter
18 than the claimed protein? So how did he account for that sort of
19 missing sequence structure?

20 MR. SUMMERS: Sure. So both parties agree that this
21 model is sufficiently reliable to look at the structure of PH20. And
22 that includes that -- I think it's 409 in the petition where there isn't
23 a solved experimental structure. And so what you're relying on is
24 the homology model to give you that based on other sequences.
25 That's how we accounted for it.

1 One of the other things that the experts have said,
2 though, is with those changes, as you get out to that end, you know
3 the effect from the mutagenesis data of changing those positions.

4 And as a general reminder, they're far away from the active site.

5 So it's also known that that HyalEGF domain is essential.
6 That's taught in the prior art, as the Petitioner suggested that we
7 needed to identify that in spec. It's taught in the prior art that that's
8 a structural feature of these PH20s. And Petitioner made that
9 point in their appeal in the opening petition.

10 So the Petitioner has made much about the size of the
11 genus. The Amgen case on enablement said, while we agree with
12 Amgen that enablement is not measured against the cumulative
13 time and effort it takes to make every embodiment of the claim,
14 right, we're not so sure the Federal Circuit thought otherwise. The
15 Amgen Court actually went out of its way to say, the way to
16 evaluate enablement is not by looking at the cumulative time and
17 effort it takes to practice it. It's still that in Rewan's (PHONETIC)
18 framework, when I go sit down to do it, am I surprised so often
19 that I'm -- that it results in undue experimentation? I mean --

20 JUDGE FREDMAN: Quantity of experimentation is an
21 element. Quantity of experimentation is an element --

22 MR. SUMMERS: Yes. But quantity of experimentation,
23 as Amgen makes clear, what you're talking about is that sort of
24 trial and error experimentation versus identifying something that's
25 a common quality running through the genus. The Amgen talks

1 about that here, right?

2 And here, in Amgen, what you had was, well, it binds to
3 a target with a certain affinity, right? It was functionally defined.
4 It was acknowledged. There was no way to actually get to all of
5 the possible structures that could perform that function. There was
6 no way to even know them. So you effectively had an unbounded
7 claim, or at least a claim that encompass things you had no idea
8 that anybody knew about.

9 You have that same kind of evidence in AbbVie. You
10 have that same kind of evidence in Ariad. That's why the priority
11 date was so significant in Ariad because the only evidence that
12 they had that you could get to inhibiting the function was 1990 and
13 1991, as the priority date was 1990.

14 You don't have that here. You are starting in these
15 claims with a known active structure with a D320 mutation. And
16 you are limited to structures that are structurally similar to that.
17 And so the question becomes whether there is a reasonable
18 certainty that you can practice the invention. That's the standard.
19 And Wands points you to undo experimentation.

20 So when you talk about making and testing all of these,
21 just every single one, and you don't know what might work and
22 what might not, what structures might actually be active and what
23 aren't, that's not what we're talking about here. You know what
24 structures are active. You know what they look like. And you're
25 able from the spec to then make those multiple mutations with

1 reliability sufficient to not aggravate activity.

2 If I can, I want to go to Slide 45. And my colleague has
3 hopefully noted the -- just to clarify my answer to your question,
4 Judge Hardman, the model doesn't have all of the positions out.
5 That's where Dr. Petsko says you would rely on that mutagenesis
6 data, knowing where that EGF domain lies. But the model itself
7 doesn't model that. And I apologize if I misspoke. I just want to
8 clarify that.

9 JUDGE HARDMAN: Okay.

10 MR. SUMMERS: So I want to go to Slide 45 now.
11 Again, doing what we're doing here, what Dr. Petsko does is
12 common and expected. We asked Dr. Park, Petitioner's rational
13 protein designer, whether that was correct. He said in the year
14 2011, to consider a mutation, it would have been very common
15 and expected for a POSA to generate a model in considerate
16 substitution in the context of that structural model.

17 I want to make one other point about Dr. Park while
18 we're here. Petitioner noted a couple of times, Dr. Park didn't get
19 that mutagenesis data. He's the one rational protein designer that
20 Petitioner has on their side. They didn't let him look at the patent's
21 mutagenesis data. He said, I can reliably predict -- if you think
22 back to B11, that white space, he said, I can reliably predict up to
23 five mutations.

24 But then they made sure not to show him that patent's
25 mutagenesis data. He did not get it. They showed it to other

1 people but not their rational protein designer who was asked to
2 evaluate the substitutions. I think that's significant. I think when
3 you're weighing the credibility of the experts, that's something that
4 has to be weighed.

5 So let me go now to Slide 46. We talked to their experts,
6 again, their rational protein designer here, about what it allows you
7 to do. For written description, it allows you to visualize. That's
8 what it's doing. That's the test for written description. Can I
9 visualize the scope of this genus? That's what it allows you to do.
10 So having the structural model, it allows you to visualize what's
11 active and inactive.

12 I actually want to go now to the common structural
13 features section here. And if you can take us to Slide 33.
14 Petitioner talked a lot about the a/b barrel fold. The a/b barrel
15 tertiary structure, I agree with Your Honor, it's really semantics
16 that they are playing here. We made sure to call it the PH20 a/b
17 barrel fold or the PH20 tertiary structure, because what we're
18 referring to is the fold structure.

19 But I just want to be clear about something. Our position
20 is it's not in any individual one of these, it's not the common
21 structural feature. So Petitioner was saying, well, the a/b barrel
22 fold, that doesn't describe all the inactives. It doesn't let you
23 distinguish between actives and inactives.

24 But you have a lot of common structural features here.
25 And primary among them is just the primary sequence, 95 percent

1 identical to an identical amino acid sequence. Then you have a
2 key mutation, the D320 mutation. And then for actives, what
3 allows you to distinguish them from inactives? You have a
4 common active site. You're not going to make changes to that
5 active site. And that's going to break it.

6 You have same catalytic and binding residues. Again,
7 you're not going to make changes to your catalytic binding
8 residues. You have conserved disulfide bridges in central
9 glycosylation sites. And then you have a lack of disclosed
10 inactivating changes based on that mutagenesis data that tells you
11 every single substitution broke the protein there. So if you look
12 and you --

13 JUDGE FREDMAN: Essentially, you wrote a claim
14 that's 95 percent of the whole thing. What you really want is a
15 claim that, well, for these -- for the active site region, we have 100
16 percent identity. For the catalytic binding residues, we want 100
17 percent identity. For the disulfide bridges and oxidation sites, we
18 want maybe 90 percent identity. (INDISCERNIBLE) variations,
19 we don't want any changes that would inactivate it. We didn't put
20 that in the claim.

21 MR. SUMMERS: So I think, Your Honor, it's --

22 JUDGE FREDMAN: You could have.

23 MR. SUMMERS: I think we're looking at the claims
24 that were drafted here and that sufficient --

25 JUDGE FREDMAN: But I'm saying -- but that's the

1 question.

2 MR. SUMMERS: And they provide sufficient structure

3 --

4 JUDGE FREDMAN: You're the master of your claim.

5 You made a choice.

6 MR. SUMMERS: I agree with that. I think it's the
7 proper choice because the law is clear that you don't have to list
8 out in your claim all of the things that don't work. That's why we
9 have the test for, for instance, experimentation. That's why we
10 have a common structural features test. Because the law works
11 -- it says, we work by example, right? If you think about Ariad, if
12 you think about Identix, it says we work by example in the
13 specification.

14 Tell us what's common, right? Or give us a
15 representative number of species. And in doing that, you're giving
16 -- you're able to give examples of what's going to work. And a
17 POSA is not somebody who's just off the street here. They have a
18 lot of information. What are the physical chemical properties?
19 Amino acids. If I put a tryptophan in for alanine, I'm expecting
20 that to break it. But now you can check the mutagenesis data and
21 actually see that.

22 If I'm changing out a polar for a bipolar -- or a polar for a
23 non-polar residue, I might expect that to break it, right? And Dr.
24 Park -- actually, their rational protein designer, takes those things
25 on. But I just -- I want to make one point about this. We are not

1 saying any individual one of these is sufficient to distinguish. You
2 have all of the common structural features.

3 And I think that's consistent with the law. What common
4 structural features do you identify? That was lacking in AbbVie,
5 right? You talked about AbbVie. And in AbbVie, there was a
6 known -- this is a very -- there's a distinct difference between this
7 case and AbbVie. In AbbVie, you had species that was in
8 evidence that was inside of the genus but was not described by the
9 common structural features. You do not have that here.

10 In Ariad, you have evidence of a species that is outside
11 the genus but is not actually described. That's that 1989 date was
12 so important. They said, well, maybe you could do it with decoys.
13 But they didn't know -- they had no information that you could do
14 it with decoys, right?

15 And we talked about Amgen. It was acknowledged that
16 the roadmap and the conservative substitution map couldn't get
17 you there. I want to talk for one minute about why this isn't the
18 conservative substitution route in Amgen. Because what you have
19 here and what was different there is you -- it was acknowledged
20 that you could not get via the conservative substitution route.

21 You could not get to all of the structures that fell within
22 the genus. And you had evidence of that. You don't have that
23 here. It's acknowledged that all of the things that fall within this
24 genus, you can get to them by practicing the claims. You have that
25 mutation. You have 95 percent identity to that structure.

1 If I may, I want to talk about this alleged variability in
2 the data that Petitioner relied on. So there's a couple of things that
3 Petitioner brings up about the alleged variability in the data that
4 they allege shows epistasis. And I want to just point something
5 out to consolidate this down. In all of these other cases, AbbVie,
6 Amgen, Ariad, you have evidence -- some evidence that there is
7 something outside, that there's something that contradicts it.

8 They could have taken -- they showed the AlphaFold
9 slide that says that now it's as good as experimental -- it's
10 experimentally solving a structure, right? They didn't do any of
11 that. They didn't try to take the patent's guidance and show you
12 that if you follow the patent's guidance, it doesn't work.

13 You may recall in their petition they did -- they had one
14 example that said, well, it guides you to things that don't work.
15 But they were outside the scope of the claim. They were only if
16 you practiced a double mutant without the PH20 adaptation.

17 So let me not take on this idea that the data is somehow
18 variable because that's what they want to do. They want to --

19 JUDGE FREDMAN: That was a double mutation in that
20 paper, right?

21 MR. SUMMERS: That's correct. There's a double
22 mutation in the paper that was known to render -- to take out the
23 (INDISCERNIBLE) sites. And the spec says not to make that.
24 But it says if that's what you're making, there's clear guidance in
25 the spec away from it.

1 Now, Petitioner says, well, there's variation in all this
2 data about PH20. First of all, they say, when you make those C-
3 terminal truncations, you see a lot of variation in the data. And
4 that's evidence of epistasis because they don't have evidence that if
5 you follow the patent's guidance that you will end up not -- you
6 will end up having so much unreliability that it's undue
7 experimentation that you won't be able to distinguish actives from
8 inactives.

9 They don't have that evidence. So what they point to is
10 they say, well, see terminal truncations, they show a lot of
11 variation.

12 JUDGE FREDMAN: Because there -- do they have to
13 be able to show they can detect? I mean, clearly, obviously you
14 can run the assay and see what works. The question is, can you
15 predict a priority level that's (INDISCERNIBLE)?

16 MR. SUMMERS: I'm sorry, I lost the second part of
17 what you said.

18 JUDGE FREDMAN: It's not a question of whether you
19 can test activity. That's clearly going to be the simple
20 heterologous assay. The question is a priority, can you predict
21 -- and that's -- you're arguing based on all this evidence that you
22 can. And they're basically saying the scope of this genus is so
23 large that even with your mutation data, you really can't.

24 MR. SUMMERS: Yeah. And to that point, the
25 Petitioner did not take some set of the sequences that you can

1 make that actually guides you to those 43 mutations, for instance,
2 that tolerated all substitutions. They didn't run and test them and
3 see does this work or doesn't it?

4 That's what -- you know, one of the things they argued
5 over in Wands, although they ultimately found that didn't show
6 and do experimentation, was the hypothalamus, right? Many,
7 many, many of them didn't work because that was a routine
8 method. Here, we're not saying that many, many, many of them
9 won't work. You can reliably do this. But they didn't put in
10 evidence of actually --

11 JUDGE FREDMAN: When was the screening? And
12 Wands was entirely different.

13 MR. SUMMERS: Wands was a little bit --

14 JUDGE FREDMAN: Wands was a screening method
15 where you're doing -- putting them in (INDISCERNIBLE). It's not
16 the same.

17 MR. SUMMERS: Yeah. The thing that's common --

18 JUDGE FREDMAN: You're looking for what it was.

19 MR. SUMMERS: Right. The thing that's common with
20 Wands here is that the practice of the invention is routine. It's
21 rational protein design. This is a routine way of going about
22 actually making modifications to a protein. People don't just
23 randomly make them. POSAs will go and they practice rational
24 protein design by --

25 JUDGE FREDMAN: Does it have to be with the Joe-9s?

1 Was that – no, that was Janssen. There, they had the antibody and
2 it was routine to get antibodies. But that wasn't good enough. So I
3 don't know the routine is the total test.

4 MR. SUMMERS: It's not the total test. I agree. You
5 can have times when for enablement it's routine, but you don't
6 have written description. For instance, if you have like a forking
7 path through the specification through a bunch of different classes
8 where you have to make a specific decision. I agree with that,
9 Your Honor, I don't think that's here. We don't have any forking
10 path. It's very clear what the adventure is.

11 JUDGE FREDMAN: (INDISCERNIBLE).

12 MR. SUMMERS: Yeah. So I want to talk about, first of
13 all, C-term truncation variation. That's one of the things that they
14 rely on. So Petitioner's counsel said that there's a lot of variability
15 when you start to mutate the C-term truncation. And Dr. Hecht
16 claimed that Exhibit 1003, paragraph 97, he says, there's -- overall,
17 there's uncertainty in the scientific literature about the activity of
18 truncation mutants in the C-terminal region of PH20.

19 Then he went on, he said, specifically, changes
20 terminating at positions between 430 and 442 were not
21 characterized other than position 432. So that's the range he gave.
22 He said there's nothing known. It's 430 to 442 other than 432. But
23 the 457 publication actually did in fact characterize changes from
24 415 to 474. And that includes data on amino acids between
25 positions 430 all the way to 447.

1 So again, they said there's nothing known about PH20
2 from 430 to 442. But they just missed the 457 publication. It's
3 incorporated by reference into Exhibit 101.

4 Now, let me talk about the fact that they criticize the
5 patent's data for not having positive or negative controls. That's
6 his reply 33. And I just want to point to very briefly to Exhibit
7 1001 at 233, lines 11 to 23. This is the patent's description of the
8 assay. And you can see here, it says transfected variant or wild-
9 type PH20 supernatants generated as described in example 1.
10 That's the positive control that's been used in these.

11 Our expert, Dr. Simpson, called that out specifically.
12 That's a Simpson Exhibit --

13 JUDGE FREDMAN: They were the wild type --

14 MR. SUMMERS: Yes. That's the control 20, 68, and
15 194. And then she talks about the negative control as well. That's
16 at paragraph 201. It's a secreted alkaline phosphatase that tests that
17 what you do is you're secreting alkaline phosphatase. And lines
18 234, lines 5 to 14, in order to control for protein concentration
19 -- but you want a negative control on that so that you know how
20 much SEAP is being secreted.

21 There's a negative control for that as well. It says also
22 the criteria for each screen, that standard curves -- had a signal to
23 noise ratio of the zero UML standard. So there is a positive and
24 negative control on these assays.

25 Now, why do I want to --

1 JUDGE FREDMAN: (INDISCERNIBLE).

2 MR. SUMMERS: Why do I want to talk about these
3 assays specifically? Because they say on Petitioner Slide 31, they
4 talk about the fact that there are allegedly large swings in activity
5 for truncated PH20s. And they say that confirms long-range
6 effects, epistatic effects, in that C-term region. But those C-term
7 studies -- and specifically, there's two papers, the '429 and the '457
8 -- they're also Halozyme art.

9 Our expert addressed why there's variability in those
10 assays. It has nothing to do with some kind of epistatic effect from
11 across the protein. This is at Exhibit 2068, Simpson declaration,
12 paragraph 182 to 183 and again at 186 to 187.

13 Dr. Simpson is the president of the International Society
14 of Hyaluronidase Scientists. And I will make a second point.
15 When you're weighing the evidence of these experts, none of their
16 experts have any experience with hyaluronidase activity. They
17 simply went and hired people who had never run an assay for
18 hyaluronidase.

19 And then they said, well, don't these assays show a lot of
20 variability? But Dr. Simpson talks about the fact that people
21 -- persons of ordinary skill in the art, if you look at the art, they
22 understand it's a very physical assay. What you're doing is you're
23 chewing HA off a plate, and you have to hit the portions of it that
24 are biotinylated.

25 So the nature of those assays can be a little more

1 variable. That's especially the case where with these, in the '429
2 and the '457, they didn't control for protein concentration whereas
3 they do in the '600 Patent. So that evidence of variability they're
4 trying to say, well we have evidence of variability about PH20.
5 But that's not evidence of variability about PH20.

6 That's inherent to the assays here. That's inherent to the
7 assays that they're looking at. It's not some evidence of epistatic
8 effect about PH20. It's just evidence of inherent variability in
9 these assays.

10 I want to take on one last point. So when we were
11 talking about the fact --

12 JUDGE FREDMAN: Actually, the assays, they never
13 did actually measure the amount of the hyaluronidase itself? They
14 just measured the --

15 MR. SUMMERS: They don't directly --

16 JUDGE FREDMAN: They're measuring the surface,
17 right?

18 MR. SUMMERS: Yeah. Because what you have is a
19 non-processive -- you're sort of breaking up the HA. It doesn't
20 process it into something else. And so they just wash the plate.
21 And they hit it with OD-405 light. And they see what else would
22 get that --

23 JUDGE FREDMAN: So they really don't necessarily
24 know if there's an HA in there (INDISCERNIBLE).

25 MR. SUMMERS: I don't --

1 JUDGE FREDMAN: If you have a result where you
2 don't get any hyaluronidase activity and you don't really know if
3 hyaluronidase is there or not, so.

4 MR. SUMMERS: Because what you're doing is actually
5 removing HA that's been bound to a plate. You know that there's
6 hyaluronidase that's on the plate. And what you're seeing is it's
7 been biotinylated to reflect back. So you're seeing what's been
8 removed. So that's the evidence of hyaluronidase activity.

9 JUDGE FREDMAN: Right. But I'm saying the protein.
10 How would you know the protein was in the reaction?

11 MR. SUMMERS: Oh, thank you. The supernatant that's
12 used? That's the SE -- that's the secreted alkaline phosphatase.

13 JUDGE FREDMAN: And that's just measuring the
14 amount of secretion that's happening. It's not really telling you
15 hyaluronidase itself, right?

16 MR. SUMMERS: That the PH20 is in the supernatant?

17 JUDGE FREDMAN: Yeah.

18 MR. SUMMERS: It is because you have -- you're able
19 to normalize it.

20 JUDGE FREDMAN: You're normalizing it. But if it's
21 not processed because it didn't get expressed, you don't see it.

22 MR. SUMMERS: I see. So if you're seeing no activity
23 whatsoever --

24 JUDGE FREDMAN: You know --

25 MR. SUMMERS: -- you know if it's expressed. That's

1 right. You wouldn't necessarily know that. Dr. Simpson actually
2 talks about there are some more sensitive assays. She cites her
3 Zhang (PHONETIC) paper. That's Exhibit 1010. And that used
4 the Morgan Ellison (PHONETIC) color assay that allowed her to
5 sort of more sensitively check for how much -- these are just
6 -- POSAs knew that, right?

7 She used that assay in particular because she wanted to
8 have less variation in her data. This variation isn't evidence of
9 epistasis in PH20.

10 JUDGE FREDMAN: You're at half --

11 MR. SUMMERS: Yes, I see that.

12 JUDGE FREDMAN: I know. You can keep going if
13 you want.

14 MR. SUMMERS: I want to make one last point.

15 JUDGE FREDMAN: All right.

16 MR. SUMMERS: Because we're not just relying on the
17 43 positions that tolerated all substitutions. You saw as you fill
18 those in. The data is much more granular. And one thing that I
19 think is clear from the rational protein designer that they put up,
20 Dr. Park, he says, again, you know the physical and chemical
21 properties of these amino acids.

22 You actually know which ones can often have a more
23 stable substitution or will be a destabilizing substitution. I think
24 you mentioned alanine, phenylalanine, that's -- that would be one
25 of them. We're not talking here about somebody just making

1 random changes across the surface of the protein. But we asked
2 Dr. Park, a rational protein designer, whether -- so he said, so a
3 POSA wouldn't just make random changes and kind of hope for
4 the best.

5 He said, not a POSA, a person off the street, yes. But a
6 person who's supposed to be educated in the field and
7 understanding the factors that contribute to protein folding
8 stability, no. They wouldn't randomly try substitutions. No.
9 That's from Park Volume 1. It's at page 145, lines 2, 146, 1. And
10 that's key also here because the evidence you have in front of you
11 from Petitioner, much of it relates to things that POSAs would not
12 do.

13 Can you put up Slide 81? John Hopkins VSEL Pro is
14 really instructive in this regard. You must show that the patent's
15 disclosure was followed. Otherwise it's insufficient to prove
16 -- disprove enablement as a matter of law. And it's imperative
17 when attempting to prove lack of enablement to show that one of
18 ordinary skill in the art would be unable to make the claim of
19 invention without undue experimentation.

20 The evidence concerning the substance were insufficient
21 as a matter of law because they weren't acting as a POSA would.
22 So when you say, well, it's random changes that you're concerned
23 about for enablement or you might shove in something that's
24 against the patent's guidance, that's not relevant evidence that this
25 -- that you are not enabled.

1 You're going to act as a POSA and a rational protein
2 designer. Petitioner hasn't put up a rational protein designer,
3 seeing the mutagenesis data in full.

4 And I want to make one last point about this. This is
5 Slide 44. I'm going to go slightly over my time, Your Honor.

6 JUDGE FREDMAN: Yeah --

7 MR. SUMMERS: We'll go to Slide 44. So they put up
8 one more expert, Dr. Naismith, in reply. If you go through his
9 declaration -- it's a 250-page declaration. But he takes on the
10 mutagenesis data to some degree. But he only considers 33
11 positions. That's what you're seeing on the left here, that grayed-
12 out model. He did the same thing Dr. Petsko did.

13 He didn't dispute that what Dr. Petsko did and said was
14 correct in terms of what you could do with the model. He just
15 said, I'm just going to consider 33 positions. He applied an
16 arbitrary cutoff. There's nothing in science saying you can't
17 consider all the rest of these. He ran through all these criticisms of
18 the data that we've talked about, things like the assays have
19 variability, that there's no positive and negative controls.

20 But those aren't true. You have to consider the full set of
21 mutagenesis data. None of their experts did that. Their rational
22 protein designer, Dr. Park, he didn't consider that. Dr. Naismith,
23 he made sure to say, I'm only going to consider 33 of these
24 positions. And that's when I'm going to give away my opinion that
25 this is unreliable. So it's Petitioner's burden.

1 And the evidence that's traditionally supplied in these
2 cases, it's missing. They could have provided, they're experts that
3 didn't consider the data.

4 And with that, I'm going to sit down.

5 JUDGE FREDMAN: So seven minutes for your rest.

6 MR. KUSHAN: Can you put up Slide 37? So there are
7 a lot of things you just heard, and I'd like to try to be efficient in
8 trying to respond to as many of them as possible. And how much
9 time do I have, by the way?

10 JUDGE FREDMAN: Twenty-two.

11 MR. KUSHAN: Twenty-two. Okay. So I just want to
12 address the question of the evidence we've put on to show that
13 there's unpredictability in the field and complications in producing
14 multiple mutants. One thing that's particularly probative is we
15 asked their expert a number of questions.

16 But even before that, he wrote this in his declaration, and
17 what he pointed out was that a POSA seeking to make modified
18 PH20s that have 95 percent identity to CKD3 would not just do
19 screening. He says, if the sequences truly are random, it's likely
20 that a substantial number would include substantial modifications
21 of residues that are known to be invariant because they are
22 involved in catalysis, active site, or protein structure.

23 And then he makes a very important point, a POSA
24 would not make a library with billions of sequences that this
25 POSA expects are not going to fold into PH20 proteins. Why is

1 that relevant? The claims impose no restrictions on where changes
2 can be made in the sequence.

3 It makes no restrictions on what those changes can be to
4 the 19 alternatives. It does not have any exemplification of
5 deletions of sequences or additions. It's an unrestrained claim.

6 JUDGE FREDMAN: I have a question. Is there a
7 distinction here between written description and enablement in the
8 sense that written description to some extent captures everything?
9 Enablement definitely has a factor where the POSA is looking at it
10 and thinking, you know, what they could do. Do you see that
11 distinction or do you not? Do you think written description is
12 stronger?

13 MR. KUSHAN: So we think both of them are strong,
14 but one is that there's an absence of guidance and description in the
15 patent, right? We keep hearing how great this data set is. It's not.
16 The problem is that there's no guidance in the significance of all
17 the changes to the structure of the protein. They're basically
18 reported out with an activity readout that is suspect.

19 The second point is that for the written description,
20 you're looking to see what has been described. There are no
21 examples other than single mutant examples. There are laundry
22 lists of choices to be made. Those are not descriptions of
23 molecules under the 112 written description law.

24 The boundary isn't a description of all the molecules.
25 There's this huge set of possibilities and there's no description of

1 illustrations in it that reflect the diversity of what they're playing,
2 especially all the different lengths and all the different numbers of
3 changes.

4 What this is relevant to is saying he's acknowledging a
5 lot can go wrong when you start making changes to the protein
6 sequence. And --

7 JUDGE FREDMAN: But in the enablement context,
8 he's also saying the POSA could pick out which ones would be
9 right or at least have some guidance.

10 MR. KUSHAN: It is -- well, that's where we disagree.
11 We think that the guidance isn't illustrative of the guidance you
12 need to make multiple changes in the protein sequence. Because
13 in some of his illustrations of the protein structure, you saw colors
14 that were not red, they were blue. Those are the ones that were
15 basically a coin flip. They had 30 to 60 percent -- were tolerated.

16 So how do you get guidance out of that? He then says,
17 go into the data itself and start looking at every single position and
18 every single option that we tested. That's the thing that Dr.
19 Naismith addressed, he said, that's trillions of choices to put
20 together in combination. It's just you can't even sample that at a
21 tiny fraction. So there's not really guidance in the patent that goes
22 to what is possible to make and what is not.

23 And again, examples are a factor in Wands. How many
24 examples have you provided that illustrate the challenges you're
25 going to face in making these proteins? They only have one kind

1 of example.

2 On the written description side, it's a possession issue.

3 On the enablement side, it's not teaching how to make changes that
4 are going to be tolerated in sets.

5 And the second point, again, we got out of Dr. Petsko,
6 he's telling us that you really -- a person of skill is not going to do
7 the thing that's needed to sample the breadth of these claims.
8 We're not saying you have to make every single one. But they're
9 like so far away from the boundary of reasonable that it's not even
10 close.

11 So the next thing I'd like to point out is that -- if we go to
12 Slide 114. So the reason Dr. -- both Dr. Hecht and Dr. Naismith
13 found this data set wanting as to a guide for making multiply
14 modified proteins is that it doesn't analyze the data. It doesn't say,
15 well, these changes affect the structure, or these changes affect the
16 folding. These changes over here affect the active site or, you
17 know, the disruptive catalytic.

18 So there's no translation of the raw data into something
19 looking like guidance that a skilled artisan in this field could use to
20 navigate the uncertainty. It's basically a readout with, really, no
21 interpretive overlay on it. They have observations in the patent
22 about don't change these, look to change these. But that isn't,
23 really, telling us anything about the impact on the structure of the
24 regions of the proteins that you're trying to modify.

25 He also mentioned the idea that they had described

1 enough. And the challenge with the written for them on their
2 inscription, common structural features, the thing is, we don't
3 know what we're shooting for, right? We don't know the structure
4 that we're trying to make. They don't describe the HyalEGF
5 domain in PH20. It wasn't known.

6 They don't describe the alpha/beta barrel fold in PH20,
7 human PH20, that was not known. So they're not -- and it's not
8 mentioned. There's no direction in the patent to find it. So how do
9 you enable or describe something that you don't know what you're
10 trying to make? I mean, that's the fundamental problem of this
11 description is they don't show us what they're actually trying to
12 achieve. And the single mutant data doesn't lead you to that path.

13 The other issue is that the data -- the inactive mutant data
14 set captures proteins that don't signal impacts on folding of the
15 protein. Under their criteria, something less than 20 percent is
16 declared inactive.

17 Our experts have pointed out that things that have 18
18 percent activity are still enzymatically active and that means they
19 have to be properly whole. So there may be a problem with
20 substrate binding, but it's still an active folded protein. And that is
21 in the inactive data set that is being used to set up this translation.

22 Now, if you look in the patent in the inactive mutant
23 report, you'll see no data. All they do is classify them as inactive
24 mutants. They don't reveal the two measurements that were made
25 of each sample. And they don't reveal the additional measurement

1 that was made, you know, the second day to show whether there
2 was any residual activity or not.

3 There's a lot of information that they omitted from their
4 disclosure that a skilled artisan would look to, to try to figure out
5 what happened that made this protein inactive. But fundamentally,
6 if you're including active mutants in your data set and calling them
7 inactive mutants and then building this tolerance rating scheme,
8 you can see where this is going. You have a weak foundation.

9 The other weak foundation -- go to Slide 115. So our
10 expert pointed out that example 5 provides measurements of the
11 unmodified human PH21 447 protein. There's 17 measurements in
12 duplicate in that example. So our experts looked at that and said,
13 well, that's the same type of assay. They ran it longer. But it's the
14 same biotinylated HA assay.

15 And what they found was that there's a 40 percent
16 variation in the measurements using this assay. It's important to
17 note in the '457 application, the '457 application points out that
18 normally you see about a 10 percent variation in activity.

19 Now, why is this important? In their rating scheme
20 -- this is the foundation of Dr. Petsko's classification table. You
21 either take a mutant and classify it as inactive or active. The line
22 for inactive is below 20 percent. The line for active is above 40
23 percent. How many mutants are misclassified if you have a 40
24 percent variability in the measured value?

25 So you can see there's a tremendous amount of noise in

1 the data. And that translates into the foundation of this
2 classification scheme they are saying is going to lead the skilled
3 artisan. All those colors may change in their colored protein
4 structures if you can't account for that variability in the
5 classification.

6 The next thing I'd like to point out -- if you can go to
7 107. This illustration was provided to show that this is just a
8 practical limit on homology models and what you can do with
9 them. You can't tell if you're a skilled artisan in 2012 looking at a
10 homology model, whether something that looks very similar in
11 size and character -- the original amino acid, it switched to
12 something different that's very similar.

13 You can't predict that this one will be inactivated. We
14 know it's inactivated because this is something on the catalytic
15 side. But as a homology modeling tool, you are a skilled artisan,
16 you can't differentiate the effect of this change. And that's built
17 into the limits of homology model. If there was a steric
18 disturbance in the environment, you could see and say, all right,
19 that's something that's going to be a problem. That's what Dr. Park
20 did.

21 I'll also point out Dr. Park was intentionally shielded
22 from the information in the patent so that he could give an accurate
23 picture of what the prior art is suggesting. It wasn't a flaw; it was
24 intentional. We didn't want him to know what the patent had in it
25 to remove any bias or hindsight.

1 So the next thing, I think I heard Counsel for Halozyme
2 say that he's trying to explain -- if you go to Slide 42. The point
3 about this data was that it is unpredictably variable between very
4 closely similar proteins. That's the point that Dr. Hecht made. He
5 was even more -- Dr. Naismith reached the same conclusion. This
6 is a lot of unpredictability in activity.

7 He is suggesting that maybe that's due to the variability
8 in the assay. Well, if you take that to the logical conclusion, you
9 can throw away Dr. Petsko's table because how many of those
10 things are untrustworthy?

11 These are 135 percent variations in activity between two
12 proteins. If you extend the 40 percent variability up to 130
13 percent, that's like most of the data they have. So I want you to
14 really appreciate, they can't point to the assay variability to explain
15 this variability in the effects of changes at the end of the protein.

16 You heard a number of comments about --

17 JUDGE FREDMAN: Pause for a second.

18 MR. KUSHAN: Sorry.

19 JUDGE FREDMAN: Oh no, you're back.

20 MR. KUSHAN: Yes.

21 JUDGE FREDMAN: Keep going. I noticed she had
22 popped off screen. I was afraid.

23 MR. KUSHAN: If you could look at Slide 87. Dr. Park
24 pointed out that the bee venom structure, the Hyal-1 structure, had
25 very clear differences at the very granular level of the pieces of the

1 alpha/beta barrel motif. The reason that's significant is this goes
2 back to the point that you have to provide enough of a precision in
3 your description of your claimed invention so that people can
4 figure out which one you're talking about, what are you describing
5 there.

6 And this is kind of an illustration of that terminology
7 they're using, which is incapable. They're the ones who came
8 forward with that alpha/beta barrel motif as a defining feature of
9 this set of proteins. And it's not capable of defining and
10 differentiating the proteins.

11 I'm going to have my colleague, Ms. Wong address some
12 of the contraceptive utility issues. I think we have about eight and
13 a half minutes. I have one other issue I'm going to come back to
14 after she's done that. So hopefully, we'll do this relatively
15 efficiently.

16 JUDGE FREDMAN: Okay.

17 MS. WONG: Thank you, Your Honors. Sue Wong from
18 Sidley Austin. So in your colloquy with Halozyme's counsel, we
19 talked about epitopes. And for sure, 15 to 20 changes to the amino
20 acid sequence, especially unbounded, and in any location along the
21 sequence is likely to change the relevant epitopes for reproduction
22 and for contraception.

23 Most epitopes are conformational. That means the three-
24 dimensional shape matters. And that's set forth in Dr. Kelsoe's
25 declaration. He explains that at Exhibit 1134, paragraph 25.

1 JUDGE FREDMAN: And may I say that they're chewed
2 up into small pieces, right? So it's not fully three dimensional. It's
3 three dimensional but (INDISCERNIBLE), right?

4 MS. WONG: The three-dimensional shape matters
5 because that's actually what's recognized by the B cells that make
6 antibodies. And that's the concept that's being described here with
7 the contraceptive. The T cells do chew up the antibodies. But
8 they provide assistance to the B cells which actually have to make
9 the antibodies.

10 JUDGE FREDMAN: Stimulate the B cells into making
11 the (INDISCERNIBLE).

12 MS. WONG: Yes. Understood. The prior art, though,
13 also identifies that epitopes matter. So Slide 125, please. And Dr.
14 Kelsoe explained this. He looked at prior art, such as the Chan
15 reference, Exhibit 2120, which characterized guinea pig PH20,
16 looking for the epitopes that are relevant to contraception. They
17 found that even with peptides, they needed structural epitopes that
18 are relevant to contraception.

19 Slide 126. Prior artists like Hardy. The Hardy authors
20 which conducted the mouse studies also suggested that the reason
21 their studies failed, whereas the guinea pig experiments worked
22 was because recombinant PH20 failed to present necessary
23 epitopes relevant for reproduction. The guinea pig studies were
24 done with affinity purified PH20.

25 They were not recombinant. The claimed PH20s here

1 would be recombinant and there would be serious doubt as to
2 whether they present the epitopes.

3 And so this isn't merely an error as Halozyme's counsel
4 likes to -- wants to represent by Dr. Kelsoe, this is grounded in the
5 prior art. The expectation in the prior art was that epitopes matter
6 and that the antigen would have to retain them.

7 JUDGE FREDMAN: (INDISCERNIBLE) in vitro assay
8 where the antibody is used to block a sperm dye.

9 MS. WONG: That is correct.

10 JUDGE FREDMAN: Because that's -- seems like it was
11 in (INDISCERNIBLE) but it's in vitro.

12 MS. WONG: In vitro assay on the left, I think, is what
13 you're pointing to.

14 JUDGE FREDMAN: Yes.

15 MS. WONG: That is a characterization of the antibodies
16 extracted from female guinea pigs.

17 JUDGE FREDMAN: Right.

18 MS. WONG: And what they're showing there is that
19 those antibodies specifically block the function of PH20. And so
20 that is a specific interaction. That actually addresses Counsel's
21 other point, which is they're now positing that a person of ordinary
22 skill would have expected any kind of finding anywhere along
23 PH20 to be effective as a contraceptive. That is contrary to the
24 prior art.

25 And so Counsel also relied upon in re Brana in his

1 argument. We actually think that case is helpful to us into
2 understanding the evidentiary burdens here. Because Brana
3 confirms that the asserted utility in a disclosure can be challenged
4 with evidence that a person would -- that a POSA would
5 reasonably doubt that asserted utility. And we've done just that
6 here by putting forward Martin DeLeon 2006.

7 The burden then shifts to the Patentee to put forward
8 evidence to convince a person of the invention's asserted utility.
9 There is no evidence that any claimed modified PH20 has ever
10 been tested for contraceptive function. None of the claimed
11 modified PH20s have been tested. What Halozyme has put
12 forward is a creative expert's opinion that is not in the specification
13 describing how it is possibly that a person of ordinary skill might
14 imagine this would work.

15 Slide 118, please. But what's actually disclosed in the
16 patent is -- on contraceptive vaccines is the extent in that right
17 hand box. That's all that's disclosed on it. And you'll see what it
18 refers to is guinea pig studies. It refers to guinea pig studies in
19 males. Halozyme doesn't even attempt to defend it. They've
20 walked away from it. So that disclosure is facially not credible.

21 And then as to females, as I said, we've put forward
22 evidence through Martin DeLeon that a person of ordinary skill
23 would have doubted this. What's not disclosed here in the
24 specification is any reference to mucosal immunization, any
25 reference to how the modification to the PH20 is relevant to

1 contraception.

2 Counsel made an argument about how the invention is to
3 the 320 mutation. There's no description here about how that
4 relates to contraceptive function. In fact, Dr. Sher admitted in his
5 deposition that his opinion doesn't really depend on where the
6 mutation is located.

7 He would have the same opinion with or without the
8 D320 mutation. And so the specification, as we have put up here,
9 we think does not teach a person of ordinary skill how to use the
10 full scope of the claimed polypeptides as contraceptive vaccine.

11 And finally, I'll just mention here the Board cited in Kirk
12 in the institution decision, and we think that is fairly applicable
13 here. The description that is set forth here is so generalized as to
14 be almost meaningless, especially if you credit Halozyme's
15 argument that any antibody, any PH20, regardless of the mutation,
16 regardless of its folding, would be sufficient so long as antibodies
17 bind anywhere along PH20. That's essentially like saying any
18 antisperm antibody would be sufficient. Thank you.

19 MR. KUSHAN: Just to kind of wrap up in my last
20 couple of minutes, I just want to make a few points. One, if you
21 put up Slide 100, you heard a number of comments about the
22 homology models and their capabilities and what we did with our
23 expert. Just to be 100 percent clear, Dr. Park used a homology
24 model to investigate the individual single mutations within a
25 confined local environment of the protein.

1 He very carefully explained the limitations of these
2 models in his declaration. One is, of course, the kept model in a
3 region that doesn't have a template. But there's also another built
4 into the model is something called a QMEAN value. It's a rating
5 of quality of the structure and that fluctuates based on the length of
6 the protein. He's very careful to only opine about positions that
7 have enough volume.

8 Second thing, he points out that the technology is
9 incapable of modeling to yield the accurate structures. I think the
10 last thing about Dr. Park, he was shielded from the data in the
11 patent so that he can give you an accurate picture of what the '429
12 Patent with knowledge in the art before 2011 would have led to.
13 That's the whole point of his role.

14 A couple of final points. You heard a number of
15 comments today that were -- have not ever been advanced by them
16 in the record. One, you have a conversation about the Dobson
17 publication, right? I'd invite you to read Dr. Naismith's discussion
18 of that to get an accurate understanding of the Dobson paper is
19 telling you, that he also read you -- testimony from Dr. Park in his
20 deposition. That's new. We've never seen that before in the
21 pleadings of the papers.

22 And I think you just have to be very careful of filtering
23 and making sure that things that were actually advanced in the
24 proceeding are accounted for. So I don't have any other additional
25 points. If you have any final questions, I'm happy to answer your

1 questions.

2 JUDGE FREDMAN: You have seven minutes.

3 MR. SUMMERS: Okay. I heard Petitioners say that the
4 fundamental problem here is you don't know what you're trying to
5 make for what you're trying to describe. And he related that to the
6 case law they rely on, cases like Ariad, Amgen, Identix. Now, I
7 just want to point out to you, Claim 1 is a structurally bound claim.
8 There's no question of knowing what you're trying to make. It's
9 perfectly clear. It distinguishes all of those cases just in its clarity
10 alone.

11 You can go to Slide 52. Petitioner's expert, Dr. Naismith
12 agreed that for active modified PH20 polypeptides, those would
13 have the same fold. We're not talking about something that's going
14 to fold into different shapes or an antigen that might -- or an
15 antibody that might be totally different like an antigen. We're
16 talking about one type of polypeptide.

17 If you can go to Slide 33. Again, you know what you're
18 looking for. These are the common structural features. There is
19 no fundamental problem here. You know that you're avoiding
20 those inactives. You know that you're conserving your disulfide
21 bridges, catalytic and binding residues, the common active site.
22 And again, there's a primary structure. If that is the fundamental
23 problem, it is solved by this specification.

24 I want to take a second thing here, Slide 60. Again,
25 Counsel didn't point you to any evidence in the record of species

1 outside the genus that are surprisingly inactive. He didn't point to
2 you any of that evidence that I noted that was lacking in their
3 record in his rebuttal.

4 But what he did point to you again is epistasis. Their
5 own expert, Dr. Park, again, he said in Exhibit 2077, page 201, line
6 7 to 13, distant residues are known to be coupled in some cases,
7 but they're not very common. And he talked about the fact that
8 you can treat mutations as independent many times. So that is an
9 agreed upon testimony here, and that defeats their evidence of
10 epistasis alone.

11 Now, given our colloquy about whether we should have
12 rewritten the claims to say, well, don't do this and don't do that. I
13 just want to point Your Honor, you may be aware, to in re
14 Anderson, 471 F.2d 1237, lines 1242. It is not the function of
15 claims to exclude all such matters, referring to a combination that
16 would render it inoperative, but to point out what the combination
17 is.

18 Again, thinking about those common structural features
19 in the mutagenesis data and specifically looking at the claim --

20 JUDGE FREDMAN: Those would be the things that
21 would be -- what you want the claim to be. But go ahead.

22 MR. SUMMERS: Sure. So --

23 JUDGE FREDMAN: But that argument really holds up
24 (INDISCERNIBLE) other way for you. I'd do that.

25 MR. SUMMERS: In what regard, Your Honor?

1 JUDGE FREDMAN: I'm just saying that it's saying you
2 should say what you really want. And you're saying -- you don't
3 say what you really want.

4 MR. SUMMERS: We have said what we really want,
5 Your Honor. And to be clear, we think the claims are structurally
6 defined only. They include actives and inactives. And we think
7 the guidance and the specification doesn't need to be imported in
8 the claims to point that that's what the specification is for.

9 I want to point you just to Dr. Petsko's declaration,
10 specifically into the evidence that he gives and the testimony he
11 gives about making multiple mutations. This is Dr. Petsko's
12 declaration, specifically paragraphs 317 to 339 and then from 343
13 to 383 and specifically 353 to 365, he talks about how a POSA
14 would go about using routine methods we've talked about to
15 maintain activity, how you use clustered sphere models to
16 visualize what substitutions to make, how a POSA would go about
17 trying to increase activity, and how they might go about addressing
18 use of inactives.

19 I want to talk about the variability that Petitioner talked
20 about in their rebuttal. So Petitioner, again, suggested that this
21 data somehow that the problems with the '429 and the '457 that he
22 alleges are there and the variability in the data that that also would
23 infect the '600 data. That's not correct. Because the assays are not
24 run in the same way. For instance, the secreted alkaline
25 phosphatase control that was used for expression, that was used in

PGR2025-00003 (Patent 11,952,600), PGR2025-00004 (Patent 12,018,298),
PGR2025-00006 (Patent 12,152,262), PGR2025-00009 (Patent 12,123,035)

1 the '600 Patent.

2 So using these -- the variability in these other assays,
3 which we would dispute, but it doesn't apply to the '600 data. Let
4 me talk very briefly -- so Dr. Sher -- about contraceptive utility.
5 Dr. Sher is a reproductive biology expert and, again, the only one
6 here in this case when you're assessing credibility. And he
7 grounds his analysis in the art. He cites a number of papers
8 relating to both the use of antisperm antibodies to allosterically
9 hinder sperm and the --

10 JUDGE FREDMAN: Is there any use like that in actual
11 systems? Is that used for any real purpose yet? Even now.

12 MR. SUMMERS: It actually exists in --

13 JUDGE FREDMAN: Is there any antisperm
14 contraceptive that exists?

15 MR. SUMMERS: Like in a commercial form? No.

16 JUDGE FREDMAN: Yes.

17 MR. SUMMERS: No, it does not. I don't think that's the
18 standard for --

19 JUDGE FREDMAN: I was curious.

20 MR. SUMMERS: Yeah. So specifically, I want to point
21 you to Exhibits 2153, 2155, and 2156. In Dr. Moon's declaration,
22 which we have not discussed a lot, but he addresses those at
23 paragraphs 33 to 37. And I think it will go to some of the points
24 you were discussing with Counsel.

25 And I want to point you then to Dr. Sher's declaration,

1 Exhibit 2072, paragraphs 32 to 34. And he cites the -- I went
2 through those exhibits earlier. But those are specifically evidence
3 of the scientific credible utility of these contraceptives.

4 One last point I want to make, Counsel suggested that
5 we've cited some new things in the art by citing to the Park
6 transcript and to their own exhibit. I don't know if there's anything
7 we can do to address that. But I don't think it's any surprise that
8 we would use those here.

9 So the last thing that I want to address is this -- is the
10 idea that you have to make trillions of choices when you're going
11 to practice this. That's not what a POSA would do. They don't go
12 in and go, I want to change every single one. They go to modify.
13 A rational protein designer goes to modify a protein with a
14 purpose. They have some idea.

15 They don't step back and sort of envision every single
16 polypeptide that they could possibly make. They say, that's a
17 region of the protein that looks interesting to me. And so trying to
18 rely on this cumulative effort, again, this exact thing that Amgen
19 warns you about, the exact thing that Wands just makes one of the
20 factors, that to me is an overreach and it's inconsistent evidentiary
21 -- with their evidentiary burden here.

22 JUDGE FREDMAN: (CROSSTALK).

23 MR. SUMMERS: With that, I'll rest. Thank you. And
24 Your Honor, I apologize if I talked over you in my eagerness a
25 little bit.

1 JUDGE FREDMAN: It's okay. I was going to return
2 these records. So thanks to both parties for appearing today, for
3 answering our questions. We'll definitely take the case under
4 advisement.
5 (Whereupon, the above-entitled matter went off the
6 record at 4:22 p.m.)