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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

- - -

CONJUPRO BIOTHERAPEUTICS, :
INC., :
Petitioner :
V. :
ASCLETIS PHARMA CHINA CO., :
LTD., :
Patent Owner :

- - -

CASE NO. PGR2025-00057
PATENT NO. 12,234,236
TITLE: GLP-1R Agonist and therapeutic method
thereof

- - -

June 23, 2026

- - -

Oral deposition of Yi Fan, Ph.D.,
held in the offices of Fox Rothschild, LLP,
2001 Market Street, Suite 1700, Philadelphia,
Pennsylvania 19103, commencing at 9:19 a.m.
on the above date, before Teresa M. Beaver, a
Professional Court Reporter and Notary
Public.

- - -

ESQUIRE DEPOSITION SOLUTIONS

A P P E A R A N C E S :

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I N D E X
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WITNESS	PAGE NO.
Yi Fan, Ph.D.	
By Ms. Agarwal	5

NO.	DESCRIPTION	PAGE NO.
Exhibit 2087	Paper from Journal of Medicinal Chemistry - Rational Design, Synthesis, and Structure-Activity Relationship of a Novel Isoquinoline-Based Series of HBV Capsid Assembly Modulators Leading to the Identification of Clinical Candidate AB-836	27
Exhibit 2088	U.S. Patent Number 10,683,302	68

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DEPOSITION SUPPORT INDEX

Direction to Witness Not to Answer

Page	Line	Page	Line
None			

Request For Production of Documents

Page	Line	Page	Line
None			

Questions Marked

Page	Line	Page	Line
None			

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YI FAN, after having been duly
sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

BY MS. AGARWAL:

Q. Hi, Dr. Fan. Could you please
state your full name for the record?

A. Yi Fan.

Q. And could you spell that?

A. Y-I first name, last name F-A-N.

Q. Okay. Great. Thank you.

My name is Isha. I'm going to
be asking you some questions today. And your
counsel may object to those questions from
time to time, but you should still answer my
questions.

Does that sound okay?

A. Yes.

Q. And if you don't understand a
question, please ask me for clarification.
Otherwise, I will assume that you have
understood my question.

1 Does that sound okay?

2 A. Sounds okay.

3 Q. And when you answer a question,
4 if you could please answer verbally rather
5 than just like nodding your head or shaking
6 your head, just so the court reporter can
7 transcribe your answers.

8 Does that sound okay?

9 A. Sounds okay.

10 Q. Great. Have you ever been
11 deposed before?

12 A. No.

13 Q. And do you understand that you
14 are under oath?

15 A. Yes, I understand.

16 Q. And so you understand that you
17 have to testify truthfully, accurately and
18 fully today?

19 A. Yes.

20 Q. And you also understand that our
21 court reporter here is creating a transcript
22 of our conversation today?

23 A. I'm aware.

24 Q. And is there any reason today

1 that you are not able to give accurate,
2 truthful and complete testimony, medical or
3 otherwise?

4 A. I can give testimony, yeah. It
5 will be okay, yeah.

6 Q. And my question is: Is there
7 any reason that you are not able to give
8 accurate, truthful and complete testimony
9 today for any reason?

10 A. No.

11 Q. And if that ever changes over
12 the course of a deposition, will you please
13 let me know?

14 A. I will.

15 Q. And if you need a break at any
16 point, just let me know. I will try to take
17 a break every hour or so. All I ask is that
18 if there's a pending question, you answer
19 that question first and then we can go on
20 break.

21 Is that okay?

22 A. Sounds good to me.

23 Q. I am going to hand you what has
24 been marked as Exhibit 1035.

1 A. Okay. So that's my declaration?

2 Q. Yes. And Exhibit 1035 is your
3 declaration; correct?

4 A. Yes.

5 Q. And if you go to the last page
6 or I guess Page 34 for your CV in this
7 exhibit --

8 A. Yes.

9 Q. That is your signature; correct?

10 A. Correct.

11 Q. And you signed it on May 27th,
12 2026; is that correct?

13 A. Correct.

14 Q. And have you noticed any errors
15 in your declaration?

16 A. Not on top of my head at
17 present.

18 Q. And when you prepared your
19 declaration, you thought everything in here
20 was truthful and accurate; is that correct?

21 A. Yeah, when I prepared, yeah,
22 that's what I view, yeah.

23 Q. And sitting here today, do you
24 believe that everything in your declaration

1 is true and accurate?

2 A. Sitting here today and on top of
3 my hand and -- it's still truthful and
4 correct.

5 Q. Okay. When were you first
6 contacted about this proceeding?

7 A. I don't remember exactly, but it
8 was around March. Maybe late March, but I
9 don't remember the exact date. So, some time
10 in March.

11 Q. March of 2026?

12 A. Yes. March, 2026, yeah. But I
13 don't remember exact date, yeah.

14 Q. That's fine. And when -- do you
15 remember when you were retained for this
16 matter?

17 A. So, contact, so, in my words, is
18 I was retained, so because I was contact,
19 drastic issue regarding GLP-1 bonding pocket
20 so it's around March, yeah.

21 Q. And when did you first start
22 considering the issues that you opine on in
23 your declaration?

24 A. Around March.

1 Q. And when did you first start
2 working on this declaration?

3 A. It's about similar time, but
4 later in the March. So, I was contacted and
5 I'm working on it, yeah.

6 So, yeah, so, it's in the same
7 months, but I don't remember exact date. But
8 maybe a week later or a little bit more than
9 seven or eight days. So, I don't really
10 remember, yeah.

11 Q. And over what period of time did
12 you work on your declaration?

13 A. Could you repeat your question?

14 Q. How long did it work on your
15 declaration for?

16 A. Oh, I don't remember the exact
17 hours, but it's more than 40 hours.

18 Q. More than 40 hours?

19 A. More than 40 hours. So, I mean
20 for to do the declaration. It's not for the
21 preparing for deposition. That's not
22 included.

23 Q. Okay.

24 A. Yeah.

1 Q. So, just on the declaration --

2 A. Yeah.

3 Q. You worked --

4 A. More than 40. That's about
5 because I don't remember exactly, yeah.

6 Q. And that was all in the March,
7 April time frame?

8 A. Yeah, some time in March
9 because -- or some time in May, I also -- I
10 writing that declaration.

11 So, I would say between the
12 March and to the end of May, so -- but, yeah.

13 Q. Okay.

14 A. Because different period of time
15 and you do different things. So --

16 Q. Yeah. Okay.

17 And have you talked to anyone
18 aside from counsel regarding your
19 declaration?

20 A. I talked to Dr. Toft. Am I
21 pronouncing right? Luke. So, I talk to
22 Luke. I talked to Dr. Chen and Dr. Zhu,
23 yeah.

24 MR. TOFT: Those are all

1 counsel.

2 BY MS. AGARWAL:

3 Q. Did you talk to anyone aside
4 from counsel regarding this proceeding
5 generally?

6 A. No.

7 Q. Have you spoken to any of the
8 other experts involved in this proceeding?

9 A. No.

10 Q. So, have you spoken to Dr.
11 Pirrung, for example?

12 A. I don't even know Dr. Pirrung is
13 a woman or man. So, I have no idea.

14 Q. Okay.

15 A. Solely based on the material I
16 read.

17 Q. So, did you review Dr. Pirrung's
18 declaration?

19 A. Yes.

20 Q. Do you know Dr. Pirrung?

21 A. I don't know.

22 Q. So you just stated that you
23 don't know --

24 A. Yeah. Yeah. Yeah.

1 Q. -- whether it's a man or woman?

2 A. Yeah.

3 Q. So, you've never met him, never
4 spoken to him?

5 A. Yeah.

6 Q. Have you reviewed any of his
7 previous research?

8 A. No.

9 Q. No. Okay.

10 And the rate that you are
11 charging for this proceeding is \$450 per
12 hour; is that right?

13 A. Yes, I was charged I think hour
14 rate 450, yes.

15 Q. So, you testified that you spent
16 more than 40 hours on your declaration.

17 How much time have you billed in
18 total to this proceeding?

19 A. You mean how much money I
20 receiving right now? Is that what you ask
21 me?

22 Q. If that's an easier number for
23 you to give --

24 A. I haven't received bill yet.

1 Q. Have you much have you -- on
2 this --

3 A. It's more than 40 hours. I
4 don't really remember. The reason I cannot
5 give to you right now because not on top of
6 my head. But it's more than 40 hour for
7 sure. And I don't receive my payment.

8 Q. You don't receive any payment?

9 A. Yeah, I don't receive any
10 payment.

11 Q. Have you worked with Conjupro
12 Biotherapeutics, Inc. prior to this
13 proceeding?

14 A. So, for this case, I'm not. I
15 did limited consulting work for them. I
16 believe it's last year.

17 Q. And do you remember what time
18 frame that consulting work was in Conjupro?

19 A. I don't remember exactly. But
20 possibly the first half year of 2025 and it's
21 limited consulting work. Nothing scientific.

22 Q. And what exactly did that
23 consulting work entail?

24 MR. TOFT: And I'll just caution

1 you to the extent that involved attorneys,
2 not to divulge the substance of any
3 communication with any attorneys because that
4 would be privileged and whatever
5 confidentiality obligations you have
6 regarding that consulting work.

7 THE WITNESS: Okay. Yeah, so
8 attorney instruct me not to disclose, so...

9 BY MS. AGARWAL:

10 Q. So, I believe your attorney
11 instructed you not to divulge any privileged
12 or confidential information. But anything
13 that's not privileged or not confidential
14 that you can just give me the subject matter
15 of what you consulted on?

16 A. It's labor work. It's just a
17 document reading, categorize and put into the
18 database.

19 Q. Did that involve any regulatory
20 work?

21 A. Could you clarify your question?
22 What means regulatory work?

23 Q. So, anything involving, you
24 know, FDA or the government sort of

1 consulting work in that regard?

2 A. I'm not talking to any
3 regulatory work. So, I'm just home. I'm
4 sure anybody can do it. It's just the label
5 work.

6 Q. I guess what I'm trying to ask
7 is what exactly do you mean by label work?
8 What sort of label?

9 A. So, I read the document and then
10 find the key word or something and categorize
11 the document, so people can read fast.

12 Q. Okay. So it's not like a drug
13 label?

14 A. It's not. That's why I state
15 label work, so even high school or something,
16 it's just I read the document and archive or
17 something. So, the lawyer can, attorney can
18 read faster.

19 Q. As the only consulting work
20 you've done with Conjupro; is that correct?

21 A. Yes. Yes.

22 Q. And to the extent that you can
23 tell me, what sort of documents were you
24 reviewing in this labeling work?

1 MR. TOFT: Again, I'm going to
2 instruct you to the extent that this involved
3 an attorney, I would instruct you not to
4 disclose any privileged information and/or if
5 you have a confidentiality obligation, keep
6 that in mind as well.

7 THE WITNESS: Okay. So -- so,
8 okay. So I reviewed Dr. Pirrung's
9 declaration and the reviewed Dr. Wiph
10 declaration and mainly my focus is Kawai's
11 paper because that's provide a starting point
12 for my analysis. She knows the pattern and
13 Yoshino Su's pattern briefly.

14 (Reporter clarification.)

15 Q. S-U pattern. And that's for
16 your current declaration; is that correct?

17 A. Yes.

18 Q. I was asking still on your
19 consulting work last year for Conjupro, sort
20 of what was the subject matter of the
21 whatever it was you were reviewing that you
22 were doing the labeling work for?

23 MR. TOFT: Again --

24 THE WITNESS: I don't know

1 anything because I already forgot. So at
2 time I just categorizing which category is.

3 So, I have no idea. I cannot
4 remember.

5 BY MS. AGARWAL:

6 Q. You have a Ph.D. in
7 computational chemistry; is that correct?

8 A. Yes.

9 Q. And the focus of that Ph.D. is
10 on computational chemistry; is that correct?

11 A. Yes, this is correct.

12 Q. And as part of your Ph.D., you
13 also focused on the modeling of structured
14 based drug design; is that right?

15 A. I'm doing molecular mechanic
16 force field development. That's the basis
17 for structure base design, the knowledge
18 development.

19 Q. And what exactly is molecular
20 mechanic force field development?

21 A. So, molecular mechanic force
22 field is how did you -- so, it's basis how
23 bonds, the atom linked together, what's the
24 force content, what's bonding angle, what's

1 the torsion angle so provide the correct
2 geometry and its foundation for the
3 structure-based design. So I'm just doing
4 parameterization, yeah.

5 Q. What do you mean by
6 parameterization?

7 A. Force constants on the angle and
8 the bond length, torsion angle and what's the
9 correct, you can develop and in order to fit
10 a whole picture, so.

11 (Reporter clarification.)

12 A. I'm sorry. So, it's force
13 constant, bonding angle, torsional angle.
14 Other people dihedral angle and you just
15 develop the parameters that you are able
16 providing the other scientists that can use
17 that to general structure. It's not level
18 one, but it's kind of universal, yeah.

19 Q. And you testified that molecular
20 mechanic force field development is the basis
21 for structure-based design; correct?

22 A. Yeah, because for protein-ligand
23 complex, they use the GEE behind that is
24 molecular mechanics force field. You need to

1 category these molecules. You need some
2 algorithm, parameters. That's molecular
3 mechanics. That's one part of it. Of course
4 docking and these things is on top of it.

5 Q. And so structure-based drug
6 design has more factors than just the
7 molecular mechanic force field development;
8 correct?

9 A. I agree.

10 Q. So, can you explain what
11 structure-based drug design is?

12 A. Yeah. Structure-based drug
13 design contains a multiple facts and am I not
14 remember every aspect, but important aspects
15 is first thing you need to have the protein
16 structures. That's your basis, right.

17 So, whether from cryo-em or from
18 x-ray. And the second you need to analyze
19 the protein ligament actions, you assess the
20 bonding molds and you work with chemist. I
21 always put that is very important. And
22 visualization and you interpreting your data
23 and create the hypothesis and to analyze the
24 structure compatibility, you know, the

1 receptor and the ligand, how they fit.

2 So, that's exactly the work I
3 did for this analysis.

4 This is structure-based drug
5 design. The first important factor you have
6 you to have structure and you're trying to
7 interpret the data and you're trying to
8 interpret the ligands in the real world.
9 That's the simple way.

10 Q. Are you familiar with the term
11 SAR?

12 A. Yes.

13 Q. What does SAR stand for?

14 A. Structure activity relationship.

15 Q. And you don't have any
16 experience with SAR; is that correct?

17 A. I work with chemistry to review
18 the SAR at a daily basis. That's part of
19 job, because when you form the hypothesis,
20 explain the things, the SAR is one important
21 aspect.

22 Q. So, in your words, what is SAR?

23 A. SAR is you have chemical
24 structures, that's drug, right, and they test

1 it and you have activity. You're trying to
2 see the structure and activity, if it
3 correlates or what's the relationship you got
4 if the molecule is potent or less potent,
5 SAR.

6 So, SAR, I use your legal words.
7 I don't know if it's exactly right. It's
8 prior art. So, I don't know if it's correct
9 word, yeah.

10 Q. And in your experience, how does
11 an SAR analysis typically work?

12 A. So, my -- I just talk about my
13 daily work.

14 So, you took the project and you
15 review the structure. You download the
16 structures. And then it might have some SAR
17 from literature and/or maybe chemistry did
18 some past in the exploratory stage or some
19 things. So you have data; right? So
20 basically it's data. So, you review those
21 data and then you design your compounds using
22 the structures and then you talk to the
23 chemist and you both discuss if my
24 interpretation consistent with data. If it's

1 not, I will use SAR data to refine my model
2 and then with the project to progress then
3 you have more data generated.

4 So, it either consistent with
5 your idea or either contradictory.

6 So, I always refer to the
7 structure-based design is iterative structure
8 based design. It's not one moment you have
9 to constantly refine, yeah.

10 Q. And you testified that you might
11 have some SAR from literature or maybe the
12 chemistry; is that right?

13 A. Yes.

14 Q. And what do you mean you might
15 have some SAR from the chemistry?

16 A. Because the chemists synthesize
17 compounds. Biologist test it and you have
18 data.

19 Q. And generally speaking, how
20 extensive is an SAR analysis?

21 A. It's --

22 MR. TOFT: Object to the form.

23 THE WITNESS: Sorry.

24 MR. TOFT: You can answer.

1 THE WITNESS: Contents

2 dependent. So, for some project, you have
3 limited SAR because you don't really have
4 lots of data accumulated; right? So you rely
5 on the structure, but for certain project,
6 you have lots of SAR.

7 So and also, when project
8 progress, the SAR data accumulated.

9 BY MS. AGARWAL:

10 Q. What exactly do you mean by that
11 the SAR data accumulated?

12 A. Because -- so, you start with
13 the project from day one, right? You might
14 not have much SAR, right?

15 But when the project progressed
16 to the -- I give example, like the second
17 year or third year, I don't know. I just
18 make example.

19 So, during these two years,
20 chemists making compounds, biologist testing
21 compounds. So the data accumulated. So you
22 have more SAR. That's what I mean.

23 Q. Okay. I got it.

24 And typically, as you progress

1 through the SAR analysis to year two or year
2 three, how many sort of compounds are
3 synthesized and tested?

4 MR. TOFT: Object to form.

5 You can answer.

6 THE WITNESS: So, the -- so,
7 that's heavily contents dependent.

8 So, it's hard to answer. And
9 this is all the scope of my analysis. In the
10 context of analysis, I'm not dealing with
11 that, yeah.

12 So, this is case dependent.

13 BY MS. AGARWAL:

14 Q. On average, how would you --
15 sorry. Strike that.

16 On average, how many structural
17 variations or modifications are created
18 during an SAR analysis?

19 A. That's, I mean depend on the
20 project and the variation is large.

21 So, I'm not able to give you one
22 number because every project is different and
23 some project only one chemist. Some projects
24 might have assorted chemists.

1 MR. TOFT: Slow down.

2 THE WITNESS: If you have
3 assorted chemists, you will have a lot of
4 compounds synthesized. But if you only have
5 one chemist explore, you might have less.

6 So, it's contents dependent and
7 I think it's -- that's not what I'm asking to
8 do the analysis.

9 BY MS. AGARWAL:

10 Q. Okay. You testified that when
11 you do structure-based drug design, you call
12 it an iterative process; correct?

13 A. Uh-huh.

14 Q. And so when trying to identify,
15 for example, an optimized lead compound --

16 A. Uh-huh.

17 Q. -- you would also use that
18 systematic iterative process; correct?

19 A. Yeah. Iterative means it's just
20 a communication.

21 So, I design a compound. I sit
22 with chemist. We look together. We review
23 SAR together. And design some compound. He
24 made it. And we test it and we'll sit down

1 again. So that means iterative. Iterative
2 basically is constant communication.

3 So, you cannot, it's just we
4 communicate in one day and then we don't have
5 any communication anymore. So, I need
6 feedback. So, iterative just mean
7 communication and the feedback.

8 Q. I'm going to hand you an
9 exhibit. We need to mark this one Exhibit
10 2087.

11 - - -

12 (Whereupon, Deposition Exhibit
13 2087, Paper from Journal of Medicinal
14 Chemistry - Rational Design, Synthesis, and
15 Structure-Activity Relationship of a Novel
16 Isoquinoline-Based Series of HBV Capsid
17 Assembly Modulators Leading to the
18 Identification of Clinical Candidate AB-836,
19 was marked for identification.)

20 - - -

21 BY MS. AGARWAL:

22 Q. This paper is titled Rational
23 Design, Synthesis, and Structure-Activity
24 Relationship of a Novel Isoquinoline-Based

1 Series of HBV Capsid Assembly Modulators
2 Leading to the Identification of Clinical
3 Candidate AB-836; is that correct?

4 A. Yes.

5 Q. How do you say that?

6 A. I think it's isoquinoline.

7 Q. Isoquinoline?

8 A. I don't know if my pronunciation
9 correct because I'm not a native English
10 speaker.

11 Q. Isoquinoline. Okay.
12 You're an author on this paper;
13 correct?

14 A. Yes.

15 Q. And you are part of this project
16 that is described in this paper; correct?

17 A. This is correct.

18 Q. And what is -- this project
19 identifies a lead compound that inhibits
20 replication of the hepatitis B virus; is that
21 correct?

22 A. Yes.

23 Q. And when identifying a lead
24 compound such as the one that is described in

1 this paper, you would assess modifications to
2 different parts of the backbone of the
3 structure; correct?

4 A. Yeah. Not the backbone. I'm
5 trying to -- what backbone you're talking
6 about?

7 Q. Sure.

8 A. Talking about, I mean what's the
9 backbone you are referring to?

10 Q. So, if we go to Figure 3 in this
11 paper.

12 A. Figure 2 and Figure 3. Yes.

13 Q. That represents a backbone of
14 the structure or a reading scaffold of the
15 structure; correct?

16 A. Yeah. I think it might be
17 better to call scaffold because that's
18 usually we call small molecule.

19 Backbone, we mostly referring to
20 the protein backbone. So, that's why I'm
21 confused.

22 Q. Okay. All right.

23 A. But it's a scaffold, yeah. It's
24 also it's just a graph, yeah.

1 Q. And so you would agree that when
2 identifying a lead compound, you would assess
3 modifications to the scaffold of a structure
4 that's been identified; correct?

5 MR. TOFT: Objection. Vague.
6 Calls for incomplete hypothetical.

7 THE WITNESS: Yeah, so I think I
8 only can speak something general because
9 arbutus, (reporter clarification)
10 A-R-B-U-T-U-S, exists. And it's part of the
11 clinical candidate.

12 So, if I relieve too much
13 information, so, sometimes I don't know, I
14 will get to their privilege space so I might
15 got trouble.

16 So, but I can't tell you general
17 idea, I mean if you ask me.

18 So that's -- because this is
19 their part of clinical candidates. I mean
20 everything in the paper was published, but I
21 don't know, I mean the company, they were
22 still use the structure for some other
23 purpose or something. So, I cannot tell you
24 too much in the detail.

1 But I mean if you ask the
2 general, I can answer, yeah.

3 BY MS. AGARWAL:

4 Q. So, like you said, this paper
5 was published?

6 A. Yeah.

7 Q. So this is public information?

8 A. Uh-huh.

9 Q. And so if we go to, that same
10 page, that Figure 3 is on.

11 A. Uh-huh.

12 Q. We go to the, we go to the
13 results and section right above Figure 3?

14 A. Yes. Yes.

15 Q. States, The conformation of the
16 Cp subunits and the binding pocket
17 accommodating the small molecule are
18 relatively well conserved for the different
19 CAMs binding at the dimer to dimer interface
20 based on the published reports.

21 Do you see that?

22 A. Yes, I do.

23 Q. And that refers to Figure 2;
24 correct?

1 A. Yeah.

2 Q. Figure 2. Yeah.

3 And so the researchers here have
4 identified some key structural parts of the
5 small molecule; correct?

6 A. So, I would say so if you look
7 at the Figure 2, so, basically is I overlay
8 three structures and identify the importance
9 features which in the middle, trip one or
10 two, Threonine 128 if you see in Figure 2,
11 which I remember. And then it's just to see
12 some pocket is not occupied, right, because
13 these are three different class.

14 Some of them, it's also belong
15 to us, but some of them is in the nature.
16 But these are previously published.

17 So then we just come up with
18 general modern strategy and design our
19 compound.

20 It's just only these compound
21 together and finding -- overlay the compound
22 together and trying to see, it's sort of like
23 a pattern recognition and to see when they
24 are bonding, which are common, which are

1 different and common one is analyzed, the
2 view is important and then it's something is
3 unique and we trying to tag it formed
4 hypothesis. That's basically it. Yeah.

5 Q. And so, this project involved
6 conducting an SAR analysis; correct?

7 A. SAR analysis always part of
8 structure-based project.

9 Q. And then once you formed your
10 hypothesis, the -- you worked together with
11 the researchers to synthesize various
12 compounds; correct?

13 MR. TOFT: Object to form.

14 THE WITNESS: Yeah. So, what
15 means I collaborate with the chemist to --
16 could you clarify?

17 BY MS. AGARWAL:

18 Q. Yeah. Sure.

19 So -- let me start over.

20 Once your hypothesis was formed,
21 then various different compounds were
22 synthesized as part of this study; correct?

23 MR. TOFT: Same objection.

24 THE WITNESS: That was pretty

1 vague.

2 So, yeah, because -- so, maybe
3 you give me example and so I might be able to
4 better answer that questions.

5 Because hypothesis, I draw here
6 is pretty broad. So, it's not specific. So,
7 that's just the general idea. So, yeah. So
8 what did you mean synthesize or something?
9 So you give me examples so I can answer more
10 specifically.

11 BY MS. AGARWAL:

12 Q. Yeah. So, you all came up with
13 a hypothesis; correct? And then different
14 substituents were sort of systematically
15 evaluated on different parts of the compound;
16 correct?

17 MR. TOFT: Same objection.

18 THE WITNESS: Yeah, so I mean
19 for the project, you usually, it's not only
20 one series. You possibly might have two or
21 three series. It's really depend on the
22 project.

23 Some project only has one but
24 lot of time have two or three series and they

1 are scaffold is all different.

2 So, if we just say something in
3 general and say you modify the substitutes or
4 something, and sometimes this one is just a
5 foundation. So, it's not something is -- so,
6 it's -- it's a foundation to evaluate is the
7 thought, yeah.

8 So, basically the Figure 3 is a
9 general thought.

10 But individually, I mean
11 scaffold, it might be different, so -- yeah.
12 So -- so, I just don't know what you want to
13 ask of me. So --

14 BY MS. AGARWAL:

15 Q. Sure. We can go to Page 16776,
16 Table 1.

17 A. Yeah.

18 Q. And Table 1 shows cellular
19 antiviral potency, EC 50, of substituted urea
20 derivatives 1b through 1h.

21 Do you see that?

22 A. Yes, I do.

23 Q. And there's kind of a, that ring
24 scaffold structure, there's an image there.

1 And then on the second nitrogen
2 of, in the middle of the structure --

3 A. Is R, yeah.

4 Q. There's an R group; correct?

5 A. Uh-huh. Uh-huh.

6 Q. So, that R group, various
7 different substituents were tested at that
8 position; correct?

9 A. Yes. It's chemist synthesized
10 and casted in the biology as listed in this
11 paper.

12 Q. And the EC 50 of each of those
13 substituents was also studied; correct?

14 A. What did you mean studied?

15 Q. Yeah. So, each of the
16 substituents listed here in this table, 1b
17 through h were tested at that R position on
18 the compound that's shown; correct?

19 A. These compound was synthesized.
20 It's listed here because they have activity.
21 So, they test it, yeah.

22 Q. Okay. And the EC 50 data that's
23 listed in Table 1 tells you the activity of
24 the compound when those substituents were

1 synthesized with the molecule; correct?

2 MR. TOFT: Object. Form.

3 THE WITNESS: Could you clarify?

4 BY MS. AGARWAL:

5 Q. For example, compound 1b at
6 position R would have a methyl group;
7 correct?

8 A. Yeah.

9 Q. And the EC 50 of that compound
10 with the methyl group was analyzed; correct?

11 A. Was tested, yeah.

12 Q. We also see that compound 1e, a
13 cyclopropyl group was synthesized onto the
14 compound; correct?

15 A. Cyclopropyl is synthesized and
16 tested, yeah.

17 Q. And the EC 50 of the cyclopropyl
18 group is worse, compared to all of the other
19 substituents that were tested; correct?

20 MR. TOFT: Object to form.

21 THE WITNESS: So, I do not want
22 to further detail and discuss this project
23 because it's beyond my scope of analysis.
24 We're today discussing for the GLP-1 targets.

1 So, it's not discuss my previous work.

2 So, I suppose shouldn't tell you
3 the -- what's going on in -- when we're doing
4 these projects. I might slip through for my
5 mouth for some information that I should not
6 say.

7 So, I don't really want -- I
8 don't really feel comfortable and to discuss
9 the SAR for the capsid (reporter
10 clarification), C-A-P-S-I-D, inhibitors.

11 Q. I'm not asking you to discuss
12 anything confidential that you did at
13 Arbutus.

14 I'm just asking you what this
15 paper tells us.

16 A. Okay.

17 Q. And in Table 1, we can see that
18 the EC 50 activity is worse compared to all
19 of the other substituents.

20 A. I can make a comment on that
21 one. I can tell you they are worse for
22 others, but for 1g, 1b, 1e, I will not
23 categorize them. They are similar.
24 Comparable because this is cell-based

1 activity. So, they are same.

2 So, you cannot use exact number
3 is point four, is more potent than point four
4 seven. That's no such rule. Because the
5 experiment assay, there is error, you know,
6 bar and I think we particularly listed here.
7 That means how many times we tested and
8 what's the standard error or standard
9 deviation there.

10 So, I mean to me, based on my
11 experience in structure-based project and I
12 would say 1b, 1e, 1g are more or less they
13 are comparable.

14 1d, yeah, the potency is better.
15 (Stenographer clarification.)

16 Q. If you could turn one before to
17 Page 16775.

18 In the second column about maybe
19 like fourth of the way up?

20 A. Four, yeah.

21 Q. There's a sentence that starts
22 the cyclopropyl urea, in parenthesis, 1E.

23 Do you see that?

24 A. Could you --

1 Q. On Page 16775?

2 A. Uh-huh. 65, right?

3 Q. Yeah. It's the one ending in
4 75, yeah.

5 A. Oh, okay.

6 Q. There's a sentence about a
7 fourth of the way up that starts, the
8 cyclopropyl urea in parenthesis, 1e.

9 A. Let me see 1b. Where is it?
10 Could you point it to me?

11 Q. Yeah. Right here.

12 A. Let me read it. Yeah.

13 Q. Okay. So, that sentence that
14 starts, The cyclopropyl urea (1e), however,
15 resulted in a reduction in antiviral activity
16 versus 1b and 1c, suggesting that a branched
17 aliphatic substituent was detrimental to
18 potency.

19 Do you see that?

20 A. Yeah, I see, yeah.

21 Q. Based on this data, the
22 cyclopropyl substituent at that position was
23 not advanced to further study; correct?

24 A. I cannot tell you. So when you

1 publish the paper at that time you might
2 realize something is -- I don't know what I
3 should say is not good, but later, so that's
4 why I going back my original word iterative.

5 So, to one point, you learn SAR
6 and after a period of time you realize what
7 do you see. It might not be true because you
8 test it again, right? Biologists always
9 repeat their assay. You might get a
10 different result, and you form a new bonding,
11 which is very important feedback to your
12 work. I cannot tell you the cyclopropyl
13 later in our study or not. I cannot say
14 that.

15 So I just saying maybe in that
16 paper at that time when we published we do
17 state that cyclopropyl, because based on the
18 exact number and if you look at the
19 experiment, because it's been a while so I
20 don't really remember. But if you look at
21 the 1e and I notice that standard error is
22 low. Because I measure the standard error,
23 how many time you measure it and how tightly
24 your data produced before this particular

1 compound, the standard error is .07.

2 So, that means the variation is
3 small. So, that's at that time, we formed
4 that conclusion. So, which is fair. But
5 whether we utilize that group later or not, I
6 cannot disclose that information.

7 Q. But in this paper, that
8 substituent was not advanced; correct?

9 A. There's no -- those things is
10 advanced or not because we advance things,
11 synthesize things, depend on which group.

12 So, for instance, for that
13 particular molecules, so, it's in Table 1,
14 right, we're talking about same, for this
15 series, that cyclopropyl might not be
16 synthesized again, right? I just make case.
17 It doesn't mean it exists in the real world.

18 But if you change the fluorine
19 chlorine (reporter clarification)
20 F-L-U-O-R-I-N-E, I hope I spelled it
21 correctly and chlorine, C-H-L-O-R-I-N-E.

22 So you the change the other
23 things because when you're bonding to the
24 pocket, you might change something.

1 So, in the different series, you
2 might use in cyclopropyl again. That's just
3 asking general. But in this particular
4 series, I don't remember because it's been
5 too long and I leave Arbutus in 2017. So,
6 no, it's 2024 or later, 2023. I don't
7 remember exactly, but it was recent years.

8 And capsid was my early project.
9 I don't remember every piece of details. So
10 I don't know if this cyclopropyl is moved
11 forward or not. And I think that question is
12 totally irrelevant with my analysis.

13 Q. So, you can't tell me in general
14 in the future if the cyclopropyl was moved
15 forward or not, but in this particular
16 series, the cyclopropyl does not seem to have
17 moved forward; correct?

18 A. Today, I mean I'm not providing
19 opinion out of the scope of GLP-1 art.

20 So, I only offering opinion,
21 whatever I describe in the contents of the
22 this declaration.

23 For anything else, I would not
24 answer. It's not what I'm not answer. So,

1 that possibly is not good word.

2 So, it's just saying I'm not
3 able to offer opinion in -- I only offer
4 opinion in the contents of my analysis
5 because that's the purpose of this
6 deposition.

7 Q. So --

8 A. We discuss that -- I think I
9 already talked too much, yeah.

10 Q. This is part of your experience
11 and your background that you bring to your
12 declaration and your opinions.

13 I'm not asking you your opinions
14 on this paper. I'm asking you what this
15 paper says, which you are an author on.

16 So, just to go back to my
17 question, in this particular series, the
18 cyclopropyl substituent was not advanced; is
19 that correct?

20 A. So, I work capsid or other
21 project, just to demonstrate I have extensive
22 experience in structure-based design. I'm
23 not talking about the discuss the SAR and
24 discuss how we come up with the scaffold,

1 because these are purely contents dependent.

2 If out of scope of contents, I
3 mean the opinion I'm offering here, it's the
4 technique and the method is applicable.

5 So, it's similar. But every
6 project that have unique feature and they
7 have their biology targets featured, so you
8 cannot put these things, you form the
9 conclusion and you use and put into here,
10 there is no -- I mean for the chemical, small
11 molecule.

12 The only thing I can say, I did
13 lots of structure-based projects and I have
14 extensive experience in structure-based
15 project and whether it is anti infective, or
16 this one is anti infective and this one is
17 GLP-1, CPCR. So to me is all the same. You
18 have 3D structure and I analyze the protein
19 ligand attaching and compound and come up
20 with my hypothesis.

21 But I do not discuss the SAR and
22 how to develop, yeah.

23 Q. So, you discuss a cyclopropyl
24 substituent in your declaration here;

1 correct?

2 A. Yes, that's correct.

3 Q. So, I'm just asking about sort
4 of similar cyclopropyl substituent in this
5 paper.

6 And it is your testimony that
7 it's context dependent; correct? And so a
8 cyclopropyl substituent in this context, the
9 capsid context, cannot apply necessarily to a
10 cyclopropyl substituent in the GLP-1R
11 context; correct?

12 MR. TOFT: Object to the extent
13 it mischaracterizes testimony.

14 BY MS. AGARWAL:

15 Q. Is that correct?

16 A. So, all I can say is every case
17 is different. Every pocket is different.
18 So, cyclopropyl just the chemical matter,
19 which I doing is characterization of the
20 protein ligand into actions. What I'm seeing
21 is not cyclopropyl. Isopropyl, of course
22 these are chemical matter, but I'm doing as a
23 modeler, I'm doing the protein ligand into
24 action. So, that's something. So, I'm not

1 offer opinion in terms of this aspect.

2 Q. I'm just going to stick with
3 your paper for just a little bit longer.

4 A. Okay. Yeah. It's a little bit
5 too long.

6 Q. Okay. So, moving on from Table
7 1.

8 A. Uh-huh.

9 Q. In Table 2, it looks like a
10 methyl substitution was added to the
11 isoquinoline; correct?

12 I'll stop there. Is that right?

13 A. Yeah.

14 Q. And then with that methyl
15 substitution at that position, a number of
16 substituents were tested again; correct?

17 A. Yes.

18 Q. And that would be compounds 3b,
19 3c, 3d, 3e and so forth all the way to 3j?

20 A. Uh-huh.

21 Q. Is that correct? Okay.

22 And then if we turn to Table 3,
23 this looks like the researchers shifted their
24 focus to a different part of the compound;

1 correct?

2 A. Yes.

3 Q. And the R group is, forgive me,
4 my chemistry is not so good, but it's on that
5 aromatic ring to the right on the compound;
6 correct?

7 A. Correct.

8 Q. And a number of substituents
9 were tested at that position; correct?

10 A. Yes, that's correct.

11 Q. And below Table 3 in Table 4 the
12 R group is now on the left side of the
13 compound; is that correct?

14 A. Yes, that's correct.

15 Q. And the researchers tested
16 substituents for I believe that's the
17 phenylurea; is that correct?

18 A. Yeah, you can call that, yeah.

19 Q. And that's on a different part
20 of the compound --

21 A. Yeah.

22 Q. -- than what we looked at
23 before; correct?

24 A. Yeah.

1 Q. And we go back a couple of pages
2 to the page ending in 777?

3 A. 777. Uh-huh.

4 Q. The last paragraph in the second
5 column --

6 A. Yeah.

7 Q. It looks like the researchers
8 also varied the electronic nature of the core
9 of this compound; is that correct?

10 A. Stacking, yes.

11 Q. Are you aware of whether a
12 patent application was filed for the compound
13 in this paper?

14 A. I don't know.

15 MR. TOFT: Object to form.

16 THE WITNESS: Which compound?

17 Which pattern are you talking about? Is
18 my -- that patent or, are you talking about
19 the GLP-1R?

20 BY MS. AGARWAL:

21 Q. This -- for this paper, do you
22 know if any patents were filed based on this
23 paper?

24 A. Yeah.

1 Q. You are aware?

2 A. I'm aware, yeah.

3 Q. So, a patent was filed based on
4 this paper?

5 A. The patent, yeah, I don't
6 remember. I do not recall if it's for a
7 particular series or for a particular
8 compound. A patent is really complicated.
9 Modeler, as a computational chemist, we are
10 not a part of writing the patent. The
11 chemist write it. So, I do not know if every
12 chemical matter were covered or not. I do
13 not know.

14 And it's been too long and I do
15 not recall.

16 Yeah, but you see general
17 scaffold it might be, but I don't know if
18 every compound they were in the patent or not
19 because patent is very long.

20 And personally, I contribute to
21 the idea. I might be in the patent, but I'm
22 not the person who formulated the patent
23 because the patent is about the activity.
24 Have you to test the compound, right?

1 So, you propose the idea. You
2 have intellectual input, but until the
3 compound synthesized, you have a result,
4 right?

5 So, chemistry have to synthesize
6 the compound and they form -- because that's
7 what they do. And sometimes the company,
8 they have some people --

9 MR. TOFT: Slow down. Slow
10 down.

11 THE WITNESS: -- doing that and
12 so if you ask me exactly, I would say I do
13 not remember.

14 BY MS. AGARWAL:

15 Q. Are you aware of whether you
16 have any patents on hepatitis B virus or
17 capsid inhibitor?

18 A. Yes.

19 Q. You do?

20 A. I do, yeah.

21 Q. And do you know if that patent
22 was a result of studies conducted within this
23 series?

24 A. That's too specific. But I -- I

1 don't remember exactly out of my head, but I
2 think it's supposed, yeah.

3 Q. And did you consult any docking
4 studies for this particular project?

5 A. Yes.

6 Q. And the docking study would have
7 evaluated all the different compounds that
8 are shown in this paper; correct?

9 A. Not necessarily, because if it's
10 obvious to the chemist -- because chemists
11 decided which compound to make, right? And I
12 provide the structure feasibility.

13 Sometimes they might take it,
14 but sometimes there's synthetic, and the
15 feasibility.

16 (Stenographer clarification.)

17 So, they are not able to make it
18 because it's too difficult.

19 So, it's really which compound
20 is moving forward. It's not my decision.
21 And sometimes they will come to ask me to
22 evaluate the compound. Sometimes I will
23 suggest a compound. But we will sit down and
24 to discuss. So, I only provide the structure

1 insights, but I'm not decide which compound
2 to make.

3 Q. How many compounds did you
4 conduct a docking study for in this paper?

5 A. I don't really remember. A lot,
6 because I talked to chemists in the daily
7 basis. And sometimes even not every compound
8 doing calculation. Because if it's obvious
9 in the pocket and the formulate and the
10 support your series and it obviously fit
11 there, like Dr. Wiph, in some cases he has
12 opinion.

13 So then if chemist agree with me
14 and we think it's reasonable and you even
15 don't need calculation.

16 But for sometimes you are not
17 able to answer the question, then you need to
18 carry out the docking. So for a period of a
19 couple years project, you ask me how many
20 compounds I evaluate. I don't know. So...

21 Q. And you said you did a lot for
22 this particular series?

23 A. Yeah. That's one of my
24 projects, yeah.

1 Q. How much would be a lot?

2 A. I cannot -- so, I, as I said,
3 when do that, I talk to chemists. I talk to
4 chemists at a daily basis. So, that's a lot.

5 So, we talking, right? The
6 daily basis is not saying, so, it's just
7 saying today if he had question, because
8 we're office is close to each other so he
9 would stop by. He possibly would stop by a
10 couple of times to ask more questions. Maybe
11 tomorrow he would not come because he's
12 synthesize or something else. But he will
13 come.

14 So, daily basis is just saying
15 we constantly has communication. And if I
16 saw something, I would stop by his office and
17 offer my opinion and if he has a set of
18 compounds, want me to evaluate, I will
19 evaluate.

20 So, it's mutual communication
21 and that's basically is refer to back
22 iterative structure-based design?

23 Q. So, my question is just how many
24 compounds would you have done a docking study

1 on for this particular series? And you
2 testified that it would have been a lot. I'm
3 just trying to get a number.

4 So, hundreds of compounds?
5 Would it be more than that?

6 A. I cannot provide a number, yeah,
7 because I didn't count it. And that was
8 five, seven years ago. Even you ask me is
9 like one year later you say how many
10 compounds that you evaluated? I cannot
11 remember.

12 It's just we constantly talk
13 about idea. So, I have no number that I can
14 give.

15 Q. But it would have been more than
16 ten?

17 A. Of course.

18 Q. More than 20?

19 A. I mean I don't want to go to
20 that -- more than 20, of course.

21 But I don't want to go that
22 detail because for the project over a period
23 of time, you have many idea were tested.

24 So, I cannot give the number

1 because I don't know the number. Just a lot.

2 Q. Yeah. I'm just going -- trying
3 to get a sense of what a lot is.

4 A. Yeah. Yeah. Yeah.

5 Q. And so more than 100?

6 A. I don't know. So, I don't want
7 to -- I mean because it's -- it's kind of --
8 I mean out of the scope, so, of this
9 analysis. So, yeah.

10 Q. Why don't we take a break, a
11 five, ten-minute break.

12 A. That would be good.

13 - - -

14 (Whereupon, there was a recess
15 commencing at 10:26 a.m. and concluding at
16 10:38 a.m.)

17 - - -

18 BY MS. AGARWAL:

19 Q. You can put aside Exhibit 2087.

20 A. Okay. Just put aside.

21 Q. So we, before we left for break,
22 or before we get to that, did you talk about
23 the substance of your testimony with counsel
24 during break?

1 A. We didn't talk about substance.
2 But we do talk about -- we did talk about the
3 (stenographer clarification).

4 MR. TOFT: She said rules.

5 THE WITNESS: About the
6 objection. I don't know about objection.

7 MR. TOFT: Don't discuss what we
8 talked about with her. But at a high level,
9 that's fine.

10 THE WITNESS: Yeah. Yeah.
11 Yeah. Slow down.

12 BY MS. AGARWAL:

13 Q. Great. Okay. And before we
14 went on break, we were talking about some
15 docking studies that you conducted for the
16 capsid inhibitor.

17 And in general you conducted
18 docking studies as part of your research
19 before; correct?

20 A. Correct.

21 Q. And over your career, how many
22 docking studies have you done, would you say?

23 A. That's hypothetical question.
24 I'm not answer. So, all I can say, a lot.

1 Lot. That means even within like a day, I
2 might calculate more than ten and over
3 months, sometimes I mean if it were to
4 screening, so what you mean is a lot? So you
5 mean one? Or you mean one compound? So
6 could you clarify that?

7 Because that's different things.
8 So, one might contain multiple compounds so
9 you might do together. You mean one compound
10 because structure-based analysis is this type
11 of work I did here is just very basic. So,
12 it's one type of analysis I did.

13 I do other things, yeah.

14 Q. But you've worked on many
15 projects in your career --

16 A. Yeah.

17 Q. -- where you have conducted
18 docking studies; correct?

19 A. That's correct, yeah. Because
20 docking is the standard tool and used in
21 structure-based design, but it's not related
22 to our say molecular visualization, pocket
23 characterization. These are also very
24 important.

1 Q. And molecular visualization, you
2 said it's not related to a docking study?

3 MR. TOFT: Object.
4 Mischaracterizes.

5 MS. AGARWAL: Is that right?

6 THE WITNESS: Molecular
7 visualization is just one form, how you
8 interpret it. How did you see? You did the
9 docking, right. You see how it fits. That's
10 a visualization.

11 BY MS. AGARWAL:

12 Q. Okay.

13 A. And you're talking to the
14 chemists, usually through visualization
15 because the chemists might not understand how
16 did you -- how you did. And they don't
17 really care, right?

18 But they just see your
19 hypothesis and to see if it's reasonable.

20 Q. Got it. So, molecular
21 visualization and pocket characterization are
22 kind of analyses you do as part of a docking
23 study?

24 A. Yeah. Yeah.

1 Q. And for the projects that you've
2 completed docking studies on in your career,
3 you said that it could either be one run or a
4 series; is that right?

5 MR. TOFT: Object to form.

6 THE WITNESS: Could you clarify
7 your question?

8 BY MS. AGARWAL:

9 Q. I'm trying to understand. You
10 said that, you know, it depends on what I
11 mean when I say a docking study. I'm trying
12 to understand when you do a docking study,
13 kind of what that captures. So, if you could
14 just explain to me at a high level what a
15 docking study typically involves?

16 MR. TOFT: Same objection.

17 THE WITNESS: Yeah, so it's kind
18 of vague. So, I would try my best to answer
19 your questions to see if I -- my -- if I
20 understand correctly your question because
21 your question is a bit vague.

22 So, one compound --
23 (stenographer clarification) you ask me to
24 bring one compound and ask me to evaluate one

1 substitution. But if you're doing virtual
2 screening, you might have a large database,
3 right? So you submit your compound and you
4 select the compound.

5 So, that might contain multiple
6 compounds in -- in one submission when you
7 do -- so that's what I mean, yeah.

8 Q. And in a virtual screening, kind
9 of how many compounds would be analyzed in
10 that run?

11 MR. TOFT: Object to the form.
12 Calls for an incomplete hypothetical.

13 You may answer.

14 THE WITNESS: It depends. Some
15 projects a little. Some projects a lot.

16 BY MS. AGARWAL:

17 Q. And some projects a little, how
18 many would be a little?

19 A. A little, like ten compounds or
20 20 compounds, right.

21 So, these are little.

22 Q. And how much would be a lot?

23 A. A lot is more than 100 or even
24 more.

1 So, it's hard to -- it's really
2 depend on the project, so what you are
3 facing. It's different, yeah.

4 Q. And in a typical research
5 project where you are trying to determine
6 like a lead compound, right, what types of
7 docking studies do you do in that particular
8 type of project?

9 MR. TOFT: Object to form.
10 Calls for an incomplete hypothetical.

11 THE WITNESS: So, again, it's
12 contents dependent. Different project, you
13 might do a little differently, but in
14 general, they are more or less the same,
15 similar.

16 So, because every pocket like
17 GLP-1 are, it's somewhat flexible and other
18 times the pocket is a little rigid. So,
19 it's -- you just keep them in mind.

20 So - but I think more or less
21 they are they are default. Yeah. So, I
22 think in general concept, they are same;
23 conceptually, what you do, they are the same.
24 It's applicable. It's not huge difference.

1 BY MS. AGARWAL:

2 Q. Okay. So, the method that you
3 apply is applicable across your project. Is
4 that correct?

5 A. I would say generally, yes.

6 If you go to detail level,
7 it's -- you would do the system differently
8 because you're dealing with different
9 biologics. Small detail might be different,
10 but in general the concept and the
11 methodology, it would be same.

12 Q. And so in a general --
13 generally, in a project where you are
14 attempting to identify a lead compound, how
15 many compounds would you typically analyze in
16 that context?

17 MR. TOFT: Object to form.
18 Calls for an incomplete hypothetical.

19 THE WITNESS: Yeah, so I don't
20 know you're talking about lead identification
21 or lead optimization. So, it's different.

22 So, which stage of drug
23 discovery projects are you talking about?

24 Q. So, if we start sort of at the

1 beginning, at the screening context, right,
2 and you're doing a virtual screening --

3 A. Uh-huh.

4 Q. -- and you're attempting to
5 identify a lead compound, on average, how
6 many compounds would you study in a docking
7 study?

8 MR. TOFT: Same objection.

9 THE WITNESS: Yeah, so it
10 depends on is the project in the lead
11 identification stage or lead optimization
12 stage.

13 So, lead identification stage,
14 you don't mind screening a lot. Also it's
15 project dependent. Yeah.

16 So, it's really, I mean it's
17 really, I mean it is content dependent.

18 BY MS. AGARWAL:

19 Q. And in a lead optimization
20 study, how many compounds would you be
21 looking at, typically?

22 MR. TOFT: Same objection.

23 THE WITNESS: Small. I cannot
24 give you a number in particular. Because the

1 question you ask is all contents dependent.

2 You cannot use what I said and to form
3 general rule.

4 So, if you have some particular
5 substitution, you have some method, you want
6 to -- the chemist want to synthesize, you
7 might have a lot to evaluate. But sometimes
8 you have small one. So, just looking at if
9 this one fits or this one not is small. Just
10 like case identify four or five, sometimes
11 even one.

12 So in general, lead
13 optimization, that's all I can say. So, lead
14 optimization you're screening less, a lot
15 less than the lead identification stage.

16 But even with lead
17 identification stage, sometimes we
18 contribute. Sometimes if they have other
19 ways to come up with the hits, we do not
20 participate.

21 So, it's really complicated
22 situation. I cannot use some general rule.
23 So you have to tell me which projects that we
24 are talking about.

1 Q. So, would there be -- sorry.
2 Strike that.

3 So, in some contexts, it would
4 make sense to limit your docking study and
5 analysis to five compounds; is that right?

6 A. Yeah.

7 Q. And that's happened before in
8 your research?

9 A. A lot.

10 Q. And for what reasons would you
11 limit your docking study to five compounds?

12 MR. TOFT: Object to form.
13 Calls for an incomplete hypothetical.

14 You may answer.

15 THE WITNESS: Okay.

16 BY MS. AGARWAL:

17 Q. Do you want me to repeat my
18 question?

19 A. Yeah. Yeah.

20 Q. For what sort of reasons in your
21 research would you limit a docking study to
22 five compounds?

23 A. Yeah, so mentioned, as I
24 mentioned earlier, two-way communication.

1 Sometimes I propose the compound to chemists.
2 If I saw something is good, right, that's my
3 idea.

4 The other cases is chemists want
5 to synthesize some compounds and they want to
6 know if they are fit in the pocket.

7 So, that's like the case I'm
8 getting with right now. They might bring
9 only one compound. They might bring two or
10 three or five. So, you don't know.

11 So, every project different and
12 also depend on which things in chemistry
13 mind.

14 So, they give me the compound to
15 evaluate and I propose the compound and the
16 number is not -- not important.

17 Q. Can you turn to your
18 declaration?

19 A. Okay.

20 Q. Look at Paragraph 4.

21 A. Okay.

22 Q. It spans Pages 2 to 3.

23 A. Okay.

24 Q. And in Paragraph 4, you discuss

1 your work on a compound called Revuforj?

2 A. I will pronounce because they
3 mark the drug they always use very difficult
4 name. I spell to you, R-E-V-U-F-O-R-J.

5 Q. That's pronounced Revuforj?

6 A. Also I would pronounce it, but I
7 don't know if it's correct or not, yeah.

8 Q. And did you receive any patents
9 on the Revuforj compound?

10 A. Yes.

11 Q. I'm going to hand you 2088.

12 - - -

13 (Whereupon, Deposition Exhibit
14 2088, U.S. Patent Number 10,683,302, was
15 marked for identification.)

16 - - -

17 BY MS. AGARWAL:

18 Q. This is U.S. Patent Number
19 10,683,302; is that correct?

20 A. Yes.

21 Q. And you are listed as an
22 inventor on this patent; correct?

23 A. Yes.

24 Q. And this patent is titled

1 Inhibitors of the Menin-MLL Interaction 2088;
2 is that correct?

3 A. That's correct. That's the
4 title there, yeah.

5 Q. And this is one of the patents
6 that you received based on your work for the
7 Revuforj compound; correct?

8 A. Yes. Yes.

9 MR. TOFT: Prosecuted by Cooley.

10 BY MS. AGARWAL:

11 Q. If you go to Column 2 of this
12 patent --

13 A. Uh-huh. Column 2 where?

14 MR. TOFT: Where?

15 MS. AGARWAL: These are not
16 numbered pages. It's after the figures.

17 MR. TOFT: So that's Column 126.

18 THE WITNESS: What's the column?

19 MR. TOFT: Two.

20 THE WITNESS: Column 2. Okay.

21 BY MS. AGARWAL:

22 Q. After Figure 23.

23 A. Yes.

24 Q. And there's a formula one there?

1 A. Uh-huh.

2 Q. Do you see that?

3 A. Yes, I do.

4 Q. And that's a generic formula?

5 A. Uh-huh.

6 Q. And then if we go to, all the
7 way in the back, Column 411.

8 A. 411. Page?

9 Q. These are unfortunately not
10 numbered pages.

11 But it's much more near the end
12 there's a Table 30, Column 411.

13 A. Yeah.

14 Q. And in Column 30 --

15 A. Column 30 or Column 411?

16 Q. Column 44 -- 411 in Table 30.
17 Sorry. Starting in Column 411.

18 A. Sorry. Yeah. Yeah.

19 Q. Table 30 spans from Column 411
20 to 414; correct?

21 A. Table 30 is over to 440; right?
22 Table 30 is including 411; correct.

23 Q. And it lists examples 1 through
24 252. Is that right?

1 A. Yes. Yes.

2 Q. This patent discloses almost 250
3 example compounds; correct?

4 A. Okay. Yeah.

5 MR. TOFT: Objection to the
6 extent it mischaracterizes.

7 BY MS. AGARWAL:

8 Q. And the patent is the result of
9 the iterative structure-based design you did
10 in close collaboration with medicinal
11 chemists that you describe in Paragraph 4;
12 correct?

13 A. Yes.

14 Q. Did you conduct a docking study
15 for the Revuforj project?

16 A. Yes, this is part of the
17 important daily practice because this is a
18 structure-based project. So I do docking and
19 also I do lots of analyzing work to see in
20 the pockets, yeah.

21 Q. And your docking study -- strike
22 that.

23 How many compounds did you
24 analyze for your project that resulted in the

1 Revuforj compound in your docking study?

2 A. I don't remember. It's more
3 than ten years ago, but I would say a lot.
4 And I think this is one of the projects when
5 we were acquired by allergen, A-L-L-E-R -- I
6 think it's G-E-N. They are not exist
7 anymore. So I think they are acquired by
8 Arbutus or something. I might be wrong.
9 (Stenographer clarification.)

10 I don't know exactly. It's
11 2020. The company ends, so, it's very
12 complicated issue. So, I don't want to go
13 that detail, but I have a lot of contribution
14 for this compound.

15 I identified initial hits and
16 then we have the -- and also we work through
17 iterative structure-based design.

18 The company doesn't exist after
19 2017. And then Allergan purchased and then
20 Syntax, so that's based on my reading from
21 the, you know, the news or something. So,
22 Syntax purchased that compound and Syntax
23 markets this compound. So, I need to be
24 careful as well.

1 So, but I did already work and
2 lots of compound generated in this project
3 given to me all these 250 compounds that I
4 propose, that's totally not true. And I
5 might suggest to offer a good idea. I
6 evaluate a lot of compound and but the
7 chemistry is very important. And they are
8 making compound. They ask me to evaluate the
9 compound. That basically is the situation.

10 Q. So, in your docking study, you
11 would have evaluated the 250 example
12 compounds that are disclosed on the patent?

13 A. I don't believe so. Some of
14 them I evaluated. Some of them I might not.
15 But I have major contribution is I identified
16 initial hits and I also work with chemists
17 and modify each pocket and going forward to
18 the (stenographer clarification) to the drug
19 development stage, the clinical stage,
20 compounds.

21 But when I leave, basically
22 they'll know if this project will move
23 forward or not. But three years later, they
24 bring that compound into the market. It was

1 surprised.

2 Q. So, you testified that in your
3 docking study you analyzed a lot of compounds
4 for this Revuforj project.

5 When you say a lot, do you mean
6 100 or more?

7 A. More.

8 Q. You can put that aside.

9 You have also testified that you
10 work with chemists in your projects; correct?

11 A. Yeah. Daily basis.

12 Q. And so you are not a medicinal
13 chemist; correct?

14 A. I'm not a medicinal chemist.

15 Q. You don't synthesize any of the
16 compounds; correct?

17 A. I don't synthesize the compound
18 in the projects.

19 Q. You don't perform any assays
20 with the synthesized compounds; correct?

21 A. These are biologists will do.
22 I'm not testing the compound because I'm
23 computational chemist, yeah.

24 Q. And so you don't perform any

1 pharmacokinetic studies; correct?

2 A. I do not perform pharmacokinetic
3 studies.

4 Q. You don't perform studies
5 measure activity such as EC 50?

6 A. I do not.

7 Q. Do you know what ADME stands
8 for?

9 A. Absorption, distribution,
10 metabolism and the excretion or something. I
11 suddenly out of mind. Too nervous, yeah.
12 Yeah.

13 Q. You don't perform experiments
14 that look into the ADME properties?

15 A. Yeah, I'm not. I'm not all
16 these things, I'm not. Because I'm not
17 experiment chemist.

18 Q. Okay. I'm going to talk about
19 your opinions in your declaration --

20 A. Uh-huh.

21 Q. -- on the flexibility of the
22 GLP-1s --

23 A. Okay.

24 Q. -- binding.

1 A. Okay.

2 Q. So, in your opinion, the GLP-1s
3 are binding pocket, particularly at the TM1,
4 TM2 interface exhibits significant
5 conformational flexibilities. Is that
6 correct?

7 A. I believe, uh-huh.

8 Q. And sometimes in your
9 declaration, you will refer to conformational
10 flexibilities and flexibility and sometimes
11 you refer to adaptive capacity.

12 A. Yes. So, this is just, is a
13 possibility. Because the conformation has
14 the flexibility, so if a different molecule
15 comes to mind into the pockets, the protein
16 will respond and change the shape.

17 So, if you can give me the
18 Kawai's paper, I might explain that better.

19 Q. I just want a clarification.
20 So, those two things kind of refer to the
21 same idea; is that right?

22 A. It is different, but is
23 referring to the flexibility. (Stenographer
24 clarification.)

1 But it wasn't totally same. It
2 is one is saying that you are able to adapt
3 to it; right? But it's not every ligand you
4 fit into the pockets. You have similar
5 response. But yes, to some extent it's
6 indicating the pocket has flexibility.

7 Q. So, they are both referring to
8 the flexibility of the pockets; is that
9 right?

10 MR. TOFT: Object to the extent
11 it mischaracterizes testimony.

12 THE WITNESS: Yeah, yeah, so I
13 mean I -- could you give me one example? So,
14 for the question you ask?

15 BY MS. AGARWAL:

16 Q. Sure. Yeah. If we go to your
17 declaration in Paragraph 24.

18 You're discussing Dr. Wiph's
19 opinions in this paragraph?

20 A. Okay.

21 Q. And you state that Dr. Wiph, the
22 first sentence, Dr. Wiph did not confirm
23 during his deposition that he considered the
24 conformational flexibility of TM1 and TM2

1 when conducting his structural analysis.

2 Do you see that?

3 A. Yes, I do.

4 Q. And then the last sentence on
5 that page states, This omission is
6 significant because static structural
7 analysis alone cannot capture the pocket's
8 adaptive capacity.

9 Do you see that?

10 A. Yes, I do.

11 Q. So, when you're referring to
12 conformational flexibility of TM1 and TM2,
13 and then the pocket's adaptive capacity,
14 those are both referring to the flexibility
15 of the pocket; is that right?

16 A. Yeah. Its pocket is flexible,
17 but in the response, the other one is the
18 pocket's nature.

19 So, it doesn't mean every
20 flexibility and every ligand coming were
21 response to that, yeah. So I think to some
22 extent, yeah, talking about the flexibility,
23 yeah.

24 Q. Sort of staying on this

1 paragraph --

2 A. If we talking about that, if you
3 give me the Kawai's paper, I can explain
4 exactly what it means.

5 Q. We can get to that.

6 A. We could go on my paper, but I
7 think the Kawai's paper is better than what I
8 wrote here because they have two pictures and
9 they are supplementing material.

10 Q. Let's do Kawai. This has been
11 previously marked Exhibit 1004.

12 A. They have two papers, but I've
13 been using one to explain my idea. It's in
14 the Page 23 of 25.

15 MR. TOFT: Sorry. What's the
16 question pending?

17 THE WITNESS: It's question
18 about adaptability and the flexibility.

19 MR. TOFT: Can you repeat the
20 question one more time?

21 BY MS. AGARWAL:

22 Q. So, you've answered my question
23 on conformational flexibility versus adaptive
24 capacity.

1 I just wasn't sure if your
2 answer is complete. If you have --

3 A. That's why because times my
4 understanding, so I think use the example is
5 the best way to talk about these things.

6 So, if you look at Figure 8, so,
7 I read through because it's been a while.
8 The two structure of GLP-1R bound to the LY
9 3502970 so this one is the (reporter
10 clarification) O-R-F-O-R-G-O-R-P-I-U-M,
11 Orforglipron, all bound to GLP, so, for the
12 970, it's green. The green for GLP-1R and
13 the magenta for the -- so, that's a pair.

14 So, that's a pair. So the
15 receptor structure is green and the ligand is
16 magenta and then they have the other one is
17 PBV 6 PCB is talking about the other small
18 molecule modulates, but it's not the same
19 structure class. They marketed as LSN
20 3160440. So, it's another small molecule as
21 it modulates.

22 And for the ligand, it's color
23 is here, it's kind of -- what's that color
24 called -- it's pink or light-ish. I would

1 just call it pink. It's light pink and
2 yellow is their receptor.

3 So, flexibility, as you can see,
4 they have flexibility, right, movement.

5 And that ligand is going towards
6 area which is beyond N-methyl.
7 (Stenographer clarification.)

8 That area is not occupied by the
9 methyl; right. So, it will not fit because
10 it's a big space, beyond massive. However,
11 the pockets can respond by shifting. So,
12 that's adaptability because you have --
13 that's called, another way to say it is
14 ligand-induced conformational change.

15 That's adaptability. So, that
16 clearly means when you have bigger group
17 coming and then the protein make a response
18 and make the pocket a little bigger.

19 But I think for the problem
20 we're dealing with here, we do not discuss
21 such movement, but it's indicating the TM1,
22 TM2 pocket has large flexibility. Because
23 obviously, that ligand, they have that
24 structure, they go into the region that's

1 beyond M-methyl and the protein has moved,
2 shifted.

3 Kawai is the paper teach me for
4 understanding.

5 So, before I'm connecting any
6 analysis, this is very important paper for me
7 to read, because I use the Kawai coordinates,
8 the PDB called the 6X0X.

9 So, that's I reviewed. This is
10 actually part of supplement material, but it
11 was there, yeah.

12 Q. So, going back to your
13 declaration in Paragraph 24, you state that
14 in that last sentence on Page 12, that static
15 structural analysis alone cannot capture the
16 pocket's adaptive capacity.

17 Did I read that correctly?

18 A. Yes.

19 Q. And so -- and you just testified
20 that you used the PDB coordinates of 6X0X
21 that's disclosed in Kawai to come to your
22 conclusion in your declaration; is that
23 correct?

24 MR. TOFT: Objection to the

1 extent it mischaracterizes.

2 THE WITNESS: That's correct. I
3 used my 6X0X as my starting structure and the
4 conclusion I formed is based on my own
5 analysis, but the Kawai is prior art.

6 BY MS. AGARWAL:

7 Q. So, you would agree that you
8 would not be able to determine anything about
9 the adaptive capacity of the binding pocket
10 of TM1 and TM2 just from Kawai's pictures; is
11 that correct?

12 MR. TOFT: Object to form.

13 THE WITNESS: Context dependent.
14 I'm not ask to carry out this analysis. So,
15 I cannot give you speculative question. I
16 need to carry out more calculation to address
17 that issue.

18 Right now I was asked to -- it's
19 for a structure similar analysis for -- close
20 to related structures.

21 So, I only -- I mean talk about
22 what I see and everything in this
23 declaration. But for the things I didn't do
24 and I'm not offering opinion. I'm only

1 offering opinion in the context of my
2 declaration.

3 BY MS. AGARWAL:

4 Q. So, I'm asking you, you opine on
5 the flexibility of the TM1 and TM2 binding
6 pocket.

7 So, looking at the pictures in
8 Kawai, you wouldn't be able to determine
9 anything about the adaptive capacity of that
10 binding pocket; correct?

11 MR. TOFT: Objection. To the
12 extent it calls for an incomplete
13 hypothetical or speculation.

14 THE WITNESS: Again, this is
15 highly context dependent.

16 So, I didn't do it. So how can
17 I know if it's able to adapt or not.

18 But protein is not static, don't
19 move and freeze, that's not the case.

20 Based on my knowledge and based
21 on what's known in the community and you can
22 ask any expert in protein, it's fixed.

23 If you see one oxygen is there,
24 they definitely cannot move. That's not the

1 case.

2 And the plus, these two residues
3 are solvent exposed flexibility is well known
4 documented in many different project.
5 Solvent exposed the region is always being
6 flexible. So you need to give the
7 flexibility in that particular pocket.

8 Q. So, my question is more narrow.
9 Is that looking at Kawai, just the paper, you
10 would not be able to determine anything about
11 the adaptive capacity of the TM1, TM2 binding
12 pockets?

13 MR. TOFT: Objection.

14 MS. AGARWAL: Is that correct?

15 MR. TOFT: Objection to the
16 extent it mischaracterizes.

17 THE WITNESS: Could you ask your
18 question again?

19 BY MS. AGARWAL:

20 Q. So, just looking at Kawai and
21 the images in Kawai, you would not be able to
22 determine anything about the adaptive
23 capacity of the TM1, TM2 binding pockets;
24 correct?

1 MR. TOFT: Let me object.

2 THE WITNESS: Okay.

3 MR. TOFT: Objection to the
4 extent it mischaracterizes Kawai or her
5 testimony and objection to the extent it
6 calls for speculation or an incomplete
7 hypothetical.

8 To the extent you understand,
9 you can answer.

10 THE WITNESS: You are already --
11 I already answered your questions. Based on
12 the Kawai's paper it taught you TM1, TM2
13 flexibility. In my analysis, over -- I have
14 the compound together and confirmed the
15 flexibility. So, I already mentioned that.
16 TM1, TM2 is able to move. And I also, the
17 adaptability is demonstrated in the paragraph
18 we talk about. These are prior art. You
19 don't need to perform any particular details,
20 right?

21 So, I didn't do the exact things
22 that you question, if I understand your
23 question correctly. But what I can say is
24 Kawai's papers, there are two figures,

1 actually, I just showed you one figure, shows
2 the pockets adaptability of TM1, TM2, if you
3 look at it, at the paper here.

4 BY MS. AGARWAL:

5 Q. If you turn to Page 3 in Kawai,
6 paper one.

7 A. Page 3. Is it talking about --
8 it's this one; right?

9 MR. TOFT: Yeah.

10 THE WITNESS: Okay. Okay. Page
11 3, yes.

12 BY MS. AGARWAL:

13 Q. Figure 1.

14 A. Figure 1. No, it's not. That's
15 Figure 2.

16 Q. Figure 1, Figure 1I?

17 A. Yes. I look at it, yes.

18 Q. And you agree that this is an --
19 an image of Orforglipron bound to the GLP-1
20 receptor; correct?

21 A. This imaging is orbiting based
22 on the 3D structure of 6X0X. We're not able
23 to say this is exactly in the picture because
24 if we don't have the 3D structure, you're not

1 able to generate this picture.

2 So you might get very different.

3 Because it tell you clearly what is the --

4 MR. TOFT: Slow down.

5 THE WITNESS: What the active
6 site is it. It tells you the residue there.

7 The 3D formation is illustrated in the
8 picture, yeah.

9 BY MS. AGARWAL:

10 Q. And the picture itself is 2D;
11 correct?

12 A. I won't say that because it's
13 based on the 3D information and actually, in
14 this paper, they are manning this graph and
15 if you put them altogether, it's formed the
16 3D information because it's grounded in 6X0X
17 structure. And that structure is 3D
18 information.

19 So, when you read the paper, so,
20 if it's true, you are not able to -- if it's
21 2D, you're not able to tell; right?

22 But if you see those things, you
23 see the residues around there based on the
24 picture I.

1 If you move to here, you see
2 tryptophan --
3 (Reporter clarification.)
4 T-R-P -- T-R-P.
5 MR. TOFT: I don't know how to
6 spell it.
7 MS. AGARWAL: T-R-Y --
8 MR. TOFT: It's the one at
9 Thanksgiving. T-R-Y-P-T-O-P-H-A-N.
10 THE WITNESS: You are right.
11 Yeah.
12 So, you will see that ECD that
13 stick out, so you get additional information.
14 MR. TOFT: For the record, just
15 to make sure the record is clear, she's
16 pointing to Figure 2.
17 THE WITNESS: Figure 2, yeah.
18 So you got information. You know that
19 particular position, tryptophan 33 from the
20 EC is unique; right? So that's a 3D
21 information.
22 And if you go to the picture I
23 just show you, and you see the --
24 BY MS. AGARWAL:

1 Q. And that is --

2 A. That was Figure 8 in the
3 supplement, Page 23 and you see the helix,
4 H-E-L-I-X.

5 So, that means it's rich because
6 all this information is based on 3D
7 structure. So, I will not say these are
8 totally to the image because they are 3D
9 information in the text, in the graph.

10 So, if you put all these
11 information together, you form one 3D
12 information in your brain.

13 So, and sometimes actually,
14 medicinal chemists are using these
15 information and for their design.

16 Q. So, in your opinion, you would
17 look at not only Figure 1I, but you would put
18 it together with the other images in Kawai;
19 correct?

20 A. That's not what I mean.

21 So, I just give you example.
22 It's just the level of the 3D information.

23 Clearly, if you just look at the
24 Figure 2, do you see the active size around

1 there in that's rich information. And
2 biologists, so, I'm not sure if your
3 biologist, so biologist is using these can
4 carry out the mutational experiments and know
5 what's particularly specific which is key for
6 bonding. So, their information, 3D
7 information there.

8 And all these information is
9 based on the 6X0X six structure. It's not he
10 drew a couple because these are 3D structure.

11 So I will not categorize
12 these -- the 2D imaging, yeah.

13 Q. So, to determine the flexibility
14 of the TM1, TM2 pocket, you took into account
15 all of the 3D information from the 6X0X
16 deposit on the PDB; correct?

17 A. Could you clarify your question?

18 Q. Yeah. So, in forming your
19 opinions for your declaration --

20 A. Uh-huh.

21 Q. -- and specifically regarding
22 the conformational flexibility of the TM1,
23 TM2 binding pocket, you determined that by
24 looking at the 3D information that is

1 disclosed in Kawai and the 6X0X; correct?

2 A. I carry out the analysis. I
3 downloaded the structures and I not totally
4 rely on that. These I have 3D information,
5 yes, but I need to carry out the docking
6 experiment; right? I downloaded the
7 structures.

8 Q. Okay. Let's go to Figure 2 in
9 your declaration. I believe that's on Page
10 11.

11 A. Yes.

12 Q. And this is an overlay of the
13 TM1 and TM2 regions from the GLP-1R cryo-EM
14 structures that you analyzed; correct?

15 A. Could you clarify your question?
16 So, what's -- because it sounds to me very
17 general. So, what do you mean?

18 Q. So, the caption that you have
19 here is titled Figure 2. Overlay of TM1 and
20 TM2 regions from GLP-1R cryo EM structures.

21 Did I read that correctly?

22 A. Yes. So, yes, GLP-1R
23 structures. These are different structures
24 in the database, yeah.

1 Q. And this is an overlay of the
2 TM1, TM2 regions from those GLP-1R cryo-EM
3 structures of these various compounds, from
4 PDB, correct, and you list them all here?

5 A. Yeah. These structures, yes, I
6 downloaded these structures from the PDB,
7 that's correct.

8 Q. So, you downloaded these
9 structures and then created this image; is
10 that correct?

11 A. That's correct.

12 Q. And this image does not appear
13 in Kawai; correct?

14 A. This image doesn't appear in
15 Kawai, but Kawai actually has I think
16 possibly its orientation. I think it's even
17 better. I think they mentioned that TM1, TM2
18 flexibility in their paper as well. But they
19 might not use exactly the same image I show
20 here. I put all the things together, but I
21 don't remember exactly, but I think there are
22 couple times using the overlay because these
23 structures are all mentioned in Kawai paper
24 because in the PBD they have more.

1 So, I just based on the Kawai
2 paper and downloaded this information, yeah.

3 So, all these structures were
4 mentioned in the Kawai, in the different part
5 of paper, yeah.

6 Q. Yeah. My question is just that
7 this figure you made; correct?

8 A. That's correct.

9 Q. And it does not appear anywhere
10 in Kawai; correct?

11 A. This particular view, it's not
12 appear in the Kawai.

13 So, I hope I -- but this is --
14 the picture, what I generate. So I should
15 say that at least.

16 Q. Yeah. Okay.

17 I want to turn to the docking
18 study --

19 A. Okay.

20 Q. -- in your declaration, which
21 starts at Paragraph 28, Page 15?

22 A. Okay.

23 Q. And in Paragraph 28, you state
24 that, you've conducted molecular docking

1 studies of five compounds depicted in Figure
2 3 to assess the size tolerance and
3 conformational adaptability of this pocket.

4 Did I read that correctly?

5 A. Yes.

6 Q. And if we go to Figure 3.

7 MR. TOFT: I'll just object to
8 it was an incomplete reading of the sentence.

9 BY MS. AGARWAL:

10 Q. If you go to Figure 3 on Page 16
11 of your declaration.

12 Figure 3 is captioned ligand
13 structures evaluated in docking studies; is
14 that right?

15 A. Yes.

16 Q. And this shows the five
17 compounds that you analyzed in your docking
18 study; correct?

19 A. That's correct.

20 Q. How did you pick these five
21 compounds to analyze in your docking study?

22 A. I didn't pick these compounds.
23 So, I was asked to evaluate these compounds.
24 It's just like sometimes chemist ask me to

1 evaluate compounds. I just treat as same
2 case.

3 I was asked to carry out the
4 docking study for these five compounds. And
5 I look at it. They cover enough diversity to
6 address the pocket's size and so I felt it's
7 reasonable, but I didn't pick out these
8 compounds.

9 Q. Who picked these five compounds?

10 A. I don't know specifically who
11 pick it, but --

12 MR. TOFT: I'll just caution you
13 not to disclose any communications with
14 counsel.

15 THE WITNESS: Yeah. So, I
16 provide, yeah, I was retained to analyze
17 these five compounds.

18 BY MS. AGARWAL:

19 Q. And so you don't have any
20 opinion on whether a person of skill in the
21 art would or would not have chosen these
22 particular compounds for a docking study; is
23 that right?

24 MR. TOFT: Object to the extent

1 it mischaracterizes testimony.

2 You may answer.

3 THE WITNESS: Okay. So, I
4 would -- so, that's typical, my work study,
5 sometimes I come with idea, sometimes
6 chemists come with idea, ask me to evaluate
7 and address their specific questions and they
8 want to test the pocket size and to see if
9 they are fit or not. So that's the question
10 I was given to.

11 So I look at it and I just
12 perform my task.

13 BY MS. AGARWAL:

14 Q. So, my question was: You don't
15 have an opinion on whether a chemist, a
16 medicinal chemist in your field or any sort
17 of chemist that you work with would or would
18 not have chosen these compounds for docking
19 studies; correct?

20 MR. TOFT: Objection. Asked and
21 answered. And --

22 THE WITNESS: I'm only offer
23 opinions in the scope of analysis in the
24 declaration.

1 So, I'm not speak for chemist
2 because that's not what I'm asked to do.

3 I'm asked to offer opinion if
4 these molecule or substitution would fit.

5 BY MS. AGARWAL:

6 Q. So you don't have any opinions
7 on -- sorry. Strike that.

8 A. Can I use the restroom?

9 MS. AGARWAL: We can take a
10 break.

11 - - -

12 (Whereupon, there was a recess
13 commencing at 11:35 a.m. and concluding at
14 11:44 a.m.)

15 - - -

16 BY MS. AGARWAL:

17 Q. So, before we get into
18 questioning, did you talk to counsel about
19 anything substantive during the break?

20 A. No.

21 Q. Before we went to break, we were
22 discussing the five compounds that you looked
23 at in your docking study.

24 And we're looking at Figure 3

1 and there are five compounds listed there;
2 correct?

3 A. Yes, correct.

4 Q. And those compounds include
5 compound 67, compound ten, compound 26 and
6 compound 40 from Yoshino; correct?

7 A. That's correct.

8 Q. And you're aware that there are
9 at least 150 other compounds identified in
10 Yoshino; correct?

11 A. I don't know the exact number
12 because I was asked to carry out this
13 analysis; right? There's a compound this for
14 here, but I do look at Yoshino because I
15 tried to confirm that compound 10 is draw up
16 here. That's the purpose. This is compound
17 ten, 26 and 40. So that's the purpose. And
18 so I didn't look at the whole pattern in
19 great detail because that's irrelevant to my
20 analysis.

21 Q. You're aware that there are many
22 other compounds exemplified in Yoshino?

23 A. Yes, that's correct.

24 Q. And compound 175 that you looked

1 at of Su is from the Su reference; correct?

2 A. That's correct.

3 Q. And you're aware that there are
4 over 200 different exemplary compounds
5 identified in Su?

6 MR. TOFT: Object to form.

7 THE WITNESS: Su has two
8 pattern; right?

9 BY MS. AGARWAL:

10 Q. So, what I'm referring to when I
11 say Su is Su two, which is Exhibit 1007. I
12 can give that to you if that will help.

13 A. It not necessary. Yeah.
14 Because Su's patent I didn't look at. I just
15 confirmed that particular compound it was
16 there and it's called as compound 17875.

17 So, when I writing the
18 paragraph, I can cite correct number. I
19 don't want to say in compound ten, but it's
20 actually not. So, that's the purpose.

21 I mean to carry out my analysis,
22 independently, I don't need this information,
23 because it's just I need to -- I was asked to
24 assist those pockets, just based on

1 information I have, just as pockets. But I
2 do check the pattern are there.

3 Q. So you didn't look at Yoshino,
4 going back to Yoshino, you didn't look at
5 Yoshino to see how many compounds it
6 discloses?

7 A. I know there are a lot. I don't
8 know exactly is based on recall, there's
9 something called Table 3. I don't know if
10 it's table -- in the table, they have those
11 information listed, which compound. I
12 noticed.

13 But I didn't look at it every
14 each compound. I just pay attention to the
15 compound that I need to carry out the
16 studies.

17 Q. Going back to Su, where compound
18 125 is disclosed, you didn't look at Su to
19 see how many compounds are disclosed in Su?

20 A. I didn't.

21 Q. Are you aware that there are
22 other references that also disclose
23 Orforglipron derivatives?

24 A. I do not.

1 Q. You testified earlier today that
2 you, for this declaration, you reviewed some
3 references; correct?

4 A. That's correct. Major three
5 things; one is Kawai's paper. That is very
6 important one. That's form the foundation
7 for my analysis.

8 Pirrung's declaration and Dr.
9 Wiph declaration, for pattern I briefly
10 looked through. I do aware of it that there
11 other patent. I would say yes.

12 But if you're asking the detail,
13 what's there, which compound, how many
14 compounds, I don't know. But I'm aware
15 there's other patent there.

16 Q. Okay. So, just so I'm clear,
17 you reviewed Pirrung's declaration; right?

18 A. Yes.

19 Q. You reviewed Dr. Wiph's
20 declaration?

21 A. That's correct.

22 Q. You looked at Yoshino solely for
23 the compounds you were given; correct?

24 A. That's correct. When you look

1 at the paper, I cannot say only look at these
2 things because other information is there.
3 So, would look at it.

4 But I would say I didn't look at
5 a Yoshino patent in great detail. I only
6 pick the information I needed for my
7 analysis.

8 Q. And for the Su reference, you
9 also only looked at it particularly for
10 compound 175; correct?

11 A. I would say mostly, yes. But I
12 do notice that the 175 has other forms so I
13 look at it, yeah.

14 Q. And by other forms --

15 A. Deuterium. (Reporter
16 clarification.) D-E-T-U-R-I-U-M.

17 MS. AGARWAL: D-E-U.

18 BY MS. AGARWAL:

19 Q. And you reviewed Kawai for your
20 declaration; correct?

21 A. Correct.

22 Q. And did you look at any other
23 references?

24 A. I didn't look at references,

1 yeah.

2 Q. Okay. And you also went on the
3 PDP, the protein data bank; correct?

4 A. That's correct.

5 Q. And you downloaded the various
6 cryo-EM structures that you discussed in your
7 declaration?

8 A. I download the structures from
9 the PDP and they are mentioned in my
10 declaration.

11 Q. Did you look at anything else?

12 A. I don't remember anything on top
13 of my head right now. But I, what I can
14 remember right now, on top of my head, these
15 are all information I reviewed.

16 Q. Okay. So, coming back to the
17 compounds that you looked at in your docking
18 study, you testified that you are aware that
19 there are other patents and references that
20 disclose other Orforglipron derivatives;
21 correct?

22 A. Yes, it's mentioned in
23 Dr. Pirrung or Dr. Wiph.

24 So, I do -- I mean because when

1 I reading and they mention something, but I
2 didn't read it in details because it's
3 irrelevant to my analysis. But I do aware
4 that something else is -- there are other
5 patents, yeah.

6 Q. And you're aware that those
7 other references disclose other Orforglipron
8 derivatives; correct?

9 MR. TOFT: Asked and answered.

10 THE WITNESS: I do not
11 understand your question.

12 Could you rephrase your question
13 so I can understand a little better?

14 BY MS. AGARWAL:

15 Q. So, the -- you testified that
16 you are aware that there are other references
17 that, for example, Dr. Pirrung and Dr. Wiph
18 discuss in their declaration; correct?

19 A. That's correct.

20 Q. And are you aware that those
21 other references also disclose Orforglipron
22 derivatives?

23 A. I don't know.

24 Q. Now, going back to your docking

1 study in your declaration, you only evaluated
2 the flexibility of the binding pocket around
3 the indazole moiety; is that correct?

4 A. I give the flexibility to the
5 pockets. It's not entirely, but it's some
6 degrees of flexibility. It's not saying
7 ground there, but I don't change the
8 coordinates. This allows me to look to see
9 if there's still a conflict form they are
10 indicated that there are still conflicts, so
11 I can follow up. But again, the degree of
12 freedom. So I do consider the flexibility
13 and also the local that's in mind. If you
14 see the conflicts appear, the very mindless,
15 the contacts. So, it's for some exposed
16 region, that even you don't need to take into
17 account.

18 But I did follow up. I saw
19 the -- the carboxylic acid is moved toward
20 the solvent which is totally reasonable
21 because the hard part is polar. It's not the
22 inside the polar, but outside is polar and we
23 all know carboxylic acid hat and amene hat is
24 water kisser.

1 (Stenographer clarification.)

2 I called it water kissers. I
3 don't know if it's -- it's because, in other
4 words, it's saying that they like to be with
5 the water. So, that's the word.

6 So, I mean totally reasonable.
7 So...

8 MR. TOFT: Listen to the
9 questions that she's asking.

10 THE WITNESS: Okay.

11 BY MS. AGARWAL:

12 Q. Were you done with your answer?

13 A. Yes.

14 Q. You looked at the flexibility of
15 the TM1, TM2 binding pocket; correct?

16 A. TM1, TM2 bond pocket has
17 flexibility. I think that is knowledge for
18 me, right? So, TM1, TM2 bonding pockets has
19 flexibility. When I'm carrying out analysis,
20 I need to pay attention.

21 So, if something happen, so you
22 need to -- but for in the context of this
23 analysis, it's totally the conclusion is
24 based on my analysis.

1 The Kawai is just the prior art,
2 tell you TM1, TM2 has flexibility, it has
3 ligand-induced changes. That's knowledge.
4 But -- but the conclusion I formed in this
5 declaration are totally based on my own
6 analysis.

7 Because we're not talking about
8 the big shift. We're talking about minor
9 steric contact (reporter clarification),
10 S-T-E-R-I-C, C-O-N-T-A-C-T. Yeah.

11 And it's structurally close to
12 related.

13 If I give you the picture to
14 look at, could you tell me are these look
15 similar? Are they similar?

16 Q. I'm asking the questions here.
17 If you have an answer --

18 A. Yeah. Yeah. Yeah.

19 Q. -- you can give me an answer.

20 A. So, these are identical, the
21 same core structure; right? Only thing
22 difference is on the part is circle, but some
23 of them don't have it. But they are highly
24 structural close related analogs. You deal

1 with local thing. And again, one acid, so
2 it's a minor steric conflict. It's really --
3 it's -- it's not something huge. A minor
4 steric contact. I'll use that word. Minor
5 steric contact, yeah. Or slight steric
6 contact. That's the same word.

7 Q. You did this analysis only in
8 that position on the indazole moiety;
9 correct?

10 A. Yes, I was only asked to carry
11 out analysis on the indazole portion.

12 Q. And we were just discussing the
13 compound, you noted that there might be some
14 differences on the THP ring where it might be
15 missing a dimethyl; correct?

16 MR. TOFT: Object to the extent
17 it mischaracterizes testimony.

18 THE WITNESS: Could you repeat
19 your question?

20 BY MS. AGARWAL:

21 Q. Sure. So when, you were just
22 explaining what you were asked to do --

23 A. Uh-huh.

24 Q. -- you noted that you analyzed

1 these five compounds and, you know, one of
2 the compounds might be missing the dimethyl
3 group on the --

4 A. I'm aware of that.

5 Q. -- on the THP; correct?

6 A. Yes, compound 26 and compound
7 ten.

8 Q. Compound ten. Yes, correct.

9 You're aware that Orforglipron
10 derivatives disclosed in the prior art modify
11 other portions of Orforglipron; correct?

12 MR. TOFT: Object to form.
13 Calls for speculation. Incomplete
14 hypothetical.

15 THE WITNESS: Which part you are
16 referencing?

17 BY MS. AGARWAL:

18 Q. Let me rephrase my question.
19 You're aware that there are Orforglipron
20 derivatives exposed in the prior art that
21 modify Orforglipron on positions other than
22 the indazole moiety; correct?

23 MR. TOFT: Object to form.
24 Calls for speculation. Incomplete

1 hypothetical.

2 THE WITNESS: I'm only, I mean
3 talk about indazole. That's what I ask.
4 They might have modification. That's general
5 rule. If you're doing other structure based
6 project, like you're referring to my capsid,
7 they have different pocket. Same as the
8 menin project, M-E-N-I-N. You're dealing
9 with different project. (Stenographer
10 clarification.)

11 But for this specific analysis,
12 I didn't review the SIR because that's not
13 what I'm asked to do.

14 Q. But if you were asked to do
15 that, you could do that?

16 A. I don't know the answer because
17 I didn't know, they didn't ask me to do.

18 So, I don't need to pay
19 attention to that so I didn't pay attention
20 to that.

21 They -- to me, they just the
22 general scaffold. I only focus on the
23 indazole portion.

24 Q. And your docking study does not

1 take into account any other part of
2 Orforglipron or one of these Orforglipron
3 derivatives; correct?

4 A. Could you rephrase your
5 question?

6 Q. Sure. You did not perform a
7 docking study for any other portion of
8 Orforglipron other than the indazole moiety;
9 correct?

10 A. If I understand your question
11 correctly, I think this is not correct here
12 because I'm using the whole molecule. I not
13 only put the indazole, small portion there,
14 so you accomplish very different questions --
15 very different answer. So that's not what we
16 do. I including the entire molecule. That's
17 including everything because that is the
18 whole molecule. Every part of the molecule
19 contributes to the different interaction
20 part.

21 You cannot take the indazole out
22 of the ligand to do your analysis.

23 Q. And your analysis only focused
24 on these five compounds; correct?

1 MR. TOFT: Object to form.

2 THE WITNESS: I only carry out
3 the analysis what I'm asked to do.

4 So, these five compounds.

5 MS. AGARWAL: Okay. I think we
6 can break for lunch now.

7 THE WITNESS: Okay.

8 - - -

9 (Whereupon, there was a luncheon
10 recess commencing at 12:04 p.m. and
11 concluding at 12:45 p.m.)

12 - - -

13 BY MS. AGARWAL:

14 Q. Welcome back from break. Did
15 you discuss the substance of your testimony
16 with counsel during this break?

17 A. No.

18 Q. Okay. So, we were discussing
19 your docking study in your declaration. I
20 want to continue to focus on that.

21 A. Okay.

22 Q. And turning to Paragraph 11.

23 A. Paragraph 11.

24 Q. Paragraph 11 of your

1 declaration, Page 5.

2 A. Go it.

3 Q. So, we went over this earlier
4 today, but just to sort of reiterating that
5 is your opinion that the GLP-1R binding
6 pocket particularly at the TM1-TM2
7 interfacing exhibits significant
8 conformational flexibility; correct?

9 A. Yes.

10 Q. And is your opinion then that
11 the GLP-1R binding pocket particularly at the
12 TM1-TM2-interface could accommodate many
13 different substituents at the indazole moiety
14 of Orforglipron?

15 A. This is just a general
16 statement, give me the pre part and keeping
17 in mind that the TM1 and TM2 region are
18 flexible, but the conclusion that I make in
19 this declaration is solely based on my
20 analysis in term of how many compound, five
21 compound possibly, right. So, yeah, five.

22 And so it's nothing related.
23 So, because I didn't analyze these compounds.
24 So, I cannot speak for that and offer my

1 opinion. So, every opinion I need to carry
2 out that analysis.

3 Q. So you analyzed the five
4 compounds in your docking study; correct?

5 A. Uh-huh.

6 Q. And if we go to those five
7 compounds in Figure 3, which I believe is on
8 Page 16.

9 A. Uh-huh.

10 Q. So, it's your opinion that the
11 binding pocket could accommodate each of the
12 substituents on the indazole moiety shown in
13 these compounds here; correct?

14 A. That's correct. These are
15 structurally-related analogs and for the five
16 compounds I analyzed, yeah.

17 Q. And it is also your opinion the
18 receptor could accommodate substituents that
19 are bulkier than a methyl group; correct?

20 A. This is correct.

21 Q. And based on your docking study,
22 you would agree that substituents larger than
23 a cyclopropyl could also be accommodated in
24 the binding pocket of the receptor; correct?

1 MR. TOFT: Object to form.

2 Incomplete hypothetical.

3 You could answer if you

4 understand.

5 THE WITNESS: Could you repeat

6 your question?

7 BY MS. AGARWAL:

8 Q. Sure. I could rephrase it a

9 little bit.

10 Based on the results of your

11 docking study, substituents larger than a

12 cyclopropyl at the indazole moiety of

13 Orforglipron could also be accommodated in

14 the binding pocket; correct?

15 MR. TOFT: Same objections.

16 THE WITNESS: These are general

17 statements. So, I will rephrase to answer

18 your questions.

19 For the four compounds or five

20 compounds are analyzed, they are all well

21 accommodated in the pockets, but I don't

22 offer opinion. I mean if you -- indicating

23 compound 40, yes, it's accommodated in the

24 pocket.

1 Q. Compound 40?

2 A. Yeah.

3 Q. That is a TH --

4 A. F.

5 Q. THF on the indazole moiety;
6 correct?

7 A. Yes.

8 Q. And that's bigger than a
9 cyclopropyl?

10 A. Correct.

11 Q. And it's your opinion that the
12 THF rank has -- strike that.

13 It is your opinion that the THF
14 ring could also be accommodated in the
15 binding pocket of the receptor?

16 MR. TOFT: Asked and answered.

17 THE WITNESS: THF in the
18 compound 40 and if I look here, it's also
19 accommodated in the indazole pocket.

20 BY MS. AGARWAL:

21 Q. If we could turn to paragraph 34
22 of your declaration, Page 20.

23 A. Yes. I got it.

24 Q. Here the first sentence states,

1 My glide SP document analysis demonstrates
2 that the tested ligands generally reproduce
3 the experimental binding mode observed in PDB
4 structure 6X0X, adopting similar poses with
5 comparable docking scores (approximately
6 12.5).

7 A. Minus.

8 Q. Sorry. Approximately minus
9 12.5; correct?

10 A. That's correct.

11 Q. So, in your opinion -- strike
12 that.

13 The -- your docking analysis
14 shows that compound 40 has a comparable
15 docking score with compound 175 of Su and
16 compound 67; is that correct?

17 A. Compound seven?

18 Q. 67.

19 A. They are all more or less is
20 similar. And in terms of structure,
21 compatibility.

22 Q. I'm going to hand you the
23 Yoshino patent. If you could turn to Page
24 34.

1 A. Paragraph 34 or Page 34?

2 Q. Page 34. In the bottom there
3 should be pages?

4 A. Yes, I got it.

5 Q. And on Page 34 do you see
6 compound seven there? It's the first
7 compound on Page 34.

8 A. I do.

9 Q. And apologies if my chemistry is
10 not as advanced as yours.

11 So, I'm just going to try and
12 describe.

13 On the indazole moiety of
14 compound seven, the substituent there is kind
15 of like an open THF ring; correct?

16 A. No. This is called dimosol --
17 E-sol and the E-sol, something like that.

18 So, it's actually kind of like
19 MO moiety like the other one.

20 So, I also don't know how to
21 call them, yeah. So, sometimes, but I know
22 what you're referring to.

23 Q. It's like an ethyl with an
24 oxygen?

1 A. TH are only for the five
2 membrane.

3 Q. Yeah. Yeah.

4 So, there's compound seven has
5 that substituent on the indazole moiety with
6 the ethyl group and the oxygen.

7 And this would be larger than a
8 methyl group; correct?

9 A. Yes. Lighter than methyl group.

10 Q. And would you consider this
11 larger than a cyclopropyl?

12 A. Cyclopropyl fat, you know? Fat.
13 So, this one is just leading you, longer. So
14 it's a totally different situation when
15 you're fitting into the pockets, because if
16 you have narrow things, the leaner one, you
17 might go out and go through, but it's
18 really -- I think it's out of context.

19 Compound seven, if you look at
20 the molecules and I draw your attention to
21 the THP region. This is totally different.
22 If we talk about conformation, the more of
23 lingo is different than the THP here; so you
24 have two changes.

1 So, I'm not offering opinion
2 there. Plus, I didn't evaluate that part.
3 So, I don't know.

4 Q. Based on your docking study, you
5 don't have an opinion -- sorry. Strike that.

6 Based on your docking study, do
7 you have an opinion on whether this
8 substituent on the indazole moiety could be
9 accommodated by the receptor?

10 MR. TOFT: Objection to form.
11 Incomplete hypothetical. Calls for
12 speculation.

13 THE WITNESS: Yeah, I'm not
14 speculating things. So because I not carry
15 out analysis for this molecule. This
16 molecule is not in the path of my
17 declaration. So, I'm not offering my
18 opinion. So, I need to carry out the
19 analysis and I will let you know.

20 BY MS. AGARWAL:

21 Q. Okay. And let's turn to Page 49
22 of Yoshino.

23 A. I'm there.

24 Q. The first compound listed on

1 Page 49 is compound 37.

2 Do you see that?

3 A. Yes, I do.

4 Q. And the substituent on the
5 indazole moiety here looks to be for membered
6 ring structure --

7 A. Yeah, with an ether there.

8 Q. With an ether.

9 Do you have an opinion as to
10 whether the receptor could accommodate this
11 substituent on the indazole moiety?

12 MR. TOFT: Objection.
13 Incomplete hypothetical. Calls for
14 speculation.

15 THE WITNESS: So, I did five
16 analyses, five compounds. I'll only speak
17 for five compounds. This is the scope of my
18 analysis. I have to carry out analysis in
19 offering my opinion.

20 I didn't do the calculations, so
21 I'm not able to offer you an opinion.

22 BY MS. AGARWAL:

23 Q. Would you agree that the
24 substituent optical moiety is larger than a

1 cyclopropyl?

2 A. I would think so.

3 Q. How many substituents are you
4 aware of that would be bulkier than a
5 cyclopropyl group?

6 MR. TOFT: Object to form.

7 THE WITNESS: Could you -- what
8 did you mean? How many group or is bulky for
9 cyclopropyl. Are you referring to something
10 in the pattern? What did you mean?

11 BY MS. AGARWAL:

12 Q. Let me actually back up and
13 rephrase.

14 How many -- okay. Strike that.

15 You discuss the receptor at the
16 TM1, TM2 region accommodating substituents
17 larger than a methyl group; correct?

18 MR. TOFT: Objection. Asked and
19 answered.

20 THE WITNESS: I evaluate the
21 compounds in the indazole region and the
22 indazole between TM1 and TM2, yeah. So,
23 that's how I phrase it.

24 BY MS. AGARWAL:

1 Q. And if we go back to figure
2 three and the five compounds than you
3 evaluated.

4 MR. TOFT: Sorry. Figure 3 --

5 MS. AGARWAL: Figure 3 in your
6 declaration.

7 BY MS. AGARWAL:

8 Q. We were at Figure 3 in your
9 declaration?

10 A. Okay. Okay.

11 Q. And you testified you evaluated
12 the indazole region which sits between TM1
13 and TM2 on the receptor; correct?

14 A. Correct.

15 Q. And in these five compounds,
16 these substituent on the indazole region,
17 consist of, we can take them one by one,
18 consist of a methyl group; correct?

19 A. Yeah, methyl group, yeah.

20 Q. In compound ten that's like a
21 trichloroethyl?

22 A. Trichloroethyl.

23 Q. And that is larger than a methyl
24 group; correct?

1 A. Trichloroethyl is larger than
2 methyl.

3 Q. And in compound 26, the
4 substituent is an ethyl fluoro?

5 A. It's a fluoroethyl I think
6 possibly.

7 Q. And the fluoroethyl group is
8 larger than a methyl group; correct?

9 A. Correct.

10 Q. And then compound 40 has the THF
11 ring; correct?

12 A. That's correct.

13 Q. And the THF ring is larger than
14 a methyl; correct?

15 A. That's correct.

16 Q. And compound 175 of Su has a
17 cyclopropyl constituent; is that correct?

18 A. That's correct.

19 Q. That is larger than a methyl
20 group; correct?

21 A. That's correct.

22 Q. Other than these four
23 substituents that you evaluated in your
24 docking study, how many other substituents

1 are you aware of that are larger than a
2 methyl group?

3 A. So --

4 MR. TOFT: Object to form.

5 THE WITNESS: This is out of the
6 content. So, I mean there are lots of
7 chemical in the water; right? Are you
8 talking about something in the pattern or
9 something in general?

10 So, I don't know. I mean what
11 did you mean?

12 BY MS. AGARWAL:

13 Q. Just in general, based on your
14 chemistry knowledge, are you aware of
15 substituents that are larger than methyl
16 groups that you could add to compounds?

17 A. I mean there are larger
18 substitution than methyl that exist, right,
19 but I didn't analyze.

20 So, we are talking about these
21 four compounds, yeah. And they are very
22 different size and chemical -- has some
23 chemical diversity.

24 Q. I understand that that's not one

1 of the five here. But my question is just
2 that you are aware of substituents that are
3 larger than a methyl group; correct?

4 A. Correct.

5 Q. So, it is your opinion that the
6 receptor could accommodate substituents
7 larger than a methyl group; correct?

8 MR. TOFT: Objection. Asked and
9 answered.

10 THE WITNESS: Again, I'm only
11 talk about the compounds I analyzed. So, I'm
12 not offering an opinion here for the
13 compounds I didn't analyze. And for the
14 compounds analyzed, these four compounds, the
15 substituents is larger than methyl. Ten, 26,
16 40 and 175 of the Su and they have
17 substituents. So, I just ask counsel do you
18 agree with me, these residues are larger than
19 methyl?

20 BY MS. AGARWAL:

21 Q. So, again, I'm asking the
22 questions.

23 So my question to you is: Is
24 that it is your opinion in your declaration

1 that the TM1, TM2 region can accommodate
2 substituents larger than a methyl group;
3 correct?

4 MR. TOFT: Object to form.

5 Asked and answered.

6 THE WITNESS: For in the
7 contents of this declaration, I evaluated the
8 four compounds and these four compounds has
9 the substituent larger than methyl group and
10 they will accommodate in the pocket.

11 Q. Let's go to Paragraph 37 of your
12 declaration on Page 21.

13 A. Yes, I'm there.

14 Q. And the first sentence states,
15 Based on these computational results and the
16 structural observations discussed above, it
17 is my opinion that the TM1-TM2 region can
18 accommodate conformational adjustments to
19 accept substituents larger than a methyl
20 group.

21 Do you see that?

22 A. I do see.

23 Q. So, it is your opinion that the
24 TM1-TM2 region can accommodate substituents

1 larger than a methyl group; correct?

2 MR. TOFT: Asked and answered.

3 Go ahead.

4 THE WITNESS: The conclusion is
5 formed based on analysis of these four, five
6 compounds; right?

7 If we go back to Figure 3,
8 that's the same questions I'm asking, are
9 these substituents larger than methyl.

10 Q. It is your conclusion then that
11 substituents larger than the methyl group can
12 be accommodated in the TM1-TM2 region based
13 on your study; correct?

14 MR. TOFT: Same objection.

15 THE WITNESS: What I'm saying is
16 these substituents are larger than methyl and
17 in the context of this analysis, the pocket
18 seems able accommodate the substituents
19 larger than methyl because all these ones is
20 larger than methyl, but if you ask me others,
21 I don't know. I need to do analysis. Then I
22 can tell you.

23 If you didn't carry out
24 analysis, I cannot speak for the things out

1 of the scope.

2 BY MS. AGARWAL:

3 Q. And if we turn back to the
4 Yoshino reference.

5 A. So past patent 356?

6 Q. Yes. And if you could turn to
7 Page 10.

8 A. Page 10?

9 Q. Uh-huh.

10 A. Okay. Page 10. Okay. Yes.
11 Column 5. I see it.

12 Q. Did you review this portion of
13 Yoshino?

14 A. I did not.

15 Q. You did not?

16 A. No.

17 Q. Okay. You can put that aside.
18 Going back to your docking study
19 that you describe in your declaration, you
20 would agree that -- strike that.

21 As part of your docking study,
22 you did not look at how changes on the
23 indazole moiety might affect other portions
24 of the reception; correct?

1 MR. TOFT: Object to form.

2 THE WITNESS: I look at that
3 particular portion of molecule, but when I
4 dock the molecules, it's not only
5 concentrated of that. So, that question is
6 to me, because I do consider a pocket because
7 I didn't dock a particular one. I dock the
8 whole molecule there. So I would say I look
9 at other pocket because it's reflect in my
10 docking. I'm not isolate looking a
11 particular substituent. I look at the whole
12 molecules.

13 The whole molecule they have a
14 different part that's in the pocket, yeah.

15 Q. And so when you analyzed for
16 example compound 40 or compound 175, which
17 have bulkier substituents than a methyl
18 group --

19 A. Yeah.

20 Q. -- it could result in different
21 confirmations on other parts of the receptor;
22 correct?

23 A. I did not --

24 MR. TOFT: Object to form.

1 Compound. Incomplete hypothetical.

2 THE WITNESS: I did not observe
3 that change. If I observe that change, I
4 would not make that conclusion.

5 So, my conclusion is I saw
6 consistent bonding posts with comparable
7 docking score. So based on that, I draw my
8 conclusion.

9 If I see there's a change on
10 other things, I would not draw the conclusion
11 here.

12 Q. Let's go back to Paragraph 34 of
13 your declaration, Page 20.

14 A. Okay. Yes.

15 Q. And you provide a docking score
16 of negative 12.5; correct?

17 MR. TOFT: Object to the extent
18 it mischaracterizes.

19 THE WITNESS: Docking score
20 minus 12.5, yes. For the test of the
21 ligands, I doing the analysis, yeah.

22 BY MS. AGARWAL:

23 Q. And can you explain what a
24 docking score is?

1 A. This is glide SP docking score.
2 It is well documented in the Schrodinger,
3 S-C-H-R-O-D-I-N-G-E-R -- (stenographer
4 clarification) and you can add one more word
5 there because that's called a maestro,
6 M-A-E-S-T-R-O.

7 Q. So, you got this docking score
8 from the glide SP program; correct?

9 A. Yes, from the glide and SP is
10 one of the docking score.

11 Q. I'm just -- I'm just trying to
12 figure out what it means.

13 A. Uh-huh.

14 Q. What does minus 12.5 mean?

15 A. Minus 12.5, that -- there
16 contains many terms. So, it's an empirical
17 scoring function trying to see how tight the
18 ligand are bonding into the pockets.

19 So, they have ensophy (phonetic)
20 and antrophy (phonetic) so they have
21 different components there.

22 But I don't remember the whole
23 term because it's a formula.

24 Q. Yeah. So, what exactly does a

1 docking score tell you?

2 A. So, docking score tells you how
3 tight and how combatability between the
4 receptor and the ligand.

5 I'll give you an example. So,
6 there's two parts; one is shape recognition.
7 So, I always refer to that receptor has a
8 lock. So, you have the key. So when there,
9 if the shape matched so the docking score, so
10 that's one part.

11 Second part, when shape
12 recognized, you have those interaction, it's
13 also need to be matched.

14 So, that's the reflect in the
15 score. So, it's just saying how well that
16 evaluated ligand has a structure
17 compatibility with the receptor.

18 So, it's a compatibility between
19 the receptor approaching structure and the
20 ligand.

21 Q. And the docking score doesn't
22 give you any information on the
23 pharmacokinetics of a particular compound;
24 correct?

1 A. Yes, this is correct.

2 Q. And it wouldn't give you any
3 information about the effect on potency;
4 correct?

5 A. So, they might have some
6 indication, but I won't say these two value
7 are related because the docking score is just
8 a rough -- not rough -- relative estimate of
9 how tight the ligand are bonding to the
10 pocket and how many compatibility is there.

11 But this is a bonding event,
12 which is essential for compound showing
13 activity. But to showing activity they have
14 many other aspects, yeah. It's important.

15 Q. So, in order to find out the
16 potency or the activity of a compound, you
17 would have to go make it and then test it;
18 correct?

19 MR. TOFT: Object to form.

20 THE WITNESS: Not me. Make it
21 so chemist have to make the compound and the
22 biologist were tested the compound. I'm only
23 suggest a structure feasibility, that's my
24 job.

1 BY MS. AGARWAL:

2 Q. And so you testified that -- let
3 me get this right -- that the docking score
4 might have -- might show some indication of
5 potency, but that these two -- but you won't
6 say that these two values are related; right?

7 A. Yeah, the --

8 MR. TOFT: Object to the form
9 and to the extent it mischaracterizes.

10 You can answer.

11 THE WITNESS: Potency and the
12 structure compatibility is two things. So,
13 potency, so I mean -- I can ask you a
14 question if you say potency. Potency is what
15 kind of assay are you talking about?

16 BY MS. AGARWAL:

17 Q. Let's go with like EC 50
18 activity.

19 A. Yeah, EC 50 is as I said, they
20 have many components.

21 So, bonding is essential.
22 That's if you don't have bonding, then the
23 following event, it won't happen.

24 But it's not necessary you have

1 the bonding. Your compound will show potency
2 because that's two different things.

3 And I was not asked to predict a
4 potency, but I was only asked to evaluate
5 these four compound, if they are structurally
6 compatible with the receptor.

7 Q. Can you predict potency from a
8 docking study or a docking score?

9 A. As I mentioned, the potency has
10 many factor. If you are talking about EC 50,
11 I'll tell you I'm not able to predict.

12 But the bonding event, so, the
13 docking score shows how tightly the ligand
14 bonds into the pocket. So, that's very
15 important step to show the activity.

16 If you don't have the structure
17 compatibility you definitely don't have the
18 activity.

19 But if you establish the bonding
20 compatibility, it doesn't mean because there
21 are many different factors. They involve
22 different things and contribute to the
23 potency.

24 Q. And then going back to Paragraph

1 34, you state that your docking analysis
2 demonstrates that the tested ligands
3 generally reproduce the experimental binding
4 mode observed in PDB structure 6X0X, adopting
5 similar poses with comparable docking scores;
6 correct?

7 MR. TOFT: Asked and answered.

8 THE WITNESS: That's correct.

9 BY MS. AGARWAL:

10 Q. So, that -- it's -- strike that.
11 Your study showed that the five
12 ligands that you tested have a comparable
13 docking score around minus 12.5; correct?

14 A. That's correct.

15 Q. There's nothing in your docking
16 study that suggests that any of the five
17 compounds that you tested would be more
18 favorable than another; correct?

19 MR. TOFT: Object to form.

20 THE WITNESS: What you mean is
21 favorable? You're talking about one object.
22 What you mean is favorable?

23 BY MS. AGARWAL:

24 Q. So based on your docking study,

1 you don't have any opinion as to whether any
2 of these compounds are -- have better binding
3 than any other compound; correct?

4 MR. TOFT: Objection. Compound
5 to form.

6 THE WITNESS: I would say they
7 are more or less show similar structure
8 compatibility with the receptor. I will
9 rephrase in that ways.

10 So, yeah. But I'm not
11 predicting the activity. Yeah.

12 BY MS. AGARWAL:

13 Q. And if we look at compound 175
14 of Su.

15 A. Okay. Which page?

16 Q. We're on Page 16 of your
17 declaration, Figure 3.

18 A. Yeah.

19 Q. Compound 175 of Su compared to
20 compound 67 of Yoshino, which is
21 Orforglipron; correct?

22 A. Uh-huh.

23 Q. The only difference between
24 those two compounds is Su has a site on the

1 indazole moiety in the place of a methyl
2 group; correct?

3 A. Yes, that's correct.

4 Q. And based on your docking study,
5 the docking scores of these two compounds are
6 comparable; correct?

7 A. That's correct.

8 Q. And so your docking study did
9 not show that compound 175 of Su has a better
10 docking score than Orforglipron; correct?

11 A. Yeah, I don't have the number on
12 top of my head. So, I don't want to
13 exaggerate a docking score because as I
14 mentioned, is relative approximation and you
15 can't use for this highly structured similar
16 compound.

17 And I would say all these five
18 compounds are comparable.

19 Q. And so there's nothing in your
20 docking study that would give you a reason to
21 select compound 175 of Su over a compound 67
22 in, for example, the lead optimization study;
23 correct?

24 A. So, I will give a suggestion,

1 right? So I'm not making compounds.

2 If I'm doing modeling and if I
3 see these one, I think they are, because they
4 show consist bonding pose, they show good
5 structure comparability and they go into
6 additional pocket because they are larger
7 than methyl. I'll offer an opinion that the
8 chemists consider it.

9 But if the chemists would make
10 these, that's not my job, they were -- these,
11 because they are similar and they provide the
12 structure feasibility, I will propose these
13 compounds, if they never made it before.
14 Because they show consistent bonding poses.
15 They show comparable docking score. So that
16 means they have similar compatibility. So
17 it's good. Why not?

18 Q. And so you would suggest all
19 four of these compounds?

20 A. I would just give chemists,
21 yeah, these four compounds has -- look like
22 has structure feasibility.

23 But if chemists are making these
24 compounds, that's not my role because the

1 chemists have a lot of other factors. Maybe
2 they are able to make or they are not able to
3 make. So, I only offer, with my expertise,
4 saying are these worse, if these compounds
5 show good structure compatibility. That's my
6 expertise.

7 If they make it or not, that's
8 not my job.

9 Q. So, you don't have any opinion
10 on whether a chemist would select compound
11 175 of Su over any of the other compounds
12 that you looked at based on your docking
13 study; correct?

14 A. I'm not speaking for chemist
15 because I'm of the opinion -- I don't know
16 what chemist think because chemist just
17 think, select the compound. They have many
18 criteria. They review the assay and they
19 review the feasibility and many other. And
20 every chemist, so, if you ask two or three
21 chemists, they might come up with their
22 selection, based on their preference. I'm
23 not speak of -- I only provide, I say yeah,
24 these four look good. And if they make it or

1 not make it, so, that's their choice.

2 Q. Let's go to Section D of your --

3 A. Section --

4 Q. -- expert declaration.

5 A. Which section?

6 Q. Bottom of Page 26.

7 A. Yes.

8 Q. And in this section you discuss
9 the removal of the dimethyl group on the THP
10 moiety; correct?

11 A. So it's the last sentences?
12 Right?

13 Q. Yeah.

14 A. Yeah.

15 Q. If we go to Figure 8 on Page 28
16 of your declaration.

17 A. Figure 8?

18 Q. Yes.

19 A. Okay.

20 Q. And the caption here is titled
21 Figure 8 binding mode of LY 3502970,
22 Orforglipron, in the GLP-1R transmembrane
23 pocket, PDB code 6X0X; correct?

24 A. That's correct.

1 Q. And in Figure 8, you have
2 measured the distances between the two methyl
3 groups?

4 A. Yes, two methyl group, yeah.
5 One is Valine, V-A-L-I-N-E, and the other one
6 is Alamine, A-L-A-M-I-N-E. (Stenographer
7 clarification.)

8 MR. TOFT: Listen to her
9 question.

10 THE WITNESS: Okay.

11 BY MS. AGARWAL:

12 Q. And you measure the distances to
13 the valine and the alamine, which are the two
14 closest amino acid residues to the methyl
15 groups; is that right?

16 MR. TOFT: Object to form.

17 THE WITNESS: Could you rephrase
18 your questions?

19 BY MS. AGARWAL:

20 Q. Yeah. So, in Figure 8 --

21 A. Yeah.

22 Q. -- you have shown some measured
23 distances; correct?

24 A. That's correct.

1 Q. What are those measured
2 distances showing?

3 A. Measured distance is just
4 showing that methyl in contact with the
5 group.

6 So, in the whole -- I mean how
7 large -- just like with docket, same thing,
8 you just so that methyl experienced the
9 contact distance between raiding, alamine or
10 methionine sulfur and what the distance is,
11 yeah. It's more descriptive.

12 Q. So, this is -- this figure is
13 showing the distances between the two methyl
14 groups on the THP ring and to the amino acid
15 residues that they are interacting with;
16 correct?

17 A. Yeah.

18 Q. And if we turn the page to
19 Figure 9, you do the same thing here, except
20 the two methyl groups are removed; correct?

21 A. No, I didn't remove the methyl
22 group. It's still there.

23 Do you see alamine? There's a
24 distance and the valine, there's a distance

1 and also methionine, I measured the distance,
2 yeah.

3 Q. So, the Figure 9 in the caption
4 says predicted binding mode of the
5 des-dimethyl analogue in the GLP-1R
6 transmembrane pocket; correct?

7 A. That's correct.

8 Q. And it states the ligand orange
9 maintains a similar THP orientation near
10 ECL1, TM2 and TM3 after removal of the
11 dimethyl groups; correct?

12 A. The ligand, THP part maintain,
13 that's correct.

14 Q. The methyl groups in this figure
15 are removed; correct?

16 A. Correct.

17 Q. And you measure the distance
18 between the two hydrogen atoms in their place
19 to each of the amino acids that they are
20 interacting with; correct?

21 A. Yes.

22 Q. And I believe you testified
23 that -- strike that.

24 Could you explain why these

1 measured distances are important?

2 A. Just the -- want to give people
3 general feeling where these dimethyl, the
4 pockets is.

5 So, I actually made the
6 comparison, put two picture together, which
7 in the Figure 10, which I think this is
8 actually more descriptive. So the previous
9 one, I measure the distance. I just don't
10 want to get people know where this pocket is
11 located.

12 And to make my point and in the
13 Figure 10 is better because I put them into
14 the same space. So you are able to compare.
15 It's better. As you can see, the methionine
16 not in the original position. So between
17 removal and original one. So, that's my
18 point. It's a repack.

19 Q. And we can see that difference,
20 if we compare Figure 8 to Figure 9; correct?

21 A. Yeah. But it's just not
22 intuitive. Exactly the same thing. I just
23 put them together as a comparison.

24 Q. But if we compare Figure 8 and

1 Figure 9, we can see the distance from the
2 methyl group to the methionine is 2.64; is
3 that right?

4 A. Yes, that's correct.

5 Q. And then if we go to Figure 9
6 the hydrogen atom to methionine has a
7 distance of 3.32?

8 A. Did you notice that I actually
9 just didn't want to get people -- because
10 these are the contact atoms. For this one is
11 methyl two sulfur. If I'm trying to advise
12 other people I would put methyl to carbon.
13 That's far away. But I don't want to make
14 that point.

15 So, that's closest atom in the
16 methionine sulfur.

17 When I was asked to do this
18 analysis, so they asked me if remove the
19 methyl, if it has a possibility, right, I
20 quickly noticed that methionine there.
21 Because in the many biological system,
22 methionine are very flexible. It's measuring
23 the repacking. I measured the closest one.
24 I gave a pass. So if I want to, so there was

1 methyl. But the other one you see is methyl
2 to hydrogen. So really I just don't want to
3 use these distance and give people general
4 idea where it's located. And if we want to
5 talk about these things is really we should
6 have put into the bigger pen and that's the
7 better way to talk about it.

8 Q. So, you just want to give people
9 sort of an idea that this is where the methyl
10 group exists in the pocket and what the
11 closest atom to that methyl group would be?

12 A. I just don't want to give people
13 idea and that particular pocket occupied by
14 the dimethyl and the water residues
15 surrounded there.

16 So, I put the distance is just
17 to give people better feeling in how big and
18 that pocket is, yeah.

19 Q. Going back in your declaration
20 to Paragraph 21.

21 A. Going before?

22 Q. Going before, yes. Page 10.
23 TM1, TM2 binding?

24 A. Yes.

1 Q. On the indazole.

2 A. Okay.

3 Q. So, you state that in my
4 assessment, the four-fluor-1-methyl-indazole
5 moiety occupies a partially buried pocket at
6 the TM1-TM2 interface; correct?

7 A. That's correct.

8 Q. And you state that, This pocket
9 is formed by residues from both TM1 and TM2,
10 creating a binding site that is partially
11 shielded from the aqueous environment.

12 Correct?

13 A. That's correct.

14 Q. So, you would agree that the TM1
15 and TM2 pocket on the receptor is partially
16 hydrophilic and partially hydrophobic;
17 correct?

18 A. That's not correct. That pocket
19 is partially hydrophobic; even for methyl
20 experienced is multiple hydro -- hydrophobic
21 atoms. I think in the Dr. Wipf's picture --
22 I think it was good he measured the front
23 part, but he didn't indicating that
24 measurement between that methyl was the

1 lysine, those aliphatic carbon distance.

2 So the methyl -- so if we speak
3 methyl, the whole pocket is definitely for
4 indazole part entirely hydrophobic.

5 And methyl, that was for the
6 solvent. I would say largely hydrophobic.
7 Why I say largely hydrophobic, because they
8 are solvent exposed. So there are two
9 residues in the solvent expose the boundary,
10 (reporter clarification) B-O-U-N-D-A-R-Y,
11 yeah; which is the glutamate acid, the 138
12 and the other one is lysine, 202.

13 Q. We can go to Paragraph 41 where
14 you talk about that, that's on Page 22, 23.

15 A. You want to continue?

16 Q. You're referring to the
17 glutamate and the lysine, which you discuss
18 in Paragraph 41 of your declaration?

19 A. Yeah.

20 Q. If you want to go there.

21 A. It's Paragraph 41.

22 Q. Paragraph 41, Pages 22 to 23.

23 A. Let me see. Yes, okay. That
24 picture is right there, yes.

1 Q. And then you state on Page 23,
2 before this picture, with the sentence
3 starting, My analysis reveals that the pocket
4 surrounding the indazole methyl position
5 exhibits a largely hydrophobic character,
6 while the hydrophilic side chains of lysine
7 202 and glutamate 138 are oriented toward the
8 solvent exposed boundary; correct?

9 A. That's correct.

10 Q. So, it's your opinion that the
11 pocket itself is largely hydrophobic;
12 correct?

13 A. Sure.

14 Q. And there's a solvent-exposed
15 boundary on the pocket which is hydrophilic;
16 correct?

17 A. Lysine 202 carboxylic acid is
18 polar, but that's only one small portion.
19 And glutamate acid only the carboxylic acid
20 is polar.

21 So, I can tell you because I
22 didn't put here because I don't need to put
23 everything there.

24 So, the methyl experience the

1 only polar interaction is from that oxygen.

2 The entire pocket is hydrophobic.

3 So I give you example. If that
4 cup, so only that small part is polar, do you
5 call that whole cup is polar? You tell me.

6 So, all I'm phrasing different
7 ways. We say color; right? The whole cup is
8 white, but then that only one point is red.
9 Do you call this cup is white or red? Right?

10 So, or using this one. Only
11 this part is blue. And entire other things
12 is white.

13 Do you call this one is white
14 bottle or blue bottle?

15 Q. So, I'm just trying to
16 understand your opinion here, where you state
17 that the pocket is -- has a largely
18 hydrophobic character and the hydrophilic
19 side chains of lysine 202 and glutamate 138
20 are oriented toward the solvent exposed
21 boundary.

22 And so in your opinion, the
23 solvent exposed boundary is hydrophilic in
24 character; correct?

1 A. So, I'll rephrase your
2 questions.

3 So, the pocket around the
4 indazole is largely hydrophobic and the
5 methyl experiencing the submicro environment
6 is also hydrophobic, except for only one
7 polar contact with oxygen. Yeah, the amino
8 group of lysine 202 and the carboxylic acid
9 of the gluten acid 138 is in the solvent
10 boundary.

11 But the glutamate acid has two
12 carbon there. Do you agree?

13 Q. I don't know. You tell me.

14 A. So, yes, that two carbon there,
15 are they hydrophobic?

16 Q. That's what I'm asking you.

17 A. They are hydrophobic and the
18 lysine, even long chains, multiple atoms.
19 I'll tell you that the methyl group even not
20 in contact with the lysine, you know, that
21 amino group. So that amino group is in an
22 exposed region. They are boundary residues.

23 So the entire pocket inside is
24 hydrophobic and the methyl micro environment

1 is largely hydrophobic.

2 Q. And you testified that you did
3 not include measurements in your declaration
4 from the methyl group to the amino acid
5 residues like Dr. Wiph did in his
6 declaration?

7 MR. TOFT: Objection. It
8 mischaracterizes testimony.

9 THE WITNESS: So, scientist has
10 their own way to do it; right?

11 So, to address this question
12 better, you don't need to because you just
13 are trying to explain that pocket is largely
14 hydrophobic or not.

15 I assure you this is
16 (stenographer clarification) it is
17 electrostatic, E-L-E-C-T-R-O-S-T-A-T-I-C.

18 So, this is really environment.
19 So Dr. Wiph is actually biased. He uses the
20 hydrophobic scale in the assay. They covered
21 the entire residue. For instance, lysine
22 202, normally the end, that amino group is
23 polar. The rest of them long chain. All
24 hydrophobic. He colored entire side chain is

1 blue. That's misleading, because the bottom
2 is hydrophobic, but you color them, but
3 that's -- the reason is that the potential
4 for the mo -- he also generated the molecular
5 surface, yeah.

6 So, that part, we're consistent,
7 so you see the pocket.

8 But cooling large part we're
9 different. The electro potential reflects
10 the geometry component. So refracts the side
11 channel orientation. So, you see these, you
12 know, the electro part is moving to the
13 inside and the polar group is going toward
14 the solvent. So the lead pocket is
15 hydrophobic in general.

16 So, I didn't say entire
17 hydrophobic. I said largely hydrophobic and
18 the methyl experienced the largely
19 hydrophobic interaction. The majority is
20 hydrophobic interaction.

21 It's not an effort to measure
22 the distance. You can see here very well to
23 address my point.

24 Q. And you are aware that Dr. Wiph

1 did do a measurement from the methyl group to
2 the amino acid residues; correct?

3 A. To which amino acid residues
4 you're talking about?

5 Q. I can give you his declaration.

6 MR. TOFT: We've been going for
7 about an hour. Whenever is convenient.

8 THE WITNESS: In five minutes I
9 will be back.

10 MS. AGARWAL: I have maybe five
11 minutes left of questioning and then we can
12 take a break. Is that okay?

13 THE WITNESS: That's okay.

14 BY MS. AGARWAL:

15 Q. This was previously marked as
16 Exhibit 2079.

17 A. Okay.

18 Q. If you go to Paragraph 95.

19 Do you see that Dr. Wiph --

20 MR. TOFT: Feel free to take
21 time to review.

22 BY MS. AGARWAL:

23 Q. Do you see that Dr. Wiph has
24 measured the distance between the methyl

1 group on the indazole moiety and the side
2 chain of the glutamate 138 residue; correct?

3 A. Yes.

4 Q. And you don't include any
5 opinions in your declaration that his
6 measurements are wrong here; correct?

7 A. I don't remember exactly what
8 the distance is. I assume and he measures
9 possibly correct, yeah. But I don't have the
10 number on top of my head.

11 So, if Dr. Wiph indicated these
12 distance is that number, I believe that the
13 number is correct.

14 Q. And based on his measurements
15 here, you would agree that the methyl group
16 is closer to the oxygen on the carboxylic
17 acid of glutamate than it is to the carbon
18 atoms on the glutamate; correct?

19 A. I agree.

20 MS. AGARWAL: Okay. We can take
21 a break.

22 THE WITNESS: Okay.

23 - - -

24 (Whereupon, there was a recess

1 commencing at 1:51 p.m. and concluding at
2 1:56 p.m.)

3 - - -

4 BY MS. AGARWAL:

5 Q. Did you discuss the substance of
6 your testimony with counsel over the break?

7 A. No.

8 Q. I have a few more questions for
9 you.

10 A. Okay.

11 Q. Have you ever done any sort of
12 legal consulting before?

13 A. No.

14 Q. And we went over the materials
15 that you reviewed for your declaration.

16 Did you review any materials
17 that are not cited in your declaration?

18 A. So could you rephrase your
19 questions?

20 Q. Sure. So, in preparation for
21 your declaration, did you review any
22 materials or references that you did not cite
23 in your declaration?

24 A. No, but for these structures,

1 out of 60X, right, they have these compounds
2 listed. So I downloaded the structure. I
3 don't know if these consider as outside the
4 reference or not.

5 But mainly it's just the things
6 that I cited here. But they are, so, do I
7 cite Yoshino? I think I do. Yoshino Su and
8 Dr. Wiph, Dr. Pirrung and, yeah, so all these
9 five structures, yeah.

10 Q. And in preparation for your
11 declaration, did you write the entire text of
12 your declaration from start to finish?

13 A. Yeah.

14 MR. TOFT: I'm just going to --

15 THE WITNESS: Yeah.

16 MR. TOFT: Okay.

17 THE WITNESS: Yeah. Yeah. But
18 I got --

19 MR. TOFT: I'm going to -- I'm
20 going to caution you not to reveal the
21 substance of any communication with counsel.

22 But to the extent you can answer
23 without revealing that, you can answer.

24 THE WITNESS: I provide the

1 report based on scientific opinion I have
2 here.

3 But I do consult the legal term
4 or something, but I think I possibly -- so I
5 do ask for questions, yeah, because I'm not
6 formulating the legal documents before.

7 But I do know that Dr. Pirrung
8 and Dr. Wiph have some paragraph there kind
9 of similar, yeah. So, yeah, I don't -- I
10 provide scientific -- I rephrase in that
11 ways.

12 So the entire document was a
13 scientific conclusion from beginning to the
14 end. I finished independently.

15 MS. AGARWAL: Okay. I have no
16 further questions. Pass the witness.

17 MR. TOFT: I have no questions.
18 Thank you for your time.

19 THE WITNESS: Okay.

20 THE COURT REPORTER: Can I get
21 your transcript order?

22 MR. TOFT: We will take regular
23 delivery.

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(Whereupon, the deposition
concluded at 2:01 p.m.)

- - -

C E R T I F I C A T E

I hereby certify that the proceedings
and evidence noted are contained fully and
accurately in the notes taken by me on the
deposition of the above matter, and that this
is a correct transcript of the same.

Teresa M. Beaver

Teresa M. Beaver

DATE: July 1, 2026

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