

In the Matter of:

*Inari Agriculture, Inc. vs
Corteva Agriscience LLC*

J. Martin Bollinger, Jr., Ph.D.

February 29, 2024

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1 fortuitousUNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3 - - -
4 INARI AGRICULTURE, INC.) Case No.
5 Petitioner,) PGR2023-00022
6 vs.) Patent 11,371,055
7 CORTEVA AGRISCIENCE, LLC,)
8 Patent Owner.)

9 - - -
10 Deposition of J. MARTIN BOLLINGER, JR., Ph.D.
11 Thursday, February 29, 2024

12 - - -
13 The deposition of J. MARTIN BOLLINGER, JR., Ph.D.,
14 called as a witness by the Petitioner, pursuant to
15 notice and Federal Rules of Civil Procedure,
16 pertaining to the taking of depositions, taken before
17 me, the undersigned, Melissa L. Fenster, a Notary
Public in and for the Commonwealth of Pennsylvania at
1221 East College Avenue, State College, Pennsylvania
16801, commencing at 9:14 o'clock a.m., the day and
date above set forth.

1 APPEARANCES:

2 On behalf of the Petitioner:

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12 INDEX

13 EXAMINATION:

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14 BY MR. RUTT
15 BY MR. DEROO

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16 (No exhibits were marked.)
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1 J. MARTIN BOLLINGER, JR., Ph.D
2 called as a witness by the Petitioner, having been
3 first duly sworn, as hereinafter certified, was
4 deposed and said as follows:

5 EXAMINATION

6 BY MR. RUTT:

7 Q Nice to meet you Dr. Bollinger. I'm Eric
8 Rutt for Wolf Greenfield.

9 Today I'm going to be asking you questions,
10 and if you don't understand them, please let me know,
11 and I'll try to explain them better.

12 We need to speak slowly today because we
13 have a lot of technical terms, and the court reporter
14 wants us to speak slowly. I'll do my best, but I'm
15 going to ask you to also speak slowly, clearly.

16 If there's a question you don't understand,
17 just ask me to explain it, and I'll explain it. If
18 you need a break, let me know. All I ask is that you
19 answer any question that's pending before you take a
20 break.

21 Also, we're going to try not to talk over
22 each other, so the record is clear and we don't drive
23 the court reporter crazy.

24 Have you ever been deposed before?

25 A Yes.

1 Q How many times?

2 A So are you asking about individual sittings
3 or --

4 Q Sure.

5 A And when you say "deposed," you don't mean
6 in a -- in front of judges or a jury?

7 Q That's right. Like we're doing today, how
8 many times have you been in a deposition?

9 A And I assume remote counts, so I have on
10 two occasions, two different matters been deposed, and
11 one of those went to --

12 Q What were those matters?

13 A I don't know all the numbers.

14 Do you want me to talk about the subject
15 matter of that or --

16 Q No. You have a list of matters in your
17 declaration, so I'll --

18 A Yes.

19 Q -- hand that to you. That may --

20 A I have a copy, a clean copy.

21 Q Should we stop?

22 (Recess taken.)

23 BY MR. RUTT:

24 Q So Dr. Bollinger, I'm handing you a copy of

1 your declaration. Do you recognize this?

2 A Yeah, I recognize it.

3 Q So turn to Page 125 of 132. It's in
4 Appendix A.

5 A I see. Okay.

6 Q And it looks like you have listed
7 four cases in which you have served as an expert
8 witness.

9 Is that right?

10 A I think there's actually a mistake in the
11 cut and paste here as I was updating my CV here.
12 This -- this -- there's kind of an orphan entry there,
13 so I just wanted to point that out, but I believe
14 there's --

15 Dow AgroSciences case was the first. Then
16 there was a matter in which I was involved for a very
17 short time, submitted a declaration, was not deposed,
18 but appeared before what I understand was called an
19 arbitration panel. That's this second up from the
20 bottom, and then there was this case PureCircle versus
21 SweeGen. So to my count, that's three.

22 Q And were you deposed in PureCircle?

23 A Yes. That's the one that went over
24 two weeks.

1 Q And were you deposed in the Bayer
2 Cropscience versus Dow from 2011?

3 A Yes.

4 Q Were you deposed in the case involving
5 Scientific Advisory Board in 2011?

6 A That was not a case. That was -- it's
7 under the heading "Selected Service Activity," so that
8 was just meant to be a service to that particular
9 start-up company.

10 Q And at a high level, what did the case
11 involving Dow and Bayer relate to?

12 A Well, I think two of the three involved Dow
13 and Bayer.

14 Q What did the District Court case involving
15 Dow relate to?

16 A Well, the details are fuzzy, but generally,
17 it was, as I understand it, Dow AgroSciences being
18 sued for infringement of a patent that Bayer had filed
19 some time in the 1980s related to enzymes that degrade
20 herbicides and their use in transgenic plants.

21 Q And what did the case involving Dow and the
22 arbitration relate to?

23 MR. DEROO: Objection. Form.

24 A Well, it was a different type of enzyme.

1 It involved resistance to herbicides, but I was
2 involved for such a short time, kind of a rapid basis,
3 that the details of how all of those companies were
4 involved and the -- what exactly the proceeding was
5 for escapes me. I don't think I ever fully
6 appreciated it.

7 I submitted a declaration. I went to
8 court. I testified for what must have been five
9 minutes or less, and that was it, and I -- I don't
10 think I even heard how that resolved.

11 Q When were you retained by Corteva for this
12 matter?

13 A I don't know the exact date. It's in my
14 records, but I -- I don't know.

15 Q Was it in 2023?

16 A For -- okay. For this matter? I think
17 there are some related matters, and I'm not sure
18 exactly when this one was first brought up.

19 Q What other related matters have you been
20 retained for?

21 A I -- I don't know. I mean, one -- they're
22 related to the same case of transgenic plants with
23 enzymes that degrade herbicides.

24 Q Who initially reached out to you about

1 working for Corteva in these related cases?

2 MR. DEROO: I would just caution you not to
3 disclose the substance of any privileged
4 communications you may have had, but you can
5 answer to the extent you remember.

6 A I don't remember.

7 Q Was it somebody from Finnegan?

8 A I'm not sure. I don't think I know the
9 answer. It probably was someone from Finnegan.

10 Q Was it somebody from Corteva?

11 A I know at least -- I know one person -- at
12 least one person at Corteva, and we have had a few
13 conversations over the last maybe decade or so, so I
14 can't unequivocally say it wasn't mentioned in one of
15 those conversations, some of which were well before
16 this, but I just don't remember.

17 Q Who is the person you know at Corteva?

18 A His name is Robert Cicchillo. He was a --
19 he trained at Penn State under my good friend and
20 colleague friend of mine, and we knew each other since
21 he started in graduate school.

22 Q Have you consulted for Corteva or Dow
23 before these related matters -- sorry. Strike that.
24 other than the 2011 to '14 cases we have

1 talked about and other than these present cases, have
2 you consulted for Dow or Corteva on any matters that
3 don't relate to any litigation issues?

4 MR. DEROO: To the extent you have any
5 confidentiality obligations, I would just offer a
6 caution, but you can answer generally.

7 A Consulted for pay?

8 Q Right.

9 A No, not that I can recall.

10 Q Have you consulted for free?

11 A Well, Dr. Cicchillo is a friend, and he --
12 he has a few times over the last 10 to 15 years called
13 to ask questions about the same enzymes, but that's
14 the extent of it. I freely offer my advice to anyone
15 who has ever been associated with Penn State, and
16 generally anyone in the community.

17 Q Has Dow or Corteva ever funded any of your
18 research?

19 A I have -- I have had funding from so many
20 different sources, but I am certain they have not.

21 Q Have you ever performed any experiments for
22 Dow or Corteva?

23 A For pay as --

24 Q Any at all? For pay or for free?

1 MR. DEROO: The same caution.

2 A Well, there's a study that includes some
3 authors affiliated with Corteva. The primary author,
4 the last corresponding author, was a professor at
5 University of Illinois, and so they're all
6 collaborating, and my group did two relatively routine
7 experts that are reported in that paper.

8 Q Which paper is that?

9 A It's a -- first off, it was I believe
10 Chekan. He was another Penn State'er, and the last
11 author is N-a-i-r, which I have had heard pronounce
12 Nair and Nair, and it was published in 2018 or '19. I
13 think in 2019 they were proceedings of the National
14 Academy of Sciences.

15 Q What did you do prepare for the deposition
16 today?

17 MR. DEROO: I would just offer a caution
18 not to disclose any privileged communications,
19 but you can answer generally.

20 A Do you want me to include the work that
21 went into preparing the declaration?

22 Q No. Just about the deposition for now?

23 A Reviewed the patent and my declaration,
24 some of the literature cited in the declaration.

1 Q So if you turn to Appendix B in your
2 declaration, you've got a list of documents that you
3 relied on and you reviewed to prepare a declaration,
4 right?

5 A These are the ones that are formally called
6 cited in the declaration. They're not the only
7 documents that I relied on in my analysis.

8 Q What other documents did you rely on in
9 your analysis that aren't listed here?

10 A Well, I've been working in this enzymes for
11 these -- iron and alpha-ketoglutarate -- we call it
12 alpha-kg, if that matters -- oxygenations for about 22
13 or 23 years, so I have read a lot of papers, and that
14 knowledge is part of me. Sometimes it's hard to
15 associate with a particular paper because it builds
16 strength, so there are many other documents that I
17 have read that informed the opinion.

18 Q Which of the documents on Appendix B did
19 you review to prepare for today's deposition?

20 MR. DEROO: I'm going to object to that on
21 privilege or work product grounds if there are
22 things that are only reviewed in conjunction with
23 counsel.

24 If there are things that you did without

1 us, then you're free to answer.

2 A That's why that's a difficult question to
3 answer, because I spent a lot of time at my computer.
4 Sometimes --

5 well, I have another job, so it has to be
6 outside of hours, and, you know, I have called many
7 articles up as PDFs on my computer and closed them,
8 you know, so I -- there are some that I know that I
9 referred to, but it's possible that I referred to all
10 of them at some point between submitting the
11 declaration and -- and today.

12 Q When did you begin preparing for the
13 deposition today?

14 A I don't know the answer to that. To me,
15 it's -- the issues in this case, the science
16 under pending this case, is right in my area of study,
17 so periodically, I'll decide I'm interested in
18 something, and if you consider that preparation, that
19 could have gone on at any time since we began
20 preparing the -- since I began consulting for this
21 case. I don't know when I formally -- there's no way
22 for me to kind of demark the start of preparation.

23 Q Did you meet with counsel to prepare for
24 the deposition today?

1 A Yes.

2 Q When was that?

3 A Well, we met in State College yesterday,
4 and we have had a few remote meetings, you know,
5 tele-meetings before that.

6 Q How long did you meet yesterday?

7 A Three hours, give or take a half an hour.

8 Q And when was the tele-meeting that you had
9 before yesterday to meet to prepare for this
10 deposition?

11 A There were -- there was more than one.

12 Q Let's start with the first one you
13 remember.

14 A Tuesday of this week.

15 Q And about how long did you meet at that
16 meeting?

17 A 2.5 hours.

18 Q And what was the meeting before then? What
19 day?

20 A I think there was one the preceding week.
21 I would have to check my schedule.

22 Q About how long did you meet at that
23 meeting?

24 A I don't recall. There have been a series

1 of meetings. Some of them should be in my calendar,
2 but I didn't check -- I didn't check that.

3 Q Did you discuss your work on this case with
4 anybody other than counsel?

5 A No.

6 Let me amend that. My wife and I
7 periodically -- she's also a scientist interested in
8 the same enzymes. There may have been conversations
9 tangentially relevant, but just to be clear, I don't
10 want to be -- I want to be completely truthful.

11 Q Did you write this declaration yourself?

12 A There were extensive discussions before --
13 as far as I know, before anything was written. With
14 outlining and detailed guidance from me, a draft was
15 provided to me. I reviewed every line and every word
16 and edited it extensively until I was satisfied.

17 Q So your lawyers wrote that first draft and
18 you edited it?

19 MR. DEROO: Objection to form.

20 A The first draft was a product of extensive
21 discussions and outlining in remote conversations.
22 The actual document that I ended up rewriting was
23 provided to me from counsel.

24 Q About how many hours did you spend working

1 on preparing the declaration?

2 A Tens of hours. I don't know exactly how
3 many.

4 Q More than 100?

5 A I think it's unlikely, but I'm not --
6 it's -- it probably gets close enough that I don't
7 want to say for sure. It's in the tens.

8 Q About how much did Corteva pay you in 2023?
9 MR. DEROO: Object to form.

10 A I was getting my tax documents together.
11 Do you want an about number?

12 Q Right.

13 A So \$30,000, U.S. dollars.
14 You said 2023, right?

15 Q Right.
16 And how much did Corteva pay you in 2024 so
17 far?

18 A I'm not sure. I received 1 -- 2 direct
19 deposits, and they might total about 30,000. That's
20 give or take five because I haven't checked.

21 Q So about \$60,000 is what you have received
22 from Corteva for this case?

23 MR. DEROO: Object to form.
24 Mischaracterizes his testimony.

1 A And in fact, it's not all for this case.
2 So the way when you asked me was how much Corteva --
3 Sorry. I have to amend that. The question
4 before was how much did Corteva pay me?

5 Q That's right.

6 A They didn't pay me anything. I have paid
7 by Finnegan. Okay?

8 Q Okay. For your work --

9 A Yes. So --

10 Q -- on Corteva matters?

11 A -- that's important, and I didn't listen
12 carefully enough.

13 So now, that is for 2023. So I said about
14 30,000. That was Finnegan paying me, and it's not all
15 for this matter, and then this year I said, again,
16 Finnegan paid me about 30,000, and it's not all for
17 this matter.

18 Q What other matters is it for?

19 MR. DEROO: I'll just object to the extent
20 that you have any confidentiality obligations.

21 But you can answer to the best of your
22 knowledge.

23 A I just know the number. One of them is
24 0001 and one of them is 0002.

1 Q Is there anything in your declaration that
2 you wish to change?

3 A Well, I mentioned in my CV there is an
4 orphan line that I think was a cut and paste there.
5 There would be some updates, but nothing -- as of the
6 filing, I think it's correct.

7 Q As far as you know --

8 A Yeah.

9 Q -- it's accurate?

10 A Yeah. Yes. Sorry.

11 Q So I'll show you Exhibit 1001. This is the
12 U.S. Patent 11371055.

13 Do you recognize this document?

14 A Yes, I do.

15 Q About how many times have you read this
16 patent in the last year?

17 A At least two and less than six.

18 Q Turn to the last two pages of the patent
19 where the claims are.

20 A I'm there.

21 Q So Claim 1 describes a transgenic plant
22 cell. Do you see that?

23 A Yes. I think correctly --

24 Q What does "transgenic" mean?

1 A My understanding is it means introduction
2 of a gene not normally found in an organism into that
3 organism.

4 Q Is it introduction by artificial means or
5 by natural evolution?

6 MR. DEROO: Object to form and scope.

7 A I'm not sure it wouldn't be understood by
8 different scientists in different ways, so, you know,
9 to define it generally is a little uncomfortable. I
10 think in this case it's introduced by a scientist into
11 a plant cell.

12 Q Then you see Claim 32 also starts with, "A
13 transgenic plant cell."

14 Do you see that?

15 A Yes.

16 Q And then you see Claim 33 describes a
17 method.

18 Do you see that?

19 A Yes. I see the first few words of it, yes.

20 Q These three claims are the three
21 independent claims in the '055 patent, correct?

22 A Well, you know, I'm not a lawyer, and I
23 haven't studied patent law. I am not 100 percent
24 comfortable with the distinction between the defendant

1 and the claims. I have heard those terms used, but
2 I'm not the expert to confirm that.

3 Q In Claim 33, in Line 8 of the patent, it
4 uses the phrase "recombinant polynucleotide."

5 Do you see that?

6 A Yes.

7 Q What does recombinant polynucleotide mean?

8 A In a general sense, it means connecting
9 segments of nucleic acid that weren't previously
10 connected. That's what recombine means.

11 Q So does recombinant refer to connecting
12 nucleic acids by artificial means?

13 MR. DEROO: Object to the form to the
14 extent it calls for a legal conclusion.

15 You can answer.

16 A In a scientific sense, not necessarily.

17 Q So recombinant could include natural
18 evolution?

19 MR. DEROO: The same objections.

20 A Recombination occurs in nature. In this
21 case, that recombinant polynucleotide was created by
22 scientists.

23 Q Turn to Paragraph 59 of your declaration.

24 A Sorry. I'm on page -- okay.

1 Q And in Paragraph 59, you described a
2 chemical reaction that degrades 2, 4-D; is that
3 correct?

4 A Well, what it says is to degrade 2, 4-D
5 alpha-ketoglutarate dependent dioxygenase -- those are
6 enzymes -- require the presence of iron (two) as a
7 elicenter (metal co-factor), as well as oxygen and
8 alpha-ketoglutarate (alpha-kg) as a substrate, so it
9 lists the requirements for the activity of alpha-
10 ketoglutarate dependent dioxygenase.

11 Q To help the court reporter, how about we
12 refer to that as alpha-kg.

13 Does that work for you?

14 A That does, and let me just say I may say
15 2-oxo glutamate. That's the same thing.

16 Q In simple terms, what is 2, 4-D?

17 A Sorry.

18 MR. DEROO: Object to form.

19 A Well, it's hard to --

20 Q Strike that.

21 Is 2, 4-D an herbicide?

22 A Yes, it's used as an herbicide.

23 Q You used the word "co-substrates."

24 Do you see that?

1 A Yes.

2 Q What are co-substrates?

3 A Okay. First and foremost, they're
4 substrates, and one could drop the "co" and that
5 sentence would still be correct.

6 Q What is a substrate?

7 A It's a molecule -- usually a molecule that
8 an enzyme converts to a product. In other words, it
9 is reactant.

10 Q And what are the substrates that degrade
11 2, 4-D?

12 MR. DEROO: Object to form and foundation.

13 A Well, the enzyme is a catalyst to degrade
14 2, 4-D, so it's really enzyme driven.

15 Q What are the substrates involved in this
16 degradation reaction of 2, 4-D?

17 A 2, 4-D is a substrate. Alpha-kg is a
18 substrate, and dioxygen, oxygen, is a substrate.

19 Q What is the role of iron in that reaction?

20 MR. DEROO: Object to form.

21 Q In simple terms?

22 MR. DEROO: Same objection.

23 A It's -- well, we call it a co-factor
24 because the enzyme must have it bound in its active

1 site to catalyze this reaction. It is not transformed
2 in the process. It's returned to its original state.

3 I mean, it's temporarily transformed, but
4 it returns to its original state at the end of the
5 reaction, so it's not consumed. It doesn't need to be
6 replenished in general.

7 Q Turn to Paragraph 64 of your declaration.

8 A I see it. I'm on Page 64. Okay.

9 Q In Paragraph 64, you discuss Exhibit 2022.
10 Do you see that?

11 A Yes. Sorry. I was confused because it
12 says 2002. That's the year. Yes, I see that.

13 Q And you see in the second sentence of
14 Paragraph 64, you state, "The TauD motif bound to
15 alpha-k_g at two motif sites, T126 and R266."

16 Do you see that?

17 A I do.

18 Q What is a motif in simple terms?

19 MR. DEROO: Object to form.

20 A In general, it's a stretch or sequence of
21 amino acids in which some are specified and some can
22 be any identity that relates to a function.

23 Q And what does T126 refer to in that
24 sentence?

1 A That's one of the 20 common amino acids,
2 and it's known as threonine, and there's a motif and
3 there's threonine, t-h-r-e-o-n-i-n-e.

4 Q And what does the number 126 mean there?

5 A So in specifying motifs, there's often a
6 sequence alignment that goes into that, and the
7 subscript there refers to the number of that sequence
8 position that has a three, and in an alignment, those
9 will align.

10 126 here probably refers to the residue
11 number alanine, but I would need to read through the
12 context here to make sure it's specifically the number
13 of alanine and not some alignment. The numbers can be
14 different.

15 Q So I'll show you Exhibit 2022.

16 Do you recognize this document?

17 A All I have -- all I have seen so far is the
18 cover of the journal. Can I look through?

19 Q Sure.

20 A Yes, I have read these.

21 Q Turn to Figure 5 of Exhibit 2022.

22 A I see it.

23 Q At a high level, what does Figure 5 show?

24 MR. DEROO: Object to form.

1 A Figure 5 is an alignment of sequences
2 from -- an alignment of sequences of ten members of
3 this iron alpha-kg dioxygenase family.

4 Q And what do the black triangles underneath
5 the sequences mean? You can look in the second to
6 last sentence of the caption. It may refresh your
7 memory.

8 A So that second to last sentence says,
9 "Conserved iron(II) and alpha-kg binding ligands are
10 marked with black triangles," so it -- according to
11 the figure it is pointing to, these triangles are
12 pointing to, the conserved ligands to the iron and the
13 residues -- there's sort of a sloppy use of the word
14 "ligand" here, but the amino acids that interact
15 without the alpha-kg.

16 Q How many black triangles are there in
17 Figure 5?

18 A There appear to be five.

19 Q And what do these five amino acids bind to?

20 A Shall I go through one by one?

21 Q Yeah.

22 A The first from the end terminus, which is
23 the left-hand end of the figure, histidine is a ligand
24 to the iron co-factor. The next is in TauD and

1 aspartate denoted by D in most of the sequences that
2 are on there, and that's also a ligand to the iron.

3 The next is a threonine in nine out of ten
4 sequences, and that makes a hydrogen bond with
5 Alpha-kg. The next is H, for histidine, and that is a
6 ligand to the iron co-factor, and the last one is R
7 for arginine, a-r-g-i-n-i-n-e, and that is an amino
8 acid that interacts with alpha-kg.

9 Q So the HD and the H bind to iron; is that
10 right?

11 MR. DEROO: Object to form.

12 A Yeah. They -- we say they coordinate, so
13 they interact with and, yeah, bind to iron.

14 Q And the T and the R bind to alpha-kg; is
15 that right?

16 MR. DEROO: Object to form.

17 A T makes the hydrogen bond, so in that
18 sense, it's a bond with alpha-kg, and R makes what's
19 often called "a charged pair" or "a salt bridge"
20 interaction. In the broadest sense, it can be
21 considered a binding interaction.

22 Q Which of the sequences in -- strike that.

23 You see TfdA is one of the sequences shown
24 in this alignment?

1 A It is the fourth row from the top.

2 Q And TfdA is involved in degrading 2, 4-D,
3 right?

4 A I was going to say what the abbreviation is
5 for, but in fact, yes. TfdA can degrade 2, 4-D in the
6 presence of the other components.

7 Q Which of the amino acids in TfdA bind to
8 2, 4-D?

9 A Do you want to ask about a particular amino
10 acid?

11 Q No.

12 A I didn't study this issue exhaustively, but
13 I see in Figure 6 the epsilon or N7 amine of glycine
14 71 interacts with it. There are other contexts, but
15 that's just one I can see in the figure.

16 I should add this is a model, so it's --
17 there's some uncertainty associated with that.

18 Q Do any of the five amino acids with the
19 black triangles under them bind to 2, 4-D?

20 MR. DEROO: Object to form.

21 A Do you mean in this model structure?

22 Q Correct.

23 A Again, this figure is a little hard to see,
24 but I don't see any explicit depiction of any of those

1 five residues interacting with 2, 4-D, but it's a
2 model, and there are many, many missing residues in
3 that figure.

4 Q Do you know how many of the residues in
5 TfdA interact with 2, 4-D?

6 A Well, I haven't studied this model.
7 Are you asking about the model?

8 Q I'm just asking in your experience with
9 studying alpha-kg enzymes, are you aware of which
10 amino acids binds to 2, 4-D in the TfdA sequence?

11 A I'm not.

12 Q Keep Elkins Exhibit 2022 nearby. We'll
13 come back to it, but I'll show you an exhibit marked
14 2003.

15 Do you recognize this document?

16 A I do.

17 Q The authors of this article are -- strike
18 that.

19 Do you know how to pronounce the last name
20 of the lead author?

21 A His name has the same issue as mine, and I
22 think it's Hausinger.

23 Q Hausinger?

24 A Yeah.

1 Q what about the other author?

2 A I don't know that person personally, so

3 I --

4 Q I'll call them Hotopp?

5 A That's fine.

6 Q Are you -- do you know of Dr. Hausinger?

7 A I do.

8 Q Have you ever worked with Dr. Hausinger on
9 any projects?

10 A He was editor of a book on these enzymes
11 and solicited a contribution from my team. I believe
12 that's the only -- I invited him to speak at our
13 conference at Penn State, and I think those are the
14 only two formal associations we have had.

15 Q what sort of reputation does Dr. Hausinger
16 have in the field?

17 MR. DEROO: Object to form and foundation.

18 A I don't know. I could tell you my opinion.

19 Q what is your opinion?

20 A I think he is a good scientist, and he's
21 also a good person.

22 Q In the abstract on the first page, the
23 second sentence mentions Elkins.

24 Do you see that?

1 A I do.

2 Q And it's citing to the article by Elkins
3 that we were just looking at in Exhibit 2022, right?

4 A I just want to make sure. Yes.

5 Q And the second sentence identifies several
6 amino acids that Elkins hypothesized would interact
7 with 2, 4-D, right?

8 MR. DEROO: Objection to form.

9 A It says, "On the basis of the
10 recently-published TfdA structural model," and it's
11 citing that Elkins paper, "Histidine214, glycine 71,
12 arginine 278 and the backbone amide of serine117 are
13 suggested to bind 2, 4-D carboxylate," and then two
14 others, of which I mentioned one to a previous
15 question, are hypothesized to interact with the 2, 4-D
16 ether atom.

17 Q So it identifies five amino acids that bind
18 to or interact with 2, 4-D, right?

19 A There are -- just let me check.

20 There are six listed.

21 Q Sorry. Six, you're right.

22 Are any of those six amino acids the ones
23 that were identified in Elkins with a black triangle
24 underneath them in Figure 5?

1 A Okay. So what I'm struggling to do here is
2 get the exact number of the arginine in the TauD
3 sequence because of the way alignments sometimes have
4 to introduce gaps, so -- and they have to count.

5 Q The note is TfdA that Hotopp is discussing,
6 not TauD.

7 A Well, so arginine74 is one of those. 274
8 is one of those, and it's mentioned as being suspected
9 to bind to alpha-kg, but of the six, none are among
10 the residues indicated to interact with 2, 4-D.
11 However, some of those are within the motif expanse.

12 MR. DEROO: We've been going about an hour,
13 if you get to a good stopping point to take a
14 break?

15 MR. RUTT: About five minutes.

16 MR. DEROO: Okay.

17 BY MR. RUTT:

18 Q In Hotopp, turn to Page 9792.

19 A Okay.

20 Q On the right column, about eight lines down
21 there's a sentence that begins, "We conclude."

22 Do you see that?

23 A Right column, 9792?

24 Q Correct.

1 A "We conclude," yes, I see that.

2 Q The authors that glycine 71 and arginine
3 278 have important roles in binding the carboxylate of
4 2, 4-D and that lysine 95 interacts with the 2, 4-D
5 ether oxygen, right?

6 A Yes, I see that sentence.

7 Q And these three amino acids in TfdA are not
8 any of the amino acids that Elkins identified as
9 binding to alpha-kg or iron, right?

10 A Okay. So to clarify your question, the
11 sentence says, "We conclude that glycine 71 and
12 arginine 278 have important roles in binding the
13 carboxylate of 2, 4-D and that lysine 95 interacts
14 with the 2, 4-D ether oxygen."

15 So you asked me -- can you repeat your
16 question?

17 Q Those are -- those three amino acids that
18 binds to 2, 4-D are different from the five amino
19 acids that Elkins identified as binding to alpha-kg
20 and iron, the five with the black triangles in
21 Figure 5 in --

22 A Elkins identifies as binding to those in
23 TfdA. Okay. So first of all, that is a model. The
24 alignment identifies those, and I need to verify that

1 those aren't the models.

2 Q Please do.

3 A That is correct. Those three residues,
4 glycine 71, arginine 278 and lysine 95 are different
5 from the five that interact with iron and with aKG,
6 alpha-kg.

7 MR. RUTT: Let's take a break.

8 (Recess taken.)

9 BY MR. RUTT:

10 Q Welcome back, Dr. Bollinger. During the
11 break, did you discuss anything with counsel?

12 A No.

13 Q Turn to your declaration, Paragraph 111 on
14 Page 65.

15 A I see it.

16 Q In Paragraph 111, you have reproduced a
17 figure from the '055 patent and annotated it, right?

18 A That's correct.

19 Q What does Figure 2 from the '055 patent
20 show at a high level?

21 MR. DEROO: Object to form.

22 A The figure is an alignment of the
23 sequences of 5 iron and aKG dioxygenases, and with a
24 numbering -- a number line across the top, and we have

1 added five arrows to denote that motif residues --
2 that specify motif residues.

3 Q And some of those enzymes include TfdA and
4 TauD, right?

5 A That's right.

6 Q And those were also included in Figure 5 of
7 the Elkins sequence alignment, right, those two?

8 A The two you mentioned again were TauD and
9 TfdA?

10 Q That's right.

11 A They're both in the Elkins figure.

12 Q And your colorful arrows identify the same
13 five amino acids that the black triangles identified
14 in Elkins, right?

15 A That is correct.

16 Q And so the five arrows you have added
17 identify H, D, T, H and R, correct?

18 A That is correct.

19 Q And you said the H, D and second H bind to
20 or coordinate with iron, right?

21 MR. DEROO: Object to form.

22 A They do.

23 Q And T and R bind to or interact with
24 Alpha-k_g, right?

1 A That is correct.

2 Q Do you recall when we were looking at
3 Hotopp, there were three amino acids identified in the
4 conclusion that interacted with 2, 4-D?

5 A I will not trust my recall. I'll look.

6 Q Hotopp, Page 9792, lower right corner.

7 A So can you -- could you -- I'm not sure
8 what your question is.

9 Q My question is: Do you recall that we
10 had -- Hotopp identified three amino acids that bind
11 to or interact with 2, 4-D in TfdA?

12 A Well, they proposed that lysine 21 and
13 arginine 278 interact -- have important roles in
14 combining the carboxylate of 2, 4-D and that lysine 95
15 interacted with the 2, 4-D ether oxygen.

16 Q In your declaration in Paragraph 111, can
17 you identify the position where glycine 71 in TfdA is
18 located? And by "the position," I mean, the number of
19 the sequence along the top of each sequence.

20 A I can -- I find that in this Figure 2 from
21 the patent.

22 Q What position is that? Is it position --

23 A As denoted by the number line at the top,
24 it's 90, but it's 71 in the TfdA sequence.

1 Q Right. And at position 90, the TauD does
2 not have the lysine at position 90, does it?

3 A So position 90 of TauD or position 90 in
4 the figure?

5 Q Position 90 of Figure 2.

6 A And the question is: Does TauD have lysine
7 in it?

8 Q That is correct.

9 A It does not.

10 Q Okay. And at position 90 of Figure 2, the
11 enzyme AAD-12 does not have the lysine, correct?

12 MR. DEROO: Just object to form.

13 Go ahead.

14 A At the -- again, looking at the number line
15 at the top of Figure 2 from the patent, it does not.

16 Q Hotopp identified a second lysine as
17 interacting with or binding with 2, 4-D, and it was
18 lysine 95, right, in TfdA?

19 A Again, they proposed that lysine 95
20 interacts with the 2, 4-D ether oxygen.

21 Q And in Paragraph 111 of your declaration,
22 can you identify the position in TfdA where lysine 95
23 is located using the coordinates of Figure 2? I think
24 it's position 114 to cut to the chase, but please let

1 me know if you agree or disagree.

2 A Yes.

3 Q And AAD-12 does not have a lysine at
4 position 114 of Figure 2, right?

5 A That is correct.

6 Q Can you identify the position of the
7 arginine 278 in TfdA in Figure 2 of Paragraph 111?
8 Again, I'll cut to the chase. I think it is
9 position 307, but let me know if you agree or
10 disagree.

11 A I'm just making sure here.

12 Yes, it is below on the number line 307.

13 Q And AAD-12 does not have an arginine at
14 position 307 in this figure, right?

15 MR. DEROO: Just object to form.

16 A Aligning with that position, it does not.

17 Q So AAD-12 does not have any of the
18 three amino acids that Hotopp had identified as
19 binding with 2, 4-D in TfdA, right?

20 MR. DEROO: Object to form.

21 A At the corresponding positions in this
22 alignment, AAD-12 has different amino acids at those
23 positions proposed by Hotopp to interact with 2, 4-D.

24 Q AAD-12 degrades 2, 4-D, right?

1 A Yes. AAD-12 catalyzes a breakdown of
2 2, 4-D in the presence of alpha-kg and oxygen.

3 Q In Paragraph 111, your annotations do not
4 identify which amino acids bind to 2, 4-D, do they?

5 MR. DEROO: I'm going to object to form.

6 A My annotations being the five colored
7 arrows?

8 Q That's right.

9 A They do not. They do not correspondence to
10 the residues identified by Hotopp at -- proposed by
11 Hotopp to interact with 2, 4-D.

12 Q Your arrows identify the binding locations
13 of five amino acids that -- strike that.

14 Your annotations identify the five amino
15 acids that bind with alpha-kg and with iron. Not with
16 2, 4-D, right?

17 MR. DEROO: Object to form.

18 A In this particular reproduction of
19 Figure 2 -- I think we have reproduced it several
20 times -- we're identifying just the specified motif
21 residues that interact with iron and alpha-kg.

22 Q Do you know which amino acids in AAD-12
23 bind to or interact with 2, 4-D?

24 A I don't.

1 Q AAD-12 degrades triclopyr, right?

2 A The names are not completely native to me,
3 so I would prefer if you get a name on it, we look at
4 the structure in the patent.

5 Q Sure. Open the patent to Table 1, which is
6 on Column 7.

7 Do you see Table 1 identifies seven
8 structures?

9 A Yes.

10 Q And the sixth structure is triclopyr?

11 A That is correct.

12 Q So turning back to Paragraph 111 of your
13 declaration, I'll ask again, does AAD-12 degrade
14 triclopyr?

15 A Yes.

16 Q You don't identify in Figure 2 of
17 Paragraph 111, which amino acids of AAD-12 bind to
18 triclopyr, right?

19 A In this reproduction of Figure 2 from the
20 patent on page -- in Paragraph 111, no.

21 Q Do you know which amino acids in AAD-12
22 bind to triclopyr?

23 A No.

24 Q Was it known in 2005 which amino acids in

1 AAD-12 bind to triclopyr?

2 A No.

3 Q Was it known in 2005 which amino acids in
4 AAD-12 bind to 2, 4-D?

5 A I'm wondering why you're asking about 2005.
6 I -- I have been told that the relevant time frame is
7 2005/2006.

8 Q Rephrase the question then: Was it known
9 in 2005/2006 which amino acids in AAD-12 bind to
10 triclopyr?

11 A No.

12 Q Was it known in 2005/2006 which amino acids
13 in AAD-12 bind to 2, 4-D?

14 A No.

15 Q Turn to Paragraph 11 of your declaration.

16 A Okay.

17 Q You state, "One of our most successful
18 long-term projects since 2002 concerns iron and
19 Alpha-kg dependent oxygenases, which are at issue in
20 this case," is that right?

21 A You read it correctly.

22 Q And you say you have co-authored
23 39 publications focused exclusively on one or more of
24 the enzymes in this large class, right?

1 A That's what it says. The number has
2 increased.

3 Q why do you call it one of your most
4 successful long-term projects?

5 A I guess based on various metrics, number of
6 publications, grants that we have earned from National
7 Institutes of Health, National Science Foundation,
8 Department of Energy to study them and the overall
9 impact of the conclusions.

10 Q You note that three articles appeared in
11 high-profile journals and five others appeared in top
12 journals, right?

13 A Yes.

14 Q And one of the top journals is the
15 proceedings of the National Academy of Sciences,
16 right?

17 A That's one listed, yes.

18 Q So earlier today, you had mentioned this
19 article you co-authored with Chekan; is that right?

20 A Yes.

21 Q Is that one of the articles you're
22 referring to here in Paragraph 11?

23 A Yes.

24 Q And that article with Chekan appeared in

1 proceedings of the National Academy of Sciences, or
2 PNAS, right?

3 A That is correct.

4 Q Was the Chekan paper a paper -- strike
5 that.

6 You mentioned some of the papers that you
7 published here had an impact -- or I forget how you
8 put it.

9 Is Chekan one of those papers you regard
10 among the more significant of the work you have done
11 on alpha-kg?

12 MR. DEROO: Object to form.

13 A When I mentioned what I considered to be --
14 considered to be the significant impact of this work
15 on this project, it was not one that I was thinking
16 of.

17 Q What was the point of your work with Chekan
18 as described in that paper at a high level and in
19 simple terms?

20 MR. DEROO: Object to form. Vague.

21 A Well, I mean, maybe we could look at it --

22 Q Sure.

23 A -- and discuss it.

24 Q So I'll show you what has been marked as

1 Exhibit 1015.

2 A So one often -- well, I'll wait for you to
3 ask me the question.

4 Q Do you recognize this document?

5 A I do.

6 Q And this is the Chekan paper you were
7 describing?

8 A Yes.

9 Q So what was the point at a high level of
10 this paper?

11 MR. DEROO: Same objections.

12 A There were a few points. One was to
13 identify hypothetical proteins that are members of the
14 arloxyalkanoate dioxygenase class of enzymes. One was
15 to publish the structure of the enzyme AAD-1, to
16 report the structure, and those was the two main
17 points. They kind of stated in the significant
18 statement.

19 Q Was it significant to publish the structure
20 of AAD-1?

21 MR. DEROO: Object to form.

22 A Yeah. I think to structural biologists,
23 such as the anchoring author here, that was considered
24 significant he wouldn't have wanted to publish it and

1 he wouldn't have been able to publish it in PNAS.

2 Q why wouldn't he have been able to publish
3 it in PNAS?

4 MR. DEROO: Object to form.

5 A If it wasn't viewed by the community as
6 significant.

7 Q So to get something published in PNAS, it
8 has to be significant?

9 MR. DEROO: Object to form and foundation.

10 A I wouldn't say that's always true, but it
11 tends to be true more often than not.

12 Q Up until this publication in 2019, had
13 there been any publications of the structure of any
14 member of the AAD family?

15 MR. DEROO: Object to form.

16 A Well, we have -- we have looked at models
17 in terms of experimental X-ray crystal structures. To
18 my knowledge, there had not been.

19 Q So there had been as of 2019 a published
20 structure of AAD-12; is that right?

21 A To the best of my knowledge, there had not
22 been.

23 Q Would you agree that without the structure
24 of an AAD, there's not sufficient knowledge to

1 distinguish bonified AADs from other enzymes of the
2 alpha-kg class?

3 MR. DEROO: Object to form.

4 A I definitely don't agree with that
5 statement, but depending on the context.

6 Q So turn to the second page of your article
7 and the right column, and the first full paragraph
8 that begins with the word "despite," do you see that
9 paragraph?

10 A Yes.

11 Q And in the second sentence, you state, "To
12 date, no crystal structure has been reported for any
13 member of the AAD family, and there is, therefore, an
14 insufficient knowledge base to distinguish bonified
15 AADs from other enzymes of the iron(II) alpha-kg
16 dyoxegenase class."

17 Do you see that?

18 A Yes. I see you read it correctly. The
19 context is very important here because when -- when
20 new sequences or enzymes are discovered, when they
21 have low levels of identity to -- for example,
22 AAD-12 -- then one struggles to tell whether they will
23 have the same activity.

24 However, in cases of finding sequences of

1 enzymes that are highly identical, there's no problem.
2 The knowledge base is sufficient, so the context here
3 is finding distant homologs, if you will, with low
4 sequence identity to other AADs and immediately
5 knowing whether they are authentic as the word is used
6 here.

7 And you can see later in that -- in that
8 column, 44 percent sequence identity. That's a
9 moderate range of sequence identity. It's not a high
10 level as we're talking about in this case.

11 Q Turn to the first page of this article, and
12 look at the blue box that's titled "Significance."

13 Do you see that?

14 A Yes.

15 Q In the third sentence, you say, "These
16 findings have expanded our mechanistic understanding
17 of representative dyoxygenases involved in 2, 4-D
18 catabolism."

19 Do you see that?

20 A I do.

21 Q It says that has been studied -- that
22 pathway has been studied for 40 years, but you, I
23 guess, were the first to provide certain mechanistic
24 understandings of that pathway.

1 Is that right?

2 MR. DEROO: Object to form.

3 A I don't think I would characterize it that
4 way. I think the general -- and we often call it
5 consensus mechanism for these enzymes had been
6 established by this point.

7 This is again from the perspective of a
8 structural biologist, which the anchoring author is,
9 and when he says "mechanistic understanding," he is
10 implying both an understanding of details of the
11 structure in which in terms of mechanism aren't
12 particularly always important to know, and the
13 relationship of that to the mechanism, so it's sort of
14 again a context-dependent statement.

15 Q Turn to Page 13303 of Chekan.

16 A I'm there.

17 Q Do you see the Figure 5 in the upper left
18 corner?

19 A I do.

20 Q What is the beta 2-beta 3 helical insert
21 described in the caption of Figure 5?

22 A Well, it's depicted in Panel A in -- I
23 guess that's magenta, and it looks like it connects
24 the other elements of the structure which are more

1 common to the overall scaffold.

2 Q Was beta 2-beta3 delete insert an important
3 finding in this paper?

4 MR. DEROO: Object to form.

5 A Well, I think it's one of the things to
6 describe when one gets a first detailed look at a
7 structure of a protein. I don't know how important it
8 is.

9 Q So it's not important?

10 MR. DEROO: Object to form.

11 Mischaracterizes his testimony.

12 A Yeah, I didn't say that.

13 You know, there are a number of things
14 presented in this paper. I'm not sure I would rank
15 that in the top few, but, you know, it would be more
16 instructive than this particular sentence. If you
17 want me to explain, I would be happy to do it.

18 Q Well, the last sentence in the caption
19 says, "The beta 2-beta 3 helical inserts obstructs
20 bind of the R enantiomers of herbicides."

21 Do you see that?

22 A I do see that.

23 Q What does that mean?

24 A Do you want me to explain it?

1 Q what does that mean in simple terms?

2 A well, I think on this not experimentally
3 derived, but a computer-based model of AAD-2, the --
4 there's an element here that we're claiming could
5 prevent binding of R enantiomers to make these -- this
6 AAD-2 S-specific.

7 Q In that same page on the left column, you
8 describe the beta 2-beta 3 loop at about the second
9 full paragraph.

10 Do you see that?

11 A Yeah, I see it.

12 Q And in the second to last sentence of that
13 paragraph, you state, "The beta 2-beta 3 loop likely
14 results in the change in substrate stereospecificity,"
15 right?

16 MR. DEROO: Object to form.

17 Mischaracterizes the document.

18 A Yeah, I see the sentence.

19 Q Do you agree with it?

20 A well, there's a couple of key words in
21 there, "would" and "likely." It's an interesting
22 hypothesis. I didn't see any reason to reject it.
23 It's certainly not proven.

24 Q You seem like you're hedging a little bit.

1 why is that?

2 MR. DEROO: Object to the form.

3 A I'm not hedging. It's how one writes a
4 paper. One looks at one's data, tries to specifically
5 delineate what one can absolutely say about it and
6 other interesting ideas about the data, and that's all
7 this is.

8 Q It might be right. It might not be. We
9 just don't know.

10 Is that what you're saying?

11 MR. DEROO: Object to form.

12 A I'm not saying. That I'm saying that it's
13 a hypothesis that needs to be tested, and there's
14 value in presenting hypotheses.

15 Q This next sentence says, "This insertion is
16 also evident in the sequence of AAD-12 and TfdA
17 accounting for the S stereospecificity of the enzymes."

18 Do you see that?

19 A I do see that sentence, yes.

20 Q And you cite S1 Appendix Figure 10.

21 Do you see that?

22 A Well, it's SI for supporting information.
23 Appendix Figure 10, which isn't here among the things
24 that I was given.

1 Q So I'll show you a document that has been
2 marked as Exhibit 1039.

3 MR. DEROO: I'll just object to
4 Exhibit 1039 on the basis of lack of
5 authenticity, relevance, hearsay, scope. It's
6 outside the scope of the declaration.

7 A Yeah. I didn't see this among the things
8 that I was -- that I considered, but I have it.

9 Q Does this appear to be the supplementary
10 information that you were just discussing was cited in
11 Chekan?

12 A Well, I think to verify that, I would go to
13 the online PDF document and link and make sure it's
14 the link, but it does appear to be.

15 Q In the lower footer of the document, it has
16 a cite to pnas.org.

17 Do you see that?

18 A Yeah.

19 Q And on the first page, your name is listed,
20 along with the other co-authors, right?

21 A That's right.

22 Q So Chekan cited Figure S-10 in the paper we
23 were just looking at.

24 Do you remember that?

1 A SI Appendix Figure 10, yes.

2 Q And Chekan was citing that in support of
3 the statement that the beta 2-beta 3 insertion is
4 evident in the sequence of AAD-12 and TfdA, right?

5 A Sorry. I'm just looking at this.

6 Yeah. So this is -- again, it's just an
7 extension of the hypothesis that's ahead of it in this
8 same paragraph.

9 Q What is that hypothesis?

10 MR. DEROO: Object to form.

11 A "Prior structured based analysis supports a
12 role for this so-called beta 2-beta 3 loop in
13 substrate binding and the differences between AAD-1
14 and AAD-2 are the result of a 20-residue insertion in
15 the home region of the ladder."

16 Q Does Figure 10 show the 20-residue region
17 that you just mentioned?

18 A Well, so it says, "This insertion consists
19 of residues asparagine 90 through cysteine 112, and
20 what do you mean does it show? Does it list them in
21 the alignment?

22 Q Right.

23 A Yeah. It appears that these are these --
24 they appear to be the aligned sequences of IV iron

1 alpha-kg oxygenases.

2 Q In Figure 10 what do the red triangles
3 indicate?

4 A They are in this case the iron ligands.

5 Q What is a ligand?

6 A It's the residue that makes a dative bond.
7 It bonds to the iron.

8 Q So these three amino acids with red
9 triangles are the ones that bind to the iron, right?

10 A Right.

11 Q And the beta 2-beta 3 insert is upstream or
12 to the left of the first red triangle, correct?

13 A That's not how I read the figure.

14 Q How do you read the figure?

15 A It's between beta 2 and beta 3.

16 Q So I think you just identified the
17 insertion region in Chekan, right?

18 A I'm looking at a figure.

19 Q You had said Asn 90 through cysteine 112 in
20 AAD-2, right? That's what the Chekan paper says?

21 A The paper says, "This insertion consists of
22 residues Asn 0 through Cys 112 in AAD-2.

23 Q Can you identify Cys 112 in AAD-2 in Figure
24 10?

1 A I have to count again. Yes.

2 Q And where is Cys 112 of AAD-2 in relation
3 to the first red triangle?

4 A It is -- there are two residues separating
5 it from the first red triangle, the histidine marked
6 by the first red triangle.

7 Q So cysteine 112 is upstream of the first
8 red triangle, right?

9 A More towards the interim of the protein is
10 how I describe it.

11 Q So the beta 2-beta 3 insert is more towards
12 the end terminus of the protein than the first red
13 triangle, right?

14 A No, I don't think that's a correct
15 characterization. I mean, the beta 2-beta 3 elements
16 are depicted in that figure, and the insert is
17 depicted as the elements -- or the combined protein
18 stretch between those.

19 Q So you think the beta 2-beta 3 insert goes
20 beyond the cysteine 112 in AAD-2; is that right?

21 A I think --

22 MR. DEROO: Object to the form.

23 A -- the way it's being discussed here, it
24 includes the element that, you know, provides the iron

1 leads, and so when we're talking about a different
2 sequence register, you can't look at a protein
3 structure in isolation, and you know, the difference
4 in sequence length has implications for how it folds.

5 Q why does the folding matter?

6 MR. DEROO: Object to form.

7 A It says it in my declaration. There's a
8 section up front that talks about enzymes and
9 proteins. I can read from it if you would like.

10 Q You had mentioned folding. I was just
11 curious why you raised that just now?

12 A It says, "The vast majority of enzymes or
13 proteins build from 20 different amino acids. These
14 are connected in a linear chain, and the sequence of
15 the chain is called its primary structure," so that's
16 the first part of the structure, "and then this linear
17 chain folding into a globular three-dimensional
18 structure in order to function as an enzyme catalyst,"
19 so that's what matters.

20 Q So it affects its ability to function as a
21 catalyst.

22 Is that fair to say?

23 MR. DEROO: Objection to form.

24 A It has to fold into the three-dimensional

1 structure to function as a catalyst.

2 Q And you're saying the difference in
3 sequence length can affect how it folds and how it
4 functions as a catalyst, right?

5 A What I'm saying is that because they have
6 three-dimensional structures interpreting, you know,
7 this particular insertion, which is a -- you know,
8 when you align them, you find that to get them in the
9 optimal register, you have to put some gaps. It can
10 impact the entire protein, so it's not --

11 I mean, it's not a question of whether it
12 affects the folding. These enzymes fold, but it's a
13 question of how it disposes other elements of the
14 protein structure for binding and, for example, the
15 substrate, the prime substrate.

16 Q The beta 2-beta 3 insert was hypothesized
17 to affect the enzyme's ability to bind to
18 R-dichlorprop; is that right?

19 MR. DEROO: Objection to form.

20 A Could you -- that seemed pretty general.
21 Could you ask it --

22 Q Yeah. I'm just trying to get the big
23 picture here, so going back to the Chekan article --

24 A Right.

1 Q -- the Page 13303 left column, second
2 paragraph we have been looking at before, I'm trying
3 to understand that paragraph, and I'm asking if the
4 beta 2-beta 3 insert is what could prevent AAD-2 from
5 binding with R-dichlorprop?

6 Is that a fair way to characterize that
7 paragraph?

8 A I would characterize it the following way:
9 This is a hypothesis, interesting but untested, for
10 how observations that one can make in the -- in the
11 sequence alignments might correlate with this native
12 selectivity.

13 It's sort of a structure -- what we call a
14 structure function explanation. The specificity is
15 something that's observed directly experimentally, so
16 that's known, and, you know, it's quite possible to
17 correlate that to elements of primary structure
18 without knowing exactly what it is that is, you know,
19 which specific residue's contacts, and this is just
20 trying to fill in some of those gaps, but again, it's
21 a hypothesis.

22 Q And the idea is AAD-1 combined
23 R-dichlorprop, but AAD-2 cannot, right?

24 A I wouldn't say cannot. I mean, the

1 observation is that AAD-1 efficiently cleaves the R
2 enantiomer, and AAD-2 doesn't, but it could bind. You
3 know, it's possible it could have, you know, low
4 activity. I believe actually that the S-1s are less
5 in nature than selected than the R, so that would mean
6 that there is some activity, but it's not as
7 efficient.

8 Q And the idea is the beta 2-beta 3 insert
9 interferes with the cleaving of the R-dichlorprop; is
10 that right?

11 MR. DEROO: Objection to form.

12 A It's an attempt to fill in some of the
13 details of the knowledge that -- the prior knowledge
14 that when you look at this alignment, there's -- it's
15 necessary to introduce a gap for optimal alignment,
16 and so there's a stretch of protein that's longer in
17 one than the other, and that's known to correlate with
18 the -- you know, the native selectivity, so it's
19 basically --

20 You know, it's taking the big picture,
21 which is I think pretty important in trying to
22 identify details to fill it in hypothetically to
23 suggest experiments for people to do in the future.

24 Q Do you think if you removed the beta 2-beta

1 3 insert from AAD-2 it would be able to better cleave
2 R-dichlorprop?

3 MR. DEROO: Objection to the form.
4 Incomplete hypothetical.

5 A Yeah, it's a hypothetical. I think it
6 would be an interesting line of investigation. I
7 would feel a lot more confident that if one identified
8 natural sequences and aligned them that you could find
9 a set that would be R specific and a set that would be
10 S specific that might have -- that would likely
11 correlate to that, but I'm not sure.

12 Q Why do you say you would be more
13 comfortable with natural sequences as opposed to a
14 sequence where you had artificially --

15 A You raised a hypothetical.

16 Q -- a sequence where you had artificially
17 removed some amino acids?

18 A You raised a hypothetical of removing it,
19 but if you remove, it's not longer connected. It's
20 not going to work, so you would have to say how are
21 you going to remove it, right, and that is, you know,
22 a problem in protein biochemistry, right. Nature
23 solves those things, and so that's why I say that.

24 Q Nature solves them, but when you're going

1 in and artificially removing pieces, we just don't
2 know because we don't have the example to look at?

3 A No. One has to --

4 MR. DEROO: Object to the form.

5 Go ahead. You can answer.

6 Q Try to let me finish my sentence --

7 A Yeah. I'm sorry.

8 Q -- for the court reporter?

9 MR. DEROO: Do you want to ask the question
10 again?

11 Q Yeah. So I was saying nature solves these
12 problems, but when you're going in and artificially
13 removing pieces, then we don't have the example of
14 nature to look at to know what's going to happen.

15 Is that fair to say?

16 MR. DEROO: Objection to form.

17 A I don't think that's fair. One has to have
18 skill in the art, and one has to use the clues that
19 nature provides, and your hypothetical didn't include
20 any expectation that that was being done.

21 Now, I would say that reducing the size of
22 a -- of a loop is one of the trickier problems. When
23 you're changing the length of a protein, that's a
24 trickier problem than, for example, replacing amino

1 acids. That is a fairly simple problem, so a person
2 of skill in the art would probably be able to succeed
3 in chopping out a piece of the protein, reconnecting
4 it and making an enzyme that works.

5 A person of skill in the art can certainly
6 change individual amino acids and combinations thereof
7 with guidance from each other, so your hypothetical
8 didn't address whether we were using our clues and our
9 skill.

10 Q So let's say that we were using our clues
11 and our skill and we chopped out that loop in AAD-2.
12 Do you think it would then be able to cleave
13 R-dichloroprop?

14 MR. DEROO: Object to form.

15 A It would be an interesting experiment. I
16 wouldn't predict the results.

17 Q Why not?

18 A Because as I said, the -- the -- removing
19 stretches of sequence is a more advanced engineer --
20 protein engineering problem than changing residues
21 or --

22 Q So the AAD-12 molecule is specific to the S
23 enantiomers.

24 Do I have that right?

1 MR. DEROO: Object to form.

2 A Yes. That's a little bit of fuzzier
3 question. Enantiomers of --

4 Q How about this, AAD-1 is S stereospecific?

5 MR. DEROO: Same objection.

6 A We would need to have a substrate to answer
7 that, so I don't think something happens --

8 Q S-dichloroprop?

9 A Yes. It seems to select against the R
10 enantiomer.

11 Q So if removed the beta 2-beta 3 insert from
12 AAD-12, would it be able -- would AAD-12 then be able
13 to cleave R-dichloroprop?

14 MR. DEROO: Asked and answered. Object to
15 the form.

16 A Yeah. I think it's tough to predict. I --
17 I wouldn't assign a student to that project.

18 Q How about a person of skill in the art?

19 A Well, I'm trying to train people in skill
20 of the art, so I wouldn't -- I wouldn't -- I wouldn't
21 do that.

22 Q It's a tough problem?

23 MR. DEROO: Object to form.

24 A Well, I think it's not necessarily looking

1 at the right place.

2 MR. DEROO: We have been going about an
3 hour. Could we take a short break?

4 MR. RUTT: Yeah.

5 (Recess taken.)

6 BY MR. RUTT:

7 Q All right. Welcome back, Dr. Bollinger.
8 During the break, did you discuss the substance of
9 your testimony with your counsel?

10 A No.

11 Q Turn to paragraph -- in your declaration,
12 Paragraph 112.

13 A Okay. I'm there.

14 Q So in the first sentence of Paragraph 112,
15 you describe the alignments in Figure 2 between
16 AAD-12, TfdA, AAD-2, AAD-1 and TauD.

17 Do you see that?

18 A The first sentence mentions that those are
19 the five enzyme sequences aligned in Figure 2.

20 Q And you say that -- well, strike that.
21 You describe these as -- these enzymes as
22 Group II alpha-kg dependent dioxygenases, right?

23 A Yes.

24 Q That's a mouth full. I'm going to just

1 call them the alpha-kg enzymes if that's okay with
2 you?

3 A Yeah, that's fine.

4 Q And I'll be referring to these five that
5 are shown in Figure 2.

6 Understood?

7 A Yes.

8 Q So you note in the first sentence that none
9 of the alpha-kg enzymes, other than AAD-12 --
10 actually, strike that.

11 You note that one of the alpha-kg enzymes
12 have the exact specified spacer lengths recited in the
13 AAD-12 motif, right?

14 A It says none of these other, where the one
15 that's implicitly left out is AAD-12.

16 Q Right. So the four other ones are TfdA,
17 AAD-2, AAD-1 and TauD, and they don't have the exact
18 specified spacer lengths recited in the AAD-12 motif,
19 right?

20 A Correct.

21 Q And then going to the next page, you have
22 created a chart at the bottom of Paragraph 112.

23 Do you see that?

24 A Yes.

1 Q And in that chart, you show the -- well,
2 why don't you describe it? what's shown in this
3 chart?

4 A The chart shows four of the same
5 five enzymes, the five specified motif residues
6 histinine, aspartate, threonine, histinine and
7 arginine, and the number of amino acids between them.

8 Q And you call this the active site motif in
9 that chart; is that right?

10 A That's right.

11 Q And the active site motif consists of these
12 five amino acids, right?

13 A And the amino acids that connect those five
14 in terms of how long it is.

15 Q And these five amino acids in this chart
16 are the same five amino acids that we had looked at in
17 Figure 5 of Elkins that had the black triangles
18 underneath them, right?

19 MR. DEROO: Object to form.

20 A Just to make sure --

21 Q Sure, be sure.

22 A So this is -- the Elkins is the
23 Exhibit 2022?

24 Q That's right.

1 A Okay. And that -- you're talking about
2 Figure 5.

3 Q That's right.

4 A And yes, it depicts the same active site
5 motif residues that are specified.

6 Q So looking at the chart that you made in
7 Paragraph 112, what does the X mean?

8 A It means that it can be any amino acid.

9 Q And what does the number subscript beside
10 each X mean?

11 A It's the residue in the sequence of that
12 enzyme the residue number.

13 Q So, for example, between the yellow H and
14 the green D, there is one amino acid; is that right?

15 A Right, which in the AAD-12 is the amino
16 acid numbered 109.

17 Q Okay. And for the -- I'll call these
18 spacers, these X position spacers, if that's okay with
19 you.

20 A That's okay.

21 Q So for the spacers between the green D and
22 the blue T, how many spacers are there in AAD-12?

23 A Well, there are four, but in general, there
24 are three that vary across iron alpha-ketoglutarate

1 dioxygenase.

2 Q Okay. In this table, just looking at the
3 second spacer, how many amino acids are in the second
4 spacer for AAD-12? If you want, you can use your cell
5 phone to do a calculator or whatever you --

6 A No. That one is easy enough. I see that
7 if I subtract 111 from 134, I get 23. I'm sure that's
8 correct, and because it's inclusive, it's 24.

9 Q And how many amino acids are there in
10 second spacer for TfdA?

11 A So if I do 140 minus 117, I guess 23, so
12 that would be 24.

13 Q And the same question for AAD-2?

14 A 24.

15 Q And the same question for AAD-1?

16 A 24.

17 Q And the same question for TauD?

18 A 24.

19 Q So now going to the fourth spacer in
20 AAD-12 -- this is between the magenta H and the red
21 R -- how many amino acids are there in the fourth
22 spacer for AAD-12?

23 A It's 272 minus 263 is 9, so 10.

24 Q The same question for TfdA?

1 A 10.

2 Q And for AAD-2?

3 A 10.

4 Q And for AAD-1?

5 A 10.

6 Q And for TauD?

7 A 10.

8 Q So the first spacer or and the second
9 spacer and the fourth spacer in this chart for all
10 five enzymes have the same amount of amino acids --
11 strike that. It's a confusing question. Let's do it
12 one by one.

13 The first spacer has one amino acid across
14 all five enzymes; is that right?

15 A That's right.

16 Q And the second spacer has 24 amino acids
17 across all 5 enzymes; is that right?

18 A I'm just checking again.

19 Yes, that is correct.

20 Q And the fourth spacer has ten enzymes
21 across -- strike that.

22 The fourth spacer has ten amino acids
23 across all five enzymes, right?

24 A That's correct.

1 Q So the only difference in the spacers
2 across these five enzymes occurs in the third spacer,
3 right?

4 A Well, it's not the only difference because
5 those Xes represent actual sequence positions with 1
6 of 20 amino acids in them, but in terms of the length,
7 the length difference is in the third spacer.

8 Q So now the math is going to get a little
9 harder.

10 A Yeah, I imagine.

11 Q I would like to walk through the amino acid
12 length for the third spacer for each of these five, so
13 if you want to get a calculator out, that's fine with
14 me, on your cell phone.

15 A Yeah, let's do that.

16 Q And I can tell you what I think it is and
17 you can tell me whether or not you agree if that will
18 speed it up. So for the first enzyme, AAD-12, would
19 you agree there are 126 amino acids in the third
20 spacer?

21 A Yes.

22 Q For the second enzyme, which is TfdA, would
23 you agree that there are 121 amino acids in the third
24 spacer?

1 A Yes.

2 Q For the third enzyme, which is AAD-2, would
3 you agree that there are 121 amino acids in the third
4 spacer?

5 A Yes.

6 Q For the fourth enzyme, AAD-1, would you
7 agree that there are 131 amino acids in the third
8 spacer?

9 A Just a second. What number did you
10 volunteer?

11 Q 131.

12 A I agree.

13 Q And for the fifth enzyme, which is TauD,
14 would you agree that there are 128 amino acids in the
15 third spacer?

16 A Yes.

17 Q So the difference in length across all 5 of
18 these varies from about 121 amino acids to about
19 131 amino acids; is that right?

20 A Unfortunately, I don't remember the
21 numbers, but 126 and then we had 121 and 121.

22 What did you have for AAD-1?

23 Q 131.

24 A 131, and then the next one is?

1 Q 128.

2 A 128, so between 121 and 131.

3 Q Of these five amino -- of these five
4 enzymes, which ones are capable of degrading 2, 4-D,
5 if you know?

6 MR. DEROO: Object to form.

7 A I believe that four can, AAD-12, TfdA,
8 AAD-2 and AAD-1.

9 Q Do they all have about the same activity
10 against 2, 4-D, do you know?

11 MR. DEROO: Object to form.

12 A I would like to look at documents for that
13 because that's not something that I took command of in
14 my analysis.

15 Q Sure. So if you go back to Exhibit 1039,
16 which is the supplemental information to your
17 article --

18 A Yeah.

19 Q -- and turn to Table 2, which is on
20 Page 19 --

21 A Okay. I see that.

22 Q -- what does the Column KM, APP indicate?

23 A The short answer is it's -- we use the term
24 KM, so to a person of skill in the art, that's kind of

1 understood, and the "comma APP" means apparent, and
2 that typically means that it's under a specific set of
3 conditions so that it's not really a true KM. The KM
4 is the Michaelis-Menten constant.

5 It's of historical importance in the study
6 of enzymes, and the broadest definition is it's the
7 substrate concentration giving one half the maximal
8 rate, so that's KM. And the apparent means it's under
9 specific experimental conditions, so it's not really a
10 true KM.

11 Q Is it used as a measure of activity or how
12 would you describe it?

13 A Because it's relatively trivial to measure,
14 it's often used as an indication of -- this is a word
15 that -- the affinity of enzyme for the substrate.
16 It's not proper to do that, but because it's easy and
17 sometimes correct, it's done.

18 What it means is if there's a high KM, you
19 need a higher concentration of the substrate to get to
20 the maximum velocity that the enzyme can go -- the
21 maximum rate that the enzyme can go.

22 Q So to try to simplify it for lay people,
23 higher KM means less activity or less ability to
24 degrade a substrate?

1 MR. DEROO: Object to form.

2 A Unfortunately, that's not correct, and I
3 understand that there are two parameters that matter,
4 K_M apparent in this case -- and I can tell you what
5 the specific experimental condition that matters that
6 they're keeping constant, and K_{cat} apparent -- and
7 both of those determine how efficient an enzyme will
8 be at a given substrate concentration.

9 So the best measure of the efficiency of an
10 enzyme is this K_{cat} apparent over K_M apparent. It's
11 the ratio of those two parameters. Yes.

12 Q So looking at 2, 4-D, which enzyme has more
13 activity power to degrade, whatever you want to call
14 it, AAD-1 or AAD-2?

15 MR. DEROO: Object to form.

16 A Well, the K_{cat} apparent over K_M apparent
17 is a higher -- oh, boy.

18 Okay. So the units are different, and they
19 are multiplying by ten to the third in the AAD-1
20 column and by ten to the second in the AAD-2 column.
21 The numbers are about the same in those columns for K_{cat}
22 over K_M . And so because we had to multiply the
23 value for AAD-1 by one more power of ten, it's the
24 smaller of the two numbers.

1 Q Okay.

2 A So AAD-2 has the higher efficiency
3 parameter under these experimental conditions, meaning
4 the apparent part of it.

5 Q Okay. Does that mean AAD-2 can degrade
6 2, 4-D more or less than AAD-1?

7 A Under conditions of this assay in the test
8 tube -- am I misreading this legend?

9 Yeah. Under the conditions of the assay,
10 AAD-2 degrades 2, 4-D better than AAD-1 by less than a
11 factor of ten.

12 Q Okay.

13 A And I think it's relevant to note that some
14 of these are drawn out of the literature, so it
15 doesn't appear that they, we, did these -- some of
16 these numbers together to compare.

17 Q So what I was hoping you could explain to
18 me was when we look at the table in Paragraph 112,
19 that you would be able to tell me in a simple way
20 which of those enzymes is most able to degrade 2, 4-D
21 and which one is least able?

22 A At this point, all we have is AAD-1 and
23 AAD-2.

24 Do you have other literature?

1 Q I do, but --

2 A Okay.

3 Q -- I'm struggling to follow. So which was
4 it? AAD-2 was more than AAD-1?

5 A Yes. In terms of the specificity constant,
6 K_{cat} over K_M apparent, under these conditions, AAD-2
7 is.

8 Q And that's what a person of skill would
9 look at, the ratio?

10 A It's one number that would be -- of the
11 numbers in this table, that's the one that's most
12 instructive.

13 Q And you call it efficiency. Is that
14 shorthand?

15 A K_{cat} over K_M is always often recognized as
16 the efficiency constant of an enzyme.

17 Q Okay. So higher efficiency generally can
18 mean greater ability to degrade 2, 4-D?

19 MR. DEROO: Object to form.

20 A You know, it depends on the conditions.
21 Enzymes saturate. You will see in this -- in this
22 legend, NS, not saturated. What that means is at very
23 high substrate, they reach a maximal rate and they
24 can't go any faster.

1 At a lower substrate concentration, one can
2 calculate their rate using this K_{cat} over K_M
3 parameter, but K_{cat} is an -- you know, it's a
4 parameter that's measured separately, and at high
5 substrate, you can't go any faster than that, right,
6 so they don't report any K_{cats} in there.

7 So to answer that question, I need to know
8 both parameters, K_{cat} and K_M , but when it says at low
9 substrate concentrations, when neither enzyme is
10 anywhere close to saturating, the one with the higher
11 K_{cat} over K_M would be faster.

12 Q Okay. The higher number, the higher
13 ratio --

14 A Is more efficient.

15 Q Is more efficient?

16 A Yeah, under those conditions.

17 Q All right. Do you know -- well, so if you
18 have the patent in front of you, turn to Column 48.

19 A I see it.

20 Q And at the bottom, there's a Table 10 that
21 has kinetic constants for AAD-12.

22 Do you see that?

23 A I do.

24 Q What I was hoping is you could use this

1 data to compare it to AAD-1 and AAD-2, but I'm seeing
2 that it does not have the ratio you used.

3 Right?

4 A Well, but we can calculate that.

5 Q Okay.

6 A The problem -- my reluctance -- I'm a
7 little reluctant in -- you know, the apparent tells
8 you something important here. It means a set of
9 conditions, so we want to know that these conditions
10 were the same, but the conditions that matter would
11 typically be oxygen concentration, iron concentration,
12 presence or absence of a reductant, like, acerbate and
13 then temperature. Those might likely be similar.

14 Q Okay.

15 A Right? It's possible. We don't know.

16 Q Okay. Understood. So that's the --

17 A We could do the calculation to compare it.

18 Q Okay. Can you do that, understanding
19 there's that caveat?

20 A So this is for AAD-12?

21 Q For 2, 4-D, right.

22 A And this is 2, 4-D in the top line. Okay.
23 On the fly, this is a little bit tough because none of
24 the units are matching.

1 well, so for AAD-12, the KM listed is a
2 little bit lower and the K cat per minute is lower. I
3 don't get K cat here.

4 So I get a number that seems not a
5 comparable. I'm wondering if there's a mistake in the
6 units.

7 okay. I think I understand. So this
8 multiplier that they are using -- that we're using
9 here is confusing. I initially thought that they were
10 multiplying the value by to the third, but it seems
11 they're, in fact, dividing by that, so this -- the
12 units are 1,000 per mole per minute effectively, and
13 so you get 27,000 for AAD-1, 2,200 for AAD-2 which
14 would imply that AAD-1 is faster than AAD-2.

15 So I think because there's a little bit of
16 lack of clarity in this table, I answered incorrectly.
17 It should be that AAD-1 is the faster, and according
18 to this table, AAD-12 is faster still.

19 Q okay. That's helpful to understand.

20 what number does AAD-12 have?

21 A I calculate 500,000 in the units of the --
22 or, let's say, 500 in the units of this per mole per
23 minute times ten to the third, so it would be about a
24 factor of 20 larger than AAD-1 according to this

1 table.

2 Q I thought AAD-1 was 27,000?

3 A Yeah, 27,000. This is 500,000.

4 Q Okay. So to summarize everything, the
5 efficiency ratio AAD-2 is 2,200, AAD-1 is 27,000 and
6 AAD-12 is 500,000?

7 MR. DEROO: Objection to form.

8 A Under the caveats that we laid out, I don't
9 know that these experiments were done under the same
10 conditions.

11 Q Okay. So if you have your Chekan article,
12 Exhibit 1015, I see that that mentions this efficiency
13 ratio on Page 13300, the second page. The left
14 column, the second paragraph, which begins, "On the
15 basis," the last -- second to last sentence mentions
16 these efficiencies.

17 Do you see that?

18 A Yeah. So this is for AAD-2, right? I just
19 want to make sure I'm on the right -- I might be in
20 the wrong part here.

21 Q The sentence I'm looking at says, "Neither
22 of these AAD homologs" -- well, let's go back to the
23 sentence before. So the sentence before says, "AAD-1
24 has been deployed in Enlist corn. AAD-12 confers

1 herbicide resistance."

2 Do you see that sentence?

3 A I think I'm in the wrong place. Can you
4 tell me again?

5 Q Second page, left column.

6 A Okay. Yeah, I see that.

7 Q Yeah, "On the basis," and then go to the
8 third sentence of that paragraph, and just read
9 silently to yourself the third and fourth sentence.
10 That's what I'm looking at.

11 A Okay.

12 Q So if I'm understanding this right, TfdA
13 has an efficiency for 2, 4-D of about 250 fold greater
14 than AAD-12 and an efficiency of 10,000 fold greater
15 for AAD-1.

16 Is that how you read it?

17 A Yes.

18 Q All right.

19 A And we could check the math then because
20 500,000 with respect to 27,000, that's about right.

21 Q Okay. So going back to your chart of all
22 of these enzymes in Paragraph 112 of your declaration,
23 TfdA is even higher in its efficiency against 2, 4-D
24 than AAD-12, right?

1 A Against 2, 4-D, yes.

2 Q Yeah. And it's about 250 times greater --
3 TfdA is about 250 times greater in its efficiency
4 against 2, 4-D than is AAD-12, right?

5 A Well, that's what it says here.

6 Q Yeah.

7 A You know, I would need to check the cited
8 references to put my stamp of approval on it, check
9 conditions and also make sure the numbers are right,
10 but yeah, that's what it says.

11 Q Is there a correlation between these
12 four enzymes' efficiencies against 2, 4-D and the
13 spacer length of the third spacer, do you think?

14 A I didn't study that. I mean, I'm just
15 doing these calculations on the fly, so I didn't
16 particularly delve deeply into K cat and KM.

17 Q So one thing that I notice is TfdA and
18 AAD-2 both have an identical spacer length, right?
19 They're both 121 amino acids at the third spacer?

20 A So we went through that, right?

21 Q Yeah. Feel free --

22 A That's back to my declaration.

23 Q Feel free to write it down if you want
24 because we'll come back to those spacer lengths.

1 A Is that okay?

2 MR. DEROO: You don't need to write it down
3 if you can remember.

4 Q It's up to you.

5 A Okay. Well, I would like to write it down.
6 I don't know if I'm not supposed to, but yeah. So
7 126 -- and you were asking about?

8 Q TfdA and AAD-2.

9 A 121 and 121. So can you repeat the
10 question, please?

11 Q Yeah. So the question was: Do you think
12 there's a correlation between the spacer lengths of
13 TfdA and AAD-2 for the third spacer and the efficiency
14 of their abilities to degrade 2, 4-D?

15 MR. DEROO: Object to form. Relevance.

16 A Well, for those two, I mean, that would be
17 a pretty lame correlation, but if -- you know, they
18 both degrade 2, 4-D, so in that sense it's correlated.

19 Q And TfdA on that chart has the highest
20 efficiency --

21 A Right.

22 Q -- against 2, 4-D --

23 A Right.

24 Q -- and AAD-2 has the lowest efficiency

1 against 2, 4-D, right?

2 MR. DEROO: Object to form to the extent it
3 mischaracterizes the testimony.

4 A I think that rank order was TfdA, AAD-12
5 and AAD-1, yes.

6 Q And AAD-2 at the end?

7 A I don't remember where we got the AAD-2
8 number, but that -- oh, here. Yes.

9 Q So there doesn't appear to be a correlation
10 between the third spacer length and the ability to
11 degrade 2, 4-D.

12 Is that fair to say?

13 MR. DEROO: Objection. Form. Relevance.

14 A Well, I mean what you're -- you're asking
15 me to look at these quantitative measures, which have
16 so many caveats because I don't know what the
17 conditions are.

18 I mean, undoubtedly you're asking just
19 about in a test tube, but the conditions matter,
20 right, so we don't know, but they all degrade 2, 4-D,
21 and the length of AAD-1 is the greatest and the length
22 of AAD-12 seems to be intermediate, so yeah, I guess
23 they can all degrade 2, 4-D.

24 Q But there doesn't appear to be a

1 correlation between the third spacer length and that
2 ability to degrade 2, 4-D, right?

3 MR. DEROO: The same objections. Asked and
4 answered.

5 A Yeah, I did kind of answer it. They -- I
6 think there are three spacers lengths represented 121,
7 126 and 131, and they all degrade 2, 4-D, that one
8 particular herbicide.

9 Q why doesn't TauD degrade 2, 4-D?

10 MR. DEROO: Object to form. Outside the
11 scope.

12 A Yeah. I said "they all." I shouldn't have
13 said that. TauD doesn't.

14 Q why doesn't it?

15 MR. DEROO: Same objections.

16 A Probably it relates to its binding
17 different substrate. I should say that binding is not
18 the only thing though.

19 Q One last line of questions and then we can
20 get lunch.

21 You mentioned these are in vitro
22 measurements and you said conditions matter.

23 Do you recall that?

24 A Yes.

1 Q So turn in Chekan, Exhibit 1015, back to
2 that paragraph we were just looking at on the second
3 page that involved --

4 A Is it the supporting information or the
5 main?

6 Q The main?

7 A Okay. The second paragraph. Okay. I see
8 it.

9 Q In there, it says -- in the sentence where
10 it lists the deficiencies, it says, neither were
11 active against 2, 4-D -- "Neither were highly active
12 against 2, 4-D in vitro," and then the next sentence
13 says, "Nevertheless, both were found to confer
14 tolerance to 2, 4-D in transgenic plants."

15 Do you see that?

16 MR. DEROO: Objection to form.

17 A I see the -- I think -- just to be a
18 stickler, I think you said deficiencies or the
19 efficiencies.

20 Q Sorry. The efficiencies.

21 A Yes. This is setting a -- this is saying
22 neither were highly active against 2, 4-D, but the
23 fact that they are providing parameters means that
24 they are active against 2, 4-D, and they both confer

1 tolerance to 2, 4-D.

2 So we know from that sentence even though
3 the emphasis is on the efficiency in vitro that they
4 are active against 2, 4-D and they confer tolerance to
5 2, 4-D. That's what those two sentences tell us.

6 MR. RUTT: Okay. We can take a break.

7 (Recess taken.)

8 BY MR. RUTT:

9 Q Welcome back, Dr. Bollinger. During lunch,
10 did you discuss the substance of your testimony with
11 your counsel?

12 A No.

13 Q So turn to Paragraph 23 of your
14 declaration.

15 A Okay.

16 Q In Paragraph 23, you describe the Enzyme
17 Commission for EC number.

18 Do you see that?

19 A Yeah. I see my having mentioned that
20 there.

21 Q And you discussed what the -- well, let me
22 ask you what is the EC number?

23 A It's a way to classify enzymes according to
24 the four-digit code for each enzyme to classify the

1 reaction -- to classify it according to the reaction
2 of the catalysts.

3 Q And what does the last digit usually
4 represent?

5 A It says here the last -- well, the last
6 digit usually represents the substrate specificity of
7 a reaction.

8 Q And then in the next sentence, you provide
9 an EC No. 1.14.11.43.

10 Do you see that?

11 A Yes.

12 Q Is that the number for AAD-12, the EC
13 number for AAD-12?

14 A I believe it is, yes.

15 Q I wasn't sure since you used the long
16 formula, which I didn't know if that's what AAD-12
17 meant, but if you go to the next page, you have a
18 Footnote 2 at the end of Paragraph 23.

19 Do you see that?

20 A Yes.

21 Q And the footnote is what made we think this
22 was AAD-12 because in there you mentioned that "The
23 Enzyme Commission has not yet assigned a separate EC
24 number for the degradation for pyridyloxy auxin

1 substrates, such as triclopyr."

2 Do you see that?

3 A Yes.

4 Q Can you explain how that works? How does
5 the Enzyme Commission go about assigning numbers?

6 MR. DEROO: Objection to form and scope.

7 A Well, I mean, I can tell you generally what
8 each digit means.

9 Q What I'm interested in is in the footnote,
10 you said, "The EC has not yet assigned a separate EC
11 number?"

12 A Right.

13 Q What is the process that goes into
14 assigning an EC number?

15 MR. DEROO: Same objections.

16 A I'm not really familiar with the process.
17 I'm familiar with the system and the numbers and how
18 to use them, but not how they come about.

19 Q Okay. But in the footnote, it mentions
20 pyridyloxy auxin substrates, such as triclopyr, right?

21 A Right.

22 Q And that's one of the categories of
23 herbicides that the '055 patent claims are directed
24 to, right?

1 MR. DEROO: Objection to form.

2 A Yeah. The claims are directed towards
3 AAD-12 and its ability to degrade two distinct classes
4 of herbicides.

5 Q why don't we actually look at Claim 1, so
6 it's not a memory test here. So Claim 1 recites
7 two categories of herbicides that AAD-12 can degrade,
8 right?

9 MR. DEROO: Objection to form. Calls for a
10 legal conclusion.

11 But you can answer.

12 A Well, transgenic plant cell comprising a
13 recombinant polynucleotide that encodes an AAD-12
14 protein that exhibits aryloxy alkanoate dioxygenase
15 activity where is said activity endomatically degrades
16 an phenoxy auxin herbicide and a pyridyloxy auxin
17 herbicide and then some more.

18 I think that answers your question. Did
19 you want to ask me --

20 Q The question was: Are there two categories
21 of herbicides -- I was just trying to make it easier
22 on the court reporter just by mentioning the two
23 herbicides.

24 They are phenoxy auxin and a pyridyloxy

1 auxin herbicide, right?

2 A That is correct.

3 Q And going back then to your declaration and
4 Footnote 2 of Paragraph 23 of your declaration,
5 pyridyloxy auxins, such as triclopyr, are one of the
6 categories of herbicides that Claim 1 is directed to,
7 right?

8 A Yes.

9 Q In your last sentence of Paragraph 23, you
10 say, "The fourth digit, 43, indicates that its,"
11 meaning AAD-12's, "substrate is 2, 4-D;" is that
12 right?

13 MR. DEROO: Object to form.

14 A The last sentence there is, "In the fourth
15 digit, 43, indicates that its substrate is," and it
16 gives the long form name of 2, 4-D.

17 Q Okay.

18 A No. Sorry. This is not 2, 4-D. Sorry.
19 This is the phenoxy propanoate, so this would be
20 dichlorprop -- S-dichlorprop. Sorry. I needed to
21 read that through.

22 Q All right. So the fourth digit indicates
23 the substrate is S-24 dichlorprop?

24 A Yeah. I think it's typically just called

1 dichlorprop, but we can look back into the -- do you
2 remember where we looked before --

3 Q Table 1 --

4 A -- if you will remind me.

5 Q -- Column 7 has the chart. I don't know if
6 it's in there.

7 A Yeah. It doesn't seem to be in there, but
8 the proper first in the propanoate as opposed to the
9 ethynate acetate as it's commonly called, so that's
10 S-dichlorprop.

11 Q So does -- is there an EC number that would
12 be assigned to describe AAD-12's ability to degrade
13 2, 4-D or would it fall under this EC number here?

14 MR. DEROO: Object to form.

15 A So a large number of enzymes can accept
16 substrates that are -- or analogs that are modified
17 from the normal substrate and have some resemblance to
18 it. That doesn't normally generate a separate EC
19 number.

20 In principle, there could be an enzyme
21 isolated that degrades just that one, and it would
22 generate a separate EC number.

23 Q Okay. So the fourth digit here would be
24 broad enough to cover something like 2, 4-D.

1 Is that what you're saying?

2 MR. DEROO: Object to form.

3 A Well, I think where this EC number came
4 from was the initial publication that this degrades
5 S-dichlorprop. And like I said, most -- many enzymes
6 will take slightly modified versions of their natural
7 substrate and operate. It doesn't ordinarily generate
8 a separate EC number.

9 Q But in Footnote 2, if I understand it
10 correctly, it indicates there would be a separate EC
11 number for --

12 A It's not meant to indicate that. It was
13 probably a frituatous footnote just to be absolutely
14 precise.

15 Q Okay. What does the third digit mean in
16 the EC number for AAD-12?

17 A It means -- it actually means two things.
18 One is using two oxoglutarate as one substrate and
19 incorporating both oxygen atoms from O2 into products.
20 One into the succinate co-products and one into the
21 prime product, if you will.

22 Q So when a skilled artisan, like yourself,
23 looks at the EC number for AAD-12, would you expect
24 that it indicates AAD-12 can degrade 2, 4-D or not?

1 A It calls for some speculation I think
2 but -- well, a skilled artisan looking at that EC
3 number recognizes that somewhere it was reported that
4 its natural and presumably best substrate -- that's
5 not always the case -- is what's listed there, right.
6 That's the last digit.

7 whether I would expect it to degrade 2,
8 4-D, I think in general I would because the change to
9 the substrate there is replacing a methal group of the
10 hydrogen, and that's smaller, and that usually --
11 usually can be accommodated.

12 Q would you have expected it to degrade a
13 pyridyloxy auxin like triclopyr?

14 MR. DEROO: Object to form.

15 A Is the question you're asking knowing
16 nothing else? You want me to speak pretending that I
17 haven't done all of the reading that I have done, is
18 that what you're saying?

19 Q I'm trying to understand what kind of
20 functionality a person of skill in the art would
21 expect from an EC number.

22 A well, one would expect it to be -- to
23 prefer the substrate listed, this S-dichlorprop, and
24 then what a person of skill in the art would typically

1 do is compare substrates and identify the different
2 substructures that distinguish them and then usually
3 ask the question -- I mean, it's for empirical
4 determination -- can it tolerate changes to what's
5 considered the best substrate?

6 You asked me about the specific one of
7 replacing the metho group in that one, and that's
8 hydrogen. That generally -- if you're going to make a
9 change, that's one that's likely -- more likely to be
10 tolerated than some others.

11 The pyridyloxy is a bigger change. You
12 know, it has electronic effects, so it's a tough call.
13 I don't think I would expect it to. It's something
14 that I would see as an interesting question if
15 somebody raised it to me. Like, if I'm teaching a
16 class and a student brings it up, that's a good
17 question. I don't know

18 Q I'm a little afraid to ask it because I
19 don't want a lot of chemistry terms, but is there a
20 simple way to describe the main difference between the
21 2, 4-D molecule and a triclopyr molecule?

22 MR. DEROO: I'll object to form.

23 A There's a science of a branch of this field
24 called chem informatics that seeks to sort of map

1 these things in almost a language, right, but it's not
2 very simple. So I can point to the structures and say
3 this is different and this is different. I could give
4 you some sort of broad brush thoughts about what that
5 causes.

6 Q Let's look at Table 1. I think that has
7 it, right, the structures.

8 A Well, it didn't -- I thought it didn't
9 tricloprop.

10 Q It has tricloprop it doesn't have
11 S-dichlorprop.

12 A Right. That's what I meant -- that's what
13 I meant to say.

14 Q So if you had to describe to a lay person
15 the difference between 2, 4-D in Table 1 and
16 tricloprop, what would be some of the most significant
17 differences?

18 MR. DEROO: Object to form. Vague.

19 A So 2, 4-D -- and you want me to do
20 tricloprop or dichlorprop?

21 Q Sorry. Triclopyr?

22 A Triclopyr.

23 Q Apologies.

24 MR. DEROO: Same objections.

1 A Well, so one can see that there is a --
2 Are you talking about 2, 4-D to triclopyr?

3 Q Right.

4 A There's what we call hetero cycle. That
5 means a ring that has a nitrogen or some other hetero
6 atom adhered to nitrogen. It has two of the chlorines
7 at similar positions to where they are in 2, 4-D and
8 then it's got an extra chlorine.

9 So there are huge electronic effects to put
10 the nitrogen in there and a big electronic effect to
11 put one extra chlorine there, and they could either
12 synergize or fight each other. Without doing an
13 electronic structure calculation, it's not -- it's
14 particularly intuitive. I would say there are
15 chemists who might know that, but that's not something
16 that I focus on.

17 So broadly, one of the most important ways
18 that substrates interact -- enzymes interact with
19 their substrates is by getting charge and polarity
20 complimentary correct, and all that means is where the
21 substrate has a negative charge, the enzyme puts a
22 positive charge to interact. That's what it is
23 essentially.

24 Q And are there different charges between

1 2, 4-D and triclopyr?

2 A Not outright charges, but polarity, and I
3 meant -- you know, we speak of partial positive and
4 partial negative charges in the same terms.

5 Q Okay. In 2005 or 2006 when this original
6 patent application was filed, would a person of skill
7 in the art have been surprised that AAD-12 could
8 degrade both 2, 4-D and triclopyr?

9 MR. DEROO: Objection. Outside the scope
10 of Dr. Bollinger's declaration.

11 A Yeah. I mean, I think that calls for an
12 emotional reaction to a scientific observation. I'm
13 not sure of the answer. I think a person of skill in
14 the art would have found that interesting.

15 So whether they would have thought to
16 predict it, I can't say, but I think it's not -- it's
17 not presumable. It's something that would have to be
18 experimentally demonstrated.

19 Q Do you think a person of skill in the art
20 would have been surprised in 2005 or 2006 that AAD-12
21 could degrade both 2, 4-D and S-dichlorprop?

22 MR. DEROO: Objection. Outside the scope.
23 Relevance.

24 A That's where I have kind of already

1 answered that I think that's less surprising.

2 Q why is that?

3 A well, it's just methol for hydrogen. I
4 think hydrogen for methol is generally viewed a little
5 bit of change because you're going from a smaller
6 thing to a bigger thing.

7 Q So turn to the first page of the patent.

8 A Yes.

9 Q The reason I'm asking these questions about
10 whether it's surprising or not is because of the
11 statements in the first two sentences of the abstract.

12 why don't you read that to yourself
13 quietly?

14 A Yeah.

15 Q So that's what I was asking if you agree
16 with. Do you agree with that second sentence that
17 says basically in 2005 or 2006, there was no
18 expectation or suggestion that a plant with both of
19 these advantageous properties, meaning resistance to
20 2, 4-D and also resistance to pyridyloxy acetate could
21 be produced by the introduction of a single gene?

22 MR. DEROO: Object to the form.

23 Q Do you agree with that or not?

24 MR. DEROO: Objection to form. Asked and

1 answered.

2 A well, let me say that I wasn't asked to
3 opine on specifically the plant aspects. Although,
4 I'm very familiar with them, and I think I understand
5 them, so a lot of this sentence refers to that plant.
6 From my perspective, it comes down to the ability of
7 an enzyme to degrade both.

8 And I agree that there was no expectation
9 or suggestion that a plant -- or that an enzyme could
10 be found that would degrade them both, and, thereby,
11 confer the resistance that's mentioned there, so yes,
12 I agree with that statement -- with both statements.

13 Q Does the degradation of 2, 4-D involve the
14 same chemical reaction as the degradation of
15 triclopyr?

16 A well, to be perfectly precise, the reaction
17 involves the substrate, so they're not the same
18 obviously because one is on one substrate and one is
19 on the other. Both reactions involve alpha-kg and
20 oxygen presumably at the iron co-factor, so they're
21 similar, but obviously not the same.

22 Q what's different about them in as simple
23 terms as possible?

24 A well, the identity of the substrate.

1 Q So I'll show you the document marked 2027.

2 A Okay.

3 Q Do you recognize this document?

4 A Yes.

5 Q So I want to look at the materials and
6 methods section at the end of the document on
7 Page 1139.

8 Are you able to read that?

9 A I think so.

10 Q I printed out a clearer copy, which I'll
11 give you because I think it may help everybody this is
12 marked as Exhibit 1042.

13 MR. DEROO: And just for the record, I'll
14 make objections to authenticity, relevance,
15 hearsay and scope. Let's take a look at it.

16 Q So just comparing the two documents, does
17 it appear to you to be the same article?

18 A Yeah. Just one is clearer than the other.

19 Q So let's use Exhibit 1042.

20 A Okay.

21 Q Go to the same section, the materials and
22 methods section?

23 A All right. I'm there.

24 Q So in the right column of Page 1139, the

1 third paragraph begins, "To assess the correlation."

2 Do you see that?

3 A Yes.

4 Q Go ahead and read that paragraph silently
5 to yourself to familiarize yourself with it.

6 A Okay.

7 Q Do you see the sentence that says enzymes
8 having two or more EC numbers assigned to them were
9 ignored?

10 MR. DEROO: Object to form to the extent it
11 mischaracterizes the document.

12 A Yeah. It says, "For ease of comparison of
13 EC numbers, enzymes having two or more EC numbers
14 assigned to them or those with incomplete EC numbers
15 were ignored."

16 Q So this study excluded enzymes that had two
17 or more EC numbers, right?

18 A Or incomplete EC numbers.

19 Q So I'll show you an exhibit marked as 2028.

20 A I see it. The one is a little clearer. I
21 think I can read it.

22 Q I have a clearer copy if that will help.

23 A It looks okay so far.

24 Q So turn to the materials and methods

1 section on Page 605.

2 A Yes.

3 Q The first sentence states that the data set
4 of enzymes of known function were taken from the
5 current merger of SWISS-PROT, plus SWISS-PROT_New.

6 Do you see that?

7 A Uh-huh.

8 Q What is SWISS-PROT?

9 A Well, I know what it is now, and I'm sure
10 it was the same then, but it's a curated database that
11 aims to provide highest quality assignments, so they
12 are assignments that have been verified by biochemical
13 methods.

14 Q Does it only include enzymes of known
15 function or does it include enzymes of unknown
16 function as well?

17 A I believe it's only known function. I
18 think that's the whole point.

19 Q Where do the enzymes that are cataloged in
20 there come from? Are they natural evolved? Are they
21 made in a lab? Are they both?

22 MR. DEROO: Object to form.

23 A I don't have a photographic memory of all
24 the proteins in the database.

1 Q How about most of them?

2 A I would think most of them come from a
3 natural source.

4 Q Do most enzymes that come from a natural
5 source have a function or are there some enzymes out
6 there that have no function?

7 MR. DEROO: I'm going to object to form and
8 scope.

9 A It's a very broad question because if I
10 say -- I mean, you said "most", and then you said are
11 there some that have no function --

12 Q Okay. Let's start with --

13 A -- so if we --

14 Q Let's start with natural enzymes. Are
15 there -- do all natural enzymes have a function even
16 if we don't know it?

17 MR. DEROO: Same objections.

18 A I wouldn't offer that as my opinion because
19 it's too broad. There could be exceptions.

20 Q We don't know?

21 A Yeah. I mean, when one looks at an enzyme,
22 it's possible that -- let's say an apparent enzyme.
23 It's possible that it's lost its activity through
24 evolution but --

1 And then the second technical issue is that
2 to demonstrate its activity, one has to be able to get
3 it, and so there may cases where no activity could be
4 demonstrated, but we don't know for sure that it
5 doesn't have that typically in its organism.

6 So there's a couple caveats to that, but I
7 would -- I would never say that absolutely every
8 single one has a function.

9 Q Okay. Do you think most do?

10 A Do I think that most --

11 MR. DEROO: Objection.

12 Q Most enzymes have a function --

13 MR. DEROO: Objection.

14 Q -- that are naturally evolved?

15 MR. DEROO: Vague.

16 A Most being greater than 50 percent?

17 Q Sure.

18 A I would think so.

19 Q How about --

20 A It's not -- it's not a very -- it's not a
21 question that one can answer particularly
22 definitively.

23 Q You said that there might be enzymes that
24 lost their function?

1 A Yeah.

2 Q Does that imply that enzymes that have
3 evolved typically evolve to have a function?

4 MR. DEROO: Object to the form. Scope.

5 A I think that enzymes are -- in nature are
6 generally subjected to evolutionary pressure for
7 functionality, so yes.

8 Q Returning to Exhibit 2028 that we were
9 looking at, in that same paragraph under materials and
10 methods, the author states in the second sentence that
11 they excluded all of those proteins that had more than
12 one EC number, right?

13 A Uh-huh.

14 MR. DEROO: Objection to the extent it
15 mischaracterizes the document.

16 A To characterize it fairly, there's --
17 there's three omissions, EC number contained undecided
18 digit, more than one EC number was given and
19 parenthetical domains, so that's referring to enzymes
20 that have -- that are essentially multi enzymes. They
21 are connected, but they can do two different reactions
22 at different domains -- in their different domains.

23 And then the key words contained one or
24 more of the words probable, putative, biosimilarity

1 or bio amounts, so the attempt in this study is to
2 just use validated enzymes of demonstrated function.

3 Q So I'll show you a document that has been
4 marked as Exhibit 2019, and I've got a clearer copy of
5 this one if you want. Just let me know.

6 A This seems pretty clear.

7 Q Do you recognize this document?

8 A Yeah, I do.

9 Q So turn to Page 976, and we'll go again to
10 the methods section.

11 MR. DEROO: Objection. I think --

12 A Yeah. 876 maybe?

13 Q Yeah. Thank you. 876.

14 A Yeah, I'm there.

15 Q So in the first sentence, it refers to the
16 SWISS-PROT database.

17 Do you see that under the methods section?

18 A Uh-huh.

19 Q Do you see that?

20 A Yes, I see it

21 Q And these authors have done the same
22 strategy that was done by Rost, which is the
23 Exhibit 2028 we were just looking at, right?

24 A They don't describe it exactly the same,

1 and there's an additional omission based on the key
2 word "fragment," meaning the entire sequence is not
3 deposited, not available, but they exclude or removed
4 sequences that contain EC numbers with undetermined
5 digits, have more than one EC number, have key words
6 with probable hypothetical punitive biomology or
7 biosimilarity and have the key word "fragment," so the
8 goal was again to obtain a set with well-validated
9 functions.

10 Q So I'll show you an exhibit marked 2029.

11 A Okay.

12 Q Do you recognize the document?

13 A If I'm going to be honest, this one is not
14 triggering my recollection, but it's in -- it's in the
15 declaration, so I'm sure I have seen it.

16 Q Okay. I think you cited it maybe once.

17 Turn to Page 96.

18 A Okay.

19 Q Now, you might need a little more
20 background. I was going to ask you about Table 1, but
21 if you haven't seen this at all, let's go back to
22 where this describe data sets 1 and 2, which is -- at
23 Page 94, it starts the section called data sets.

24 Do you see that?

1 A Yeah.

2 Q So just go ahead and read that section
3 basically.

4 A Under data set?

5 Q Yeah, data sets onto the next page to where
6 it says, "Characterization of the Data," just so
7 you're familiar with what these data sets are.

8 A Yeah. I'm reading this and the methodology
9 is a little obtuse to me, so I mean, we can -- I mean,
10 fire away.

11 Q Okay. So for data set 1 at the bottom of
12 94, it says, "This family of data sets originated from
13 the PDB subset of SWISS-PROT."

14 Do you see that?

15 A Yes.

16 Q What is PDB, if you know?

17 A I think that's the protein structural data
18 bank, but out of context, I'm a little bit unclear. I
19 think -- I think that's right because there's
20 structures.

21 Q Okay. Do you know what's in it generally?

22 A It's deposited coordinates of
23 experimentally determined protein structures. There
24 used to be some that were not experimented to

1 determine computation. As I understand it, they have
2 segregate those, in part, now the models from the
3 experimental structures, but that's generally --

4 There's a code, so one can search the code
5 and access those coordinates. There's additional
6 information in there, but I think that --

7 Q Okay. So is PDB -- it says here a subset
8 within SWISS-PROT. It's just what? A smaller group
9 within it? Is that how it works?

10 A Yes, a smaller group of proteins for which
11 I presume -- for which structures have been determined
12 and deposited.

13 Q And then data set 2 on the next page says
14 it was from the full release of SWISS-PROT Version 33
15 from, I guess, 1994.

16 Do you see that?

17 A I don't see that. I'm trying to find it.

18 Q It's halfway down the page, left column of
19 Page 95.

20 A On the left side?

21 Q Yeah. There's a heading data set 2?

22 A I see it. Okay.

23 Q So the question was: This data set
24 originated from the full release of SWISS-PROT

1 Version 33, which appears to have been, I guess, 1994.

2 Does that look right?

3 A I see that, yes.

4 Q So basically, these two data sets came from
5 SWISS-PROT?

6 MR. DEROO: Object to form.

7 A Well, they may have been archived there,
8 but the PDB data sets are of a very different nature.

9 Q What makes them different?

10 A They are coordinates for to determine
11 crystal structures -- well, structures. Not
12 necessarily crystal structures.

13 Q So let's now turn back to where we started
14 on Page 96 and look at Table 1?

15 A Uh-huh, yeah.

16 Q So it provides some metrics on the two data
17 sets.

18 Do you see that?

19 A We're at the top?

20 Q Yes, Table 1.

21 A Yes, I see that.

22 Q And data set 1 had about 1,000 total
23 entries and data set 2 had about 50,000 entries.

24 Do you see that?

1 A I do. And one was from the PDB, and one
2 was from the full release of the SWISS -- two was from
3 the full release of the SWISS-PROT. Okay. So I think
4 I have that correct.

5 Q So it looks like the PDB had about -- it
6 was about two percent the size of this total SWISS-
7 PROT database.

8 Is that fair?

9 A I have to use my calculator. I mean, it's
10 about 1,000 over 50,000. I think that's two percent,
11 yes.

12 Q So you're saying that those
13 1,000 structures had either the crystal structure or
14 some coordinate that is not available for the enzymes
15 in the broader SWISS-PROT database?

16 A That's what distinguishes the data sets,
17 but I want to be clear that at that time, it's
18 likely -- or let's say it's possible that some of the
19 PDB in data set 1 were model structures because at
20 that time, they were as I understand it allowing for
21 those to be deposited.

22 Q Is that different today?

23 A I believe that they -- well, I know that
24 they now distinguish, and it was possible to

1 distinguish in the past, but I think there's a
2 physical separation of them into different separate
3 databases.

4 Q why do they do that?

5 MR. DEROO: Object to the form and scope.

6 A Well, they're different types of
7 information. If there's a experimental structure,
8 it's usually by extra crystallography, and there's a
9 whole set of additional information that's provided.
10 If it's a model structure, as in alpha fold, it can
11 typically be presented just as coordinates, so they're
12 of -- there's a different nature of information of
13 data.

14 Q So in Table 1, it says there were, in the
15 third line, entries with multiple EC numbers used.

16 Do you see that?

17 A Entries with?

18 Q Or sorry. Entries with multiple EC
19 numbers, and then it says, "Not used?"

20 A In the third line, yes, entries with
21 multiple EC numbers not used.

22 Q So the author is has excluded entries with
23 multiple EC numbers from this study, right?

24 MR. DEROO: Object to the form.

1 A I would want to read something in the
2 materials and methods that told me that, but that's
3 certainly the implication in that parenthetical in the
4 table.

5 Q And those EC -- those entries with multiple
6 EC numbers were about one to two percent of the total
7 data sets, right?

8 A 1.8 percent of data set 1 and 1.0 percent
9 of data set 2.

10 Q Is that a typical percentage for the EC
11 number database, if you know? Is it typical to have
12 about one to two percent having multiple EC numbers
13 out of the total entries in the enzyme database?

14 A I don't -- I don't know the answer. I
15 assume that they're taking all of the entries in both
16 databases, so at this time, that would have probably
17 been representative.

18 MR. RUTT: Should we take a break?

19 MR. DEROO: Yeah, it's a good time.

20 (Recess taken.)

21 BY MR. RUTT:

22 Q Welcome back, Dr. Bollinger. During the
23 break, did you talk with your counsel about the
24 substance of your testimony?

1 A No.

2 Q Let's turn to Paragraph 56 of your
3 declaration.

4 A Okay.

5 Q In Paragraph 56, you identify several
6 fundamental scientific principles of protein
7 engineering in 2005 to 2006.

8 Do you see that?

9 A It says, "In summary, a skilled person
10 would have followed several fundamental scientific
11 principles of protein engineering in 2005 to 2006 when
12 designing enzyme variants based on the claimed
13 methods."

14 Q The second principle that you list is to
15 maintain the active site motif, right?

16 A Right. That's underlined as Point 2.

17 Q And in the AAD-12 molecule, the -- what is
18 the active site motif?

19 A It's what was summarized in one of the
20 tables I provided.

21 Q Is it in Paragraph 112?

22 A Yes. So it's the histidine and aspartate
23 iron ligands separated by one residue, and then we
24 decided it was -- I'm getting different math. It's

1 124 residues and -- sorry. It's 24 residues in the
2 threonine and then 126 in the histidine and then
3 10 residues in the arginine as the active site motif.
4 That's what it says in the same.

5 Q And then going back to Paragraph 56, when
6 you say, "Maintain the active site motif," what do you
7 mean by "maintain?"

8 A Sorry. I forget where we were.

9 Q Paragraph 56.

10 A 56.

11 Q Page 32. I can ask the question again.

12 A No. That's fine. You said --

13 Q Well --

14 A -- maintain the active site motif?

15 Q Yeah. So in that paragraph, in the second
16 sentence, you say, "A skilled person would be careful
17 to preserve the active site motif residues."

18 what does it mean to preserve the active
19 site motif residues?

20 A Well, the premise here is that one would
21 take a functional enzyme and make variants that
22 maintain function, and so they would not want to
23 substitute at the positions that are part of the
24 active site motif when they are specified.

1 And, you know, this was meant to be
2 general, so we have a specific motif for AAD-12, but
3 there could be other motifs in the general sense.
4 When they are known, one doesn't change them.

5 Q So applying this to AAD-12 means you
6 wouldn't change those five amino acids you identified
7 as the active site?

8 A Nor the spacing between them as exactly
9 specified.

10 Q And that's what Claim 1 requires for all of
11 the enzymes that are -- that's what Claim 1 requires,
12 right? It requires those five amino acids and it
13 requires the space in between them, right?

14 A Well, it starts with the transgenic plant
15 cell, but when one gets down to the AAD-12 protein
16 that degrades the phenoxy auxin herbicide and the
17 pyridyloxy auxin herbicide, that AAD-12 protein
18 compromises amino acid sequence having at least 85
19 percent identity -- a sequence identity with Seq ID
20 No. 2, which is AAD-12 and then the motif. So it's
21 got to have those things to that's defined for
22 four additional lines, and that's the end of Claim 1.

23 Q So Claim 1 basically requires that in
24 making variants, you would maintain the active site

1 motif, right?

2 A Well, when I read it, if I change the first
3 histidine to something else or the aspartate to
4 something else or the threonine to something else or
5 the histidine or the arginine to something else, then
6 it wouldn't have that general formula.

7 And also, if I change the spacer from
8 any -- from 24, 126 and 10 to other any other number,
9 it also wouldn't have that general formula.

10 Q So the claims require that you maintain the
11 active site motif then, right?

12 A Yes, I believe that's true.

13 Q Going back to Paragraph 56 and the
14 four principles you identify, look at the third
15 principle on Page 33.

16 A I see that.

17 Q That principle says, "Retain other
18 non-motif residues that are highly conserved across
19 related enzymes."

20 Do you see that?

21 A I do.

22 Q What does it mean to be a -- what is a
23 non-motif residue?

24 A It could have been a bit more precise, but

1 what it means is that the residues that aren't
2 specified, but the number between them has to stay the
3 same. It doesn't foreclose changing any of the Xes in
4 there to something else.

5 Q Okay. So let's take that one step at a
6 time. So in the example of AAD-12, the non-motif
7 residues would be all of the residues other than the
8 five in the active site; is that right?

9 A This point refers to highly conserved.
10 Some of the spacer residues are likely to be -- and I
11 don't have to guess.

12 So there are a number of spacer residues in
13 this multiple sequence alignments of these five
14 proteins that have fairly modest identity. One finds
15 positions that are conserved, and so the patent
16 doesn't say one shouldn't change those, but the person
17 of skill in the art knows to use the structural
18 guidance in Figure 2 from the patent to identify
19 residues to change and also what to change those to.

20 So those are not the good candidates, the
21 ones that are highlighted in my reproduction of
22 Figure 2 here with the green arrows.

23 Q What paragraph are you on?

24 A It's Paragraph 125.

1 Q Okay. So that's something I wanted to ask
2 about. In this Principle No. 3, you use the phrase
3 "highly conserved," but in Paragraph 125, you used the
4 phrase "strictly conserved."

5 What is the difference?

6 MR. DEROO: Object to form.

7 A My intent was not to create a distinction
8 between those.

9 Q Okay. And then I think in -- I'm sorry.
10 In Paragraph 126, you say "strictly conserved."

11 Do you see that?

12 A I do.

13 Q And then in Paragraph 127, you say
14 "somewhat conserved."

15 Do you see that?

16 A I'm not following you.

17 127?

18 Q I'm sorry.

19 A 126.

20 Q 126 is "somewhat conserved" -- my
21 apologies -- and 125, I think, is "strictly
22 conserved."

23 Is that right?

24 MR. DEROO: I'm just going to object to

1 form.

2 A But it just says conserved in the -- in the
3 third line. I'm not supposed to mark it. And then
4 strictly conserved in that five lines from the bottom.

5 Q Yeah. Yeah. I was looking at --

6 A So unfortunately, the literature uses these
7 terms a little bit interchangeably. Highly and
8 strictly conserved often mean the same thing, and
9 conserved without an adjective can mean the same
10 thing.

11 Q Okay.

12 A Without a adverb. Sorry. Without an
13 adverb.

14 Q Okay. But you drew two charts -- or you
15 annotated two different -- you provided two different
16 sets of annotations to Figure 2 in Paragraphs 125 and
17 126, right?

18 A That's right.

19 Q Could you help me understand what the
20 difference is between the chart in 125 and the chart
21 in 126?

22 MR. DEROO: Object to form.

23 Go ahead.

24 A At one level, the green arrows indicate

1 that every one of the five aligned sequences has, at
2 the position indicated, the same residue, and that's
3 what we call strictly or highly conserved or just
4 conserved.

5 The second figure or reproduction of
6 Figure 2 from the patent points to residues that --
7 positions that don't have the exact same amino acid in
8 all five sequences, but have amino acids that are
9 considered similar or, you know, because of the nature
10 of their sidechain, just as it sounds, one word, they
11 are generally acceptable substitutions.

12 Q Okay.

13 A If you want, I can given an example.

14 Q Sure. Give us an example.

15 A Position 58 along the number line is a
16 leucine in AAD-12 and it's a valine in all four of the
17 other sequences, so that's not a bad substitution to a
18 person of skill in the art.

19 Q So if you look at Position 68, you have
20 added an arrow there, right?

21 A Right.

22 Q In Paragraph 126?

23 A Right.

24 Q And Position 68 has SSTTT, correct?

1 A That is correct.

2 Q So why did you identify that as a somewhat
3 conserved position?

4 A It's not the same sidechain. It's not the
5 same amino acid or residue, but it's similar according
6 to what we consider a conservative substitution. So
7 conserved or strictly conserved or highly conserved
8 means it doesn't change at all, and somewhat conserved
9 mean it's conservative substitution.

10 Q And were you looking at all five of these
11 when you were determining -- well, strike that.

12 You will see what I'm getting at. In
13 Position 137, it has TSSTT.

14 Do you see that?

15 A I do.

16 Q Why didn't you pick that one or why didn't
17 you identify that one as somewhat conserved?

18 A Well, I think that one was probably
19 identified -- yeah, that one could have been
20 identified. I guess we missed one or a few.

21 Q Okay. Because I didn't see the difference,
22 and I was wondering what it was.

23 A Yeah.

24 Q So Paragraph 128, it's a long paragraph

1 that goes onto two pages, and at the end of that
2 paragraph, on Page 76, there's a chart.

3 Do you see that?

4 A Yes.

5 Q What is this? What does this chart show?

6 A It shows substitutions to each of the
7 20 common amino acids that make up enzymes that are
8 generally more well tolerated than others because
9 often of the nature of the sidechain being similar.

10 Q So in that first line, it says the amino
11 acid serine could be conservatively substituted by
12 threonine, glycine and a third one that I forget?

13 A Asparagine.

14 Q And then I guess the same is true of
15 threonine. Threonine in your chart is the fifth one
16 down, and that includes serine as a conservative
17 substitution?

18 A Right.

19 Q So is this the scheme you used to identify
20 conservative substitutions?

21 A Yes, in general, but it appears we missed
22 at least that one. There may be others.

23 Q Okay. But was --

24 A I think that the goal here was to

1 illuminate the type of what we -- to define what we
2 meant by "somewhat conserved" and that that would be a
3 residue that would could consider in making changes to
4 preserving function.

5 Q Okay. So for the amino acids identified in
6 Paragraph 126, is the idea that you would only make a
7 limited set of substitutions for those amino acids
8 that you identify with brown arrows?

9 A You're calling that brown. It looks orange
10 to me.

11 Q Sorry. Whatever you want to call it. It
12 looks brown to my eyes.

13 A Okay. So that 126 says, "A skilled artisan
14 would also understand from Figure 2 that there are
15 many needed marked in red," the third color, "that are
16 not strictly conserved across the sequences of all
17 five enzymes. These residues are somewhat conserved,
18 but have been shown to tolerate conservative changes
19 to similar amino acids as shown in the sequence
20 alignment providing guidance to skilled artisans that
21 these residues may be preferentially left
22 unsubstituted or conservatively substituted."

23 So the idea is, yeah, there are -- there
24 are some here that have some shading, but they're not

1 shaded through the entire column, and so that means
2 there's one or two or maybe three choices among these
3 related enzymes that occurred in nature and may well
4 be tolerated in terms of the change.

5 Q And were you using the chart in
6 Paragraph 128 to determine what those tolerated
7 changes are or the somewhat conserved residues in
8 Paragraph 126?

9 MR. DEROO: Just object to form.

10 A I might have marked these just for my
11 knowledge. The table is from a source that is good,
12 but the reason we might have missed one is that I went
13 through and found these on my own, so yeah. I mean,
14 that table refers to the kinds that are indicated
15 here.

16 Q Is there variation among persons skilled in
17 the art as to what counts as a conservative
18 substitution or not?

19 MR. DEROO: Objection to form. Scope.

20 A There is some fairly sophisticated
21 mathematical analysis of what makes a substitution
22 good In a set of tables that are essentially scoring
23 matrixes, and so would could set different thresholds
24 for how penalizing a given substitution is to consider

1 it good, but the matrixes are there for a person
2 skilled in the art to refer to.

3 Q How does one go about -- how would one
4 skilled in the art go about setting the penalty?

5 A It would depend on the objective.

6 Q If the objective was to preserve
7 functionality, then what would they do?

8 A I can see two alternative objectives. One
9 is to involve a new activity or property. One is just
10 to preserve the existing. I probably would be a
11 little more conservative in preserving the existing
12 one because I want to discover new things.

13 If I'm trying to find a new function, I
14 might need to broaden the search, so I would be a
15 little less -- I would tolerate a slightly larger
16 penalty for the more ambitious project of trying to
17 get different activity of a different problem than if
18 I'm just trying to preserve.

19 That's about as good an answer I can give.
20 We can look at the matrixes if you want.

21 Q Let's do that, so I'll give you an exhibit
22 that was marked 2083.

23 Do you recognize this document?

24 A I do.

1 Q Turn to the second page and look at
2 figure -- actually, strike that.

3 Turn to the fourth page and look at
4 Figure 82.

5 A Okay.

6 Q Is this one of the matrixes that you're
7 referring to?

8 A This was an early version, yeah. This is
9 very influential one, yeah, but this was an early one.

10 Q And I want to make sure I understand this
11 correctly, so let's take, as an example, column -- the
12 first column that lists alanine.

13 Do you see that?

14 A Yes.

15 Q So what is the substitution that -- well,
16 you tell me what do these numbers mean in the first
17 column?

18 MR. DER00: Which page are we on? Sorry.

19 Q Page 4, and it is Figure 82.

20 A Well, I'll just -- I'll walk down the rows,
21 I guess, if you want to start with the column.

22 Q You don't have to do every single row
23 but --

24 A Okay.

1 Q -- but if you could give me a few
2 examples --

3 A Okay. Fair enough.

4 Q -- of how you read a chart like this.

5 A That 9,867 means that of 10,000 changes in
6 100 amino acids -- well, so they're different
7 evolutionary intervals. I want to find out if there's
8 evolutionary intervals.

9 Q Take your time.

10 A It's one point accepted mutation interval,
11 and what that means is there's 1 change per 100 amino
12 acids. Okay. And then this is a probability, but
13 it's multiplied by 10,000 to get it all without
14 decimal points. And so if a protein --

15 It's a model, so, you know, there are
16 assumptions in whether it's an accurate reflection of
17 reality. Absolute accurate reflection of reality is
18 debatable, but the model is that if there's
19 1 mutation in 100 amino acids, that's an evolutionary
20 distance however long that takes, and that can be
21 context dependent. There is going to be 9,867
22 examples of alanine that didn't change, and then
23 the --

24 So that's the highest number, and that's to

1 be expected because it's a short evolutionary
2 distance. There's only 1 -- there's only 1 mutation
3 per 100 residues, so you could go to 250 mutations per
4 100 residues, and these numbers will change, but what
5 this first number tells you is that the likelihood
6 that alanine is preserved as alanine over that
7 evolutionary distance. It's a probability.

8 And then if one scans down, one finds the
9 highest -- the second highest number in that column is
10 for serine, and it's at 28, and that's a pretty high
11 number for this short evolutionary distance, so if I
12 could jump --

13 Can I continue?

14 Q Yeah. Just talk slow.

15 A Okay. Sorry. So if I could jump to
16 tryptophan, that's the 18th column, the w, and you
17 will see that the diagonal element is 9,976. That's
18 much greater than 9,867 for alanine, and it turns out
19 if you look through, that will be the highest number,
20 and that means that tryptophan is the least likely to
21 get changed without knowing the context.

22 And then if one scans up, one can find the
23 highest other number is 8 for arginine, so that means
24 in the rare occasion that tryptophan is substituted

1 that its most likely swap is to arginine, and so those
2 are extremes of alanine being relatively freely
3 substituted, and we may find a smaller number than
4 9,867.

5 Asparate has one, and glutamate has one,
6 but that's largely because those are often
7 interchanged, so basically, the larger the diagonal
8 element, the less likely a given residue is to be
9 substituted for that substitution to be tolerated, and
10 the lower the number the more likely it is, and then
11 the off diagonal elements what it's likely to be
12 changed to.

13 Q Okay. And so how does this matrix or these
14 types of matrixes relate to definitions of what a
15 conservative substitution are if they relate at all?

16 MR. DEROO: Object to form.

17 A Well, they generally relate. You know, I
18 didn't -- I didn't consider it important to go into
19 the math of it, but in general, you could see that
20 serine has a relatively small diagonal element, and
21 honestly, it might be the smallest. I haven't
22 checked.

23 It seems to be the smallest. That means
24 it's quite likely to be substituted, and it can be

1 substituted by threonine, glycine or asparagine, so
2 one would look at those off diagonal elements.
3 Asparagine is 20.

4 Sorry. I'm not sure I'm in the right place
5 here. Let me make sure.

6 Yeah. Asparagine is 20, glycine is 21 and
7 threonine is 32. So those are big numbers and well
8 tolerated.

9 Q I think asparagine is 5, right?

10 A I might have missed it. No. Asparagine is
11 20 for serine. I was using serine as an example.

12 Q It's the fourth one down, right?

13 A No. That's aspartate?

14 Q Okay.

15 A Yeah, asparagine is 20.

16 Q So one thing I was trying to understand
17 was, going back to your example of alanine having
18 serine as the most substituted, when I look at your
19 chart in Paragraph 128, it doesn't identify alanine or
20 serine as conservative substitutions?

21 A Yeah.

22 Q Why is that?

23 A This table -- you know, there's another --
24 I can point out another choice for serine is alanine,

1 and that's not listed either. This is a table from a
2 reference that was convenient, but the matrixes are
3 where the math is and where the real insight is.

4 Q Okay. There's a similar table in the '055
5 patent, if you could turn to that, in Column 22.

6 A This may be from the '055 patent. No.
7 This is from --

8 Okay. you want me at column 22?

9 Q Yeah, Column 22, Table 2 of the '055
10 patent.

11 A Yeah.

12 Q Here again, it shows -- I was looking for
13 serine and alanine in this table and -- well, before
14 we get to that, my understanding of the table is that
15 a conservative substitution would be a substitution
16 within the same class of amino acids?

17 A That tends to be true.

18 Q Okay.

19 A And it depends -- you know, there are
20 exceptions, so the one I just pointed out, serine to
21 alanine. Alanine here is listed as non-polar, but
22 serine is listed as uncharged polar, so in a sense
23 when we present them in a biochemistry class, we might
24 separate those, but the statistics tell you that

1 there -- that that's not a bad substitution, so that's
2 why Table 2 differs somewhat from Table 1, but they're
3 all relying on this sort of analysis and then the
4 iterations that occurred afterwards.

5 Q So let's go to Paragraph 128 of your
6 declaration.

7 A Okay.

8 Q And at the third sentence, you're giving
9 another example of these conservative substitutions
10 involving positively charged and negatively charged
11 amino acids.

12 Do you see that?

13 MR. DEROO: Object to the form.
14 Mischaracterizes the declaration.

15 A I see the sentence, "This guidance comports
16 with the skilled artisan's understanding that
17 positively charged amino acids, i.e., K and R, glycine
18 and arginine and negatively charged amino acids, i.e.,
19 D and E, which are aspartate and glutamate generally
20 should not be exchanged at positions with a degree of
21 conservation and sequence alignments of related
22 proteins."

23 Q So in other words, K and R should not be
24 substituted by something like E?

1 A It's not a preferred substitution.

2 Q Look at the chart at the end of that
3 paragraph, Paragraph 128.

4 A Uh-huh.

5 Q The K shows that a conservative
6 substitution can include E, right?

7 A E, yes. It says -- you know, so these are
8 somewhat context dependent. On the surface, it's
9 often true that as long as it's very -- we call it
10 hydrophilic, meaning it likes water, it can be okay,
11 but again, it's sort of the different -- the different
12 uses of the general tables that one can find and the
13 important mathematical analysis.

14 Q And the same is true for R. R shows that
15 you can substitute E in that table, right?

16 A Right. Right. I, as a person skilled in
17 the art, would not do that given a goal of taking a
18 functional protein and changing it to routine
19 function. It's not something I would immediately
20 expect to be -- it wouldn't be a preferred
21 substitution.

22 Q So then a person of skill in the art would
23 not look at this Table 1 for guidance in order to
24 change and create a variant that would preserve

1 functionality; is that right?

2 A There's some --

3 MR. DEROO: Objection. Mischaracterizes
4 the testimony.

5 A There's some useful guidance in Table 1. I
6 would use as my arbiter something more mathematical,
7 and then the conservation that was in Figure 2 of the
8 patent. So as an example, glutamate -- aspartate has
9 a relatively low diagonal element, and that's because
10 asparagine and glutamate are reasonably good changes.

11 And then glycine is not as terrible as one
12 might expect because of this issue of sometimes on the
13 surface it's okay. And so that's where, you know,
14 some of these acceptable substitutions come from, but,
15 you know, one can just look here.

16 Q So turn to Page 51 of your declaration.

17 A I'm there.

18 Q You say here, "when making enzyme variants,
19 a person skilled in the art in 2005 to 2006 would not
20 have randomly picked any of the 19 other possible
21 amino acids for a given residue as Dr. Silverstone
22 suggests, but would have instead relied on known
23 principles for generating enzyme variants," right?

24 A Right.

1 Q And so some of those principles are what we
2 were just discussing involving what kinds of
3 substitutions a POSA would or would not have made,
4 right?

5 MR. DEROO: Objection to form

6 A Also, importantly, that the Figure 2-type
7 analysis from the patent.

8 Q But I want to make sure I understood what
9 you were just saying. So would a POSA have followed
10 the kinds of conservative substitutions described in
11 Table 2 of the '055 patent or would they have followed
12 the matrixes we looked at in Exhibit 2083?

13 MR. DEROO: Objection to form.

14 A What is the POSA trying to do?

15 Q Preserve functional --

16 A So just generally different sequences that
17 preserve function.

18 Q Generate variants of AAD-12 that have the
19 ability to degrade both the phenoxy auxin herbicide or
20 pyridyloxy auxin herbicide?

21 A And you're asking whether they used this
22 Table 2?

23 Q Correct.

24 A Well, I think Table 2 provides useful

1 guidance classifying amino acids in terms of classes.
2 Many of the conservative substitutions are found
3 within -- you know, from one member of the same class
4 to a different member, but I think a person of skill
5 in the art would have relied on Table 2 and augmented
6 that with the matrixes which were available.

7 Q And does augment mean further narrow the
8 range of options presented in Table 2?

9 MR. DEROO: Objection to form.

10 A I don't think further narrow is the way to
11 look at it. It's -- you know, it's kind of a strange
12 exercise. A person of skill in the art can take a
13 functional protein and one can make a very large
14 number of variants very easily with the guidance
15 either of Table 2 or of the matrixes, but clearly,
16 with both one could do it even more trivially, and so
17 I think it's not something that people generally do.

18 You know, if you have a functional protein,
19 you have a functional protein, but Table 2 and the
20 literature, as I say, both teach the same thing, you
21 know, just slightly different risk tolerances, if you
22 will.

23 Q And which is -- which is -- which has the
24 slightly higher risk tolerance and which has the

1 slightly lower risk tolerance?

2 MR. DEROO: Objection to form.

3 A Well, I think -- I don't understand what
4 you're asking. I mean, I feel like I was instructed
5 that I'm supposed to think as a person skilled in the
6 art, right, so I see this table and I acknowledge that
7 it's useful and I know of the matrixes, so why would I
8 limit myself to one or the other?

9 Q Well, we had identified some instances
10 where they don't agree, right?

11 A Right.

12 Q So what I'm asking is how would a POSA
13 choose between the two when there's disagreement?

14 MR. DEROO: Objection to form.

15 A I think I would want the exercise to be
16 better defined.

17 Q Okay. Suppose a POSA is trying to make
18 variants of AAD-12 that are covered by Claim 1, would
19 they follow Dayhoff's matrixes in Exhibit 2083 or
20 would they follow Table 2 in the patent when there's a
21 contradiction?

22 MR. DEROO: Objection to form. I think we
23 have established that's an incomplete
24 hypothetical, but you can answer.

1 A Because it's a relatively easy exercise, we
2 can try both, and probably both work.

3 Q Would one give a broader number of possible
4 variants than the other?

5 MR. DEROO: Objection to form.

6 A I think it would just be a question of, you
7 know, a few more experiments one way or the other. I
8 like the mathematical analysis of the matrixes, but
9 this table is correct and known to the art, so.

10 Q But you didn't calculate the number of
11 variants that would be possible if you, for example,
12 followed the matrixes in Exhibit 2083 and used that to
13 restrict the number of substitutions in AAD-12, did
14 you?

15 A No.

16 MR. DEROO: Objection to form.

17 A I frankly don't see the utility of that
18 calculation. I mean, I know that Dr. Silverstone
19 presented that, but it was just an exercise in
20 statistics, and, you know, the fact is -- well, at
21 least as it's been explained to me, one doesn't have
22 to make every single one.

23 As long as there's a function correlated to
24 a structure, that's enough, and there's a recipe

1 essentially here, along with knowledge in the art, to
2 make huge numbers of these things, so I did not
3 calculate that.

4 MR. DEROO: We're coming up on an hour --

5 MR. RUTT: We can take a break now.

6 (Recess taken.)

7 BY MR. RUTT:

8 Q Welcome back, Dr. Bollinger. During your
9 break, did you discuss the substance of your testimony
10 with your counsel?

11 A No.

12 Q So let's go to Paragraph 126.

13 A Of my declaration?

14 Q Of your declaration.

15 A Okay.

16 Q So you end that paragraph by indicating
17 that Figure 2 would provide guidance to skilled
18 artisans.

19 Do you see that?

20 A Yes.

21 Q What kind of guidance would it provide?

22 MR. DEROO: Object to the form.

23 You can answer.

24 A Well, from it, one easily identifies the --

1 specifically the specified motif residues. You also
2 can easily count the spacers, how long they are. One
3 can see positions that are invariant, including those
4 that are not among the five specified motif residues,
5 and those one would be reluctant to change.

6 And then one find a set of amino acids
7 marked by red, orange or brown, as your eyes see it,
8 in Paragraph 126 of amino acids that are one --
9 sequence positions that have one, two or maybe three
10 different amino acids that would be good candidates to
11 substitute if the substitution is conservative
12 according to the statistical analyses and found in one
13 of the other examples, that's a good substitution.
14 And then a bunch of positions that are completely
15 variable, some of which have a different amino acid in
16 each one of the five proteins, and those are likely
17 the very tolerant substitutions without loss of
18 function.

19 Q Okay. So what I want to understand is
20 there's a POSA who is trying to make variants that
21 fall within the scope of Claim 1.

22 How would they use your annotations in
23 Paragraph 126 and your annotations in Paragraph 125 to
24 guide them?

1 MR. DEROO: Object to form.

2 A Well, I could make a variant, looking at
3 Figure 2, AAD-12, TfdA and AAD-2 have valine at
4 Position -- well, along the line there at Position 33,
5 and then AAD-1 and alanine have isoleucine there, and
6 so I could make a valine to isoleucine at that
7 position variant of AAD-12, and that would be very
8 likely to be functional.

9 Q Why do you say it would be very likely to
10 be functional?

11 A Because it is a conservative substitution
12 the patent tells you that valine and isoleucine are in
13 the same class in Table 2. The Dayhoff matrix tells
14 you that -- hold on.

15 I'm on evolutionary distance here. At an
16 evolution distance of one pam, valine to isoleucine
17 has an off diagonal element of 33, which is the
18 highest for valine, and one sees it in other sequences
19 in the alignment, so that suggests that's a tolerated
20 substitution even though that's a -- I'm picking one
21 that's what we call somewhat conserved, right. It's
22 only two choices, but I can change it to the other
23 choice. It's an extremely high likelihood that's
24 going to be functional.

1 Q And did you pick an amino acid that has
2 shading because those are the best candidates for --

3 A No. In fact, those are the second best
4 candidates.

5 Q What are the best candidates?

6 A The best candidates are the ones where,
7 let's say -- well, where there are five different
8 choices, and those vary across classes in Table 2 of
9 the patent, that's a particularly good residue
10 substitute.

11 Q In order to preserve functionality?

12 A Right, not to lose function.

13 Q Why is that?

14 A Because nature and doing years of doing
15 this kind of science instruct that protein structure
16 and function is relatively robust to changes,
17 individual amino acid changes.

18 Q So take a hypothetical where a POSA focuses
19 almost exclusively on changing amino acids here that
20 are not shaded. Would more than half of them have the
21 claimed dual functionality of degrading both classes
22 of herbicides?

23 MR. DEROO: Object to form.

24 A There are other important elements of

1 guidance in the art. If chosen well, yeah, I would
2 say expect more than half.

3 Q Seventy-five percent?

4 A It's speculation, but I certainly would
5 expect that if they're chosen well.

6 Q So I mean, let's be a little bit more
7 precise about what you mean by "chosen well." Let's
8 say you only change one of the somewhat -- that you
9 have identified here in somewhat conserved and you
10 change, say, 20 of the amino acids that have no
11 shading, would that be what you would call, you know,
12 well chosen to --

13 MR. DEROO: Object to the form.

14 Q -- preserve functionality?

15 MR. DEROO: Object to form.

16 A There are other consideration that are well
17 known and were well known to people skilled in the art
18 at that time, so one can look at this alignment and
19 alignment that had been published -- I think it's
20 Elkins -- and find the secondary elements common to
21 the architecture of these proteins and, for example,
22 not put proline in a alpha helix.

23 If it shows up as a position that's
24 tolerant of substitution in the alignment, one doesn't

1 put proline there if it's in an alpha helix, so there
2 are other elements. Proline is a helix break.

3 Q Is proline -- what makes proline the helix
4 breaker?

5 A It's a unique sidechain structure where
6 it's tied back around. Glycine is also not good for
7 this because it's a -- it essentially doesn't have a
8 sidechain. It's got two hydrogens.

9 Q Okay.

10 A One is conformationally inflexible and one
11 is conformationally too flexible, and not to be found
12 in another set of statistical correlations.

13 Q I didn't see that guidance though in your
14 declaration. Was it?

15 A Again, I don't have a photographic memory
16 of it. I can read through it. I would say I can't
17 point to it in my declaration as we sit here, but do
18 you want me to look through the whole thing?

19 Q Take a look through the parts you think it
20 might be located at.

21 A Well, okay. It's maybe not as explicit as
22 I could have made it, but on Page 29, Paragraph 49,
23 "Sequence alignments can thus provide guidance as to
24 regions of the enzyme that are likely to tolerate

1 substitutions without loss of function and other
2 regions in which any substitution or particular
3 classes of substitutions would likely disrupt the
4 enzyme's structure and cause loss of activity," and so
5 I'm citing Elkins there, which has the secondary
6 structural elements aligned.

7 I think this is just such a -- it's common
8 knowledge to a person skilled in the art. I probably
9 didn't map it out well, so I would argue it's in there
10 implicitly, but maybe not as explicitly as I would
11 like.

12 Q So just taking the example of Elkins
13 Figure 5, which is what I think you're referring to,
14 are you saying that when a POSA tasked with making
15 AAD-12 variants that preserve the claimed dual
16 functionality -- would they make changes at the
17 secondary structures or would they make changes
18 outside of the secondary structures?

19 MR. DEROO: Objection to form.

20 A I don't -- I would not foreclose changes
21 within the secondary structures. I would be guided by
22 the sequence alignments for those, but I would not
23 make certain classes of changes within secondary
24 structures.

1 Q what would those classes be?

2 A As I just said, I would not stick a glycine
3 or proline in an alpha helix, and I wouldn't put
4 tryptophan anywhere where it isn't because of that
5 matrix analysis, so those are things that are well
6 known to a person skilled in the art that, you know,
7 maybe might have been a very long declaration to try
8 to write everything that I know.

9 Q Are there any other ones that you can think
10 of that you wouldn't do?

11 MR. DEROO: Object to form. Foundation.

12 A I probably could have, but not off the top
13 of my head.

14 Q This is your chance to explain what other
15 institution they would or would not --

16 A I think --

17 Q -- make.
18 Do you have any?

19 A I think the declaration illustrates well
20 how the patent provides the guidance to do that. It's
21 Figure 2. It's 85 percent identity, and it's the --
22 not adding or deleting residues between the specified
23 motif residues that can't be changed, so, you know,
24 other than that, I mean, why don't -- you can ask a

1 question about a change or position, and I can answer
2 it.

3 Q I don't know. I'm not the expert on this,
4 and I'm trying to figure out what's not in your
5 declaration that you're saying that a POSA would know,
6 so you have identified two principals, the glycine and
7 proline that you wouldn't do at an alpha helix.

8 A They're not two principles. The principles
9 are mapped in my declaration.

10 Q Okay. Well, proline and glycine, that
11 example wasn't, right?

12 MR. DEROO: Objection. Mischaracterizes
13 the testimony.

14 A I think --

15 MR. DEROO: Asked and answered about three
16 times at this point.

17 A Not as explicit as I might have wanted it
18 to be, but referring to that figure with the secondary
19 structure, it's well known to people skilled in the
20 art. It's in textbooks, so.

21 Q So what's another example that a POSA would
22 have followed?

23 MR. DEROO: Objection. Asked and answered.
24 Form of the question.

1 A A POSA usually has objectives. I'm not
2 understanding what your objectives are here, so maybe
3 formulate a more precise question.

4 Q Sure. The objective is to take an AAD-12,
5 modify it --

6 A Right.

7 Q -- so it's within the scope of the claims
8 and --

9 A Right.

10 Q -- preserve its -- the dual functionality
11 of the claims.

12 A I thought I answered that.

13 Q well, you're saying there's more principles
14 you follow. I'm trying to figure out what they are.
15 You have identified --

16 A I gave you an example.
17 Do you want another example?

18 Q Yeah.

19 A Okay. So at position 58 of the number
20 line, there's no shading. It has alanine, serine,
21 alanine, glutamine and glutamine. That position is
22 tolerant to substitution, and I could surely put
23 serine in place of alanine in there and preserve
24 function in AAD-12.

1 Q You have selected two examples from closer
2 to the end -- the terminal end of the --

3 A That's just where I started reading. You
4 want me to go closer to --

5 Q Well, one of my questions is: Does it
6 matter where in the sequence you make these changes?
7 For example, does it matter if matter if it's inside
8 one of the spacers of the active site motif or not?

9 A I'm very confident I can select positions
10 either inside or outside and formulate substitutions I
11 think that will preserve function. So I'm not going
12 to say it doesn't matter, but the likelihood is
13 extremely high that I can do it anywhere where it's
14 not a strictly conserved residue and we know we're not
15 changing motif residues.

16 So I think there are 28, 29. I may have
17 missed a few, but there's something like 60 residues
18 strictly conserved or somewhat conserved, and then by
19 difference, there's a large number that aren't
20 conserved.

21 Q So in looking at that Figure 2, would
22 position 17 be a good one to change to Q in AAD-12?

23 MR. DEROO: Objection to form.

24 A I suspect that it would be. I might steer

1 clear of that one in my first design just because it's
2 right next door to the initiator L-theonine, so
3 there's a bunch of things that happen when a protein
4 gets translated. In fact, one of the sequences in the
5 patent has alanine in the position, so.

6 Q So that would be a good example of one that
7 would change or not?

8 A Well, that's a given.

9 Q And that would preserve functionality?

10 A Yes.

11 Q What about position 35, would that be a
12 good one to change to preserve functionality in
13 AAD-12?

14 MR. DEROO: Objection to form.

15 A It's not my favorite.

16 Q Why not?

17 A There's a glycine in four out of five
18 sequences, and glycine is special with a greater
19 confirmation flexibility.

20 Q How about Position 47? AAD-12 has a F.
21 would that be a good candidate to change?

22 MR. DEROO: Objection to form.

23 A It's intermediate.

24 Q What does intermediate mean?

1 A It means that I see there some differences
2 in the type of amino acid that gives me pause, F being
3 large -- relatively large and bulky. Tryptophan being
4 large and bulky. It's not a terrible choice, but not
5 the best.

6 Q Are there regions in Figure 2 that you
7 would stay away from, that you would not make changes
8 to other than the five active site residues?

9 MR. DEROO: Objection. I thought this was
10 asked and answered.

11 A Well, so there are five that we won't
12 change because they're known to be, as we have
13 discussed, part of the motif, and there are
14 approximately 28, unless we have missed one. I think
15 it's 28 that are invariant across all five sequences.
16 I would not make those my -- I would not substitute
17 there.

18 Q And those are identified by the green
19 arrows --

20 A Right.

21 Q -- in Paragraph 125?

22 A Right. And one can also see clustering of
23 the bars that suggests regions of particularly high
24 conservation. I would be more selective with what

1 substitutions to make within that.

2 Just because you're going to ask, in this
3 highly conserved region of RAYDAL, there is a
4 aspartate, and so it probably wouldn't matter. You
5 could change it to the other one, but beyond that, I
6 would be cautious.

7 Q What do the asterisks mean in this figure,
8 if you know?

9 A Could we look at it in the original
10 version?

11 Q Sure.

12 A I think I know, but I want to be sure.
13 Would you remind me where it is?

14 Q Yes. Figure 2 is --

15 A I know where Figure 2 is.

16 Q It's at the front.

17 A But then we need the brief description of
18 the figures.

19 Q I believe it is on Column 5.

20 A It doesn't say. I believe -- so I don't
21 know. That's the short answer.

22 Q Do you have any ideas?

23 A I do.

24 MR. DEROO: Object to the form. Calling

1 for speculation.

2 A I think it is indicating what are
3 considered -- yeah. Actually, I don't know. I'm
4 looking at this, and I really don't know what the
5 asterisks mean, so I don't want to speculate.

6 Q Are the first five positions of this chart
7 omitted?

8 MR. DEROO: Object to form.

9 Go ahead.

10 A I'm not sure I understand.

11 Q So it looks to me like the numbering starts
12 at six.

13 Am I misreading that in Figure 2?

14 A I see the same thing you do. It does seem
15 to start at six.

16 Q So staying with our hypothetical of trying
17 to make variants that have the claimed dual
18 functionality and are within the scope of the claim,
19 is it fair to say you would focus on changing the red
20 arrowed amino acids in Paragraph 126?

21 MR. DEROO: Object to form.

22 A No, I think that's not correct. The red
23 ones are somewhat conserved, and what's useful about
24 them is they typically have one, two or three

1 different choices, and so those would suggest
2 favorable substitutions that would not abolish
3 function, but the ones that are neither highlighted
4 green -- by the green arrows, nor by the
5 orange/brown/red arrows -- that's one color, but it
6 has been called three different things -- are residues
7 that are not conserved.

8 And so those would be the richest source of
9 acceptable substitutions and also the majority.

10 Because these sequences are of modest identity to
11 start with, which is a good thing to do, there are
12 many more that are not conserved, so there's
13 opportunities to change many more residues and with
14 multiple things suggested by the alignment.

15 Q There's something like -- what -- 230 or
16 240 sequence that aren't shaded?

17 A I haven't done the math, but I think --
18 adding one or two that we missed in the orange, I
19 think it's about 30 of each, so it's ability 6,293, so
20 about 230, give or take.

21 Q Okay. So those 230 amino acids would be
22 generally good candidates for making substitutions if
23 you're trying to create AAD-12 variants within the
24 scope of the claims that preserve the dual

1 functionality.

2 Is that fair?

3 MR. DEROO: Objection to form.

4 A With that goal, I would still scan residue
5 by residue across the AAD, and there may be some there
6 that are not at all conserved that I would shy away
7 from, but by enlarge, those would all be good
8 candidates for substitution.

9 Q So can you turn to Paragraph 54 in your
10 declaration? In Paragraph 54, you mention something
11 called S-I-F-T.

12 Do you see that?

13 A Yes.

14 Q What is SIFT?

15 A So it was a program that was made available
16 by a server. The acronym means Sorting Intolerant
17 From Tolerant substitutions, and it was designed to
18 predict whether an amino acid substitution would
19 affect the protein function by looking into position
20 and the type of amino acid change, so it incorporated
21 information from this and other information and would
22 offer a prediction.

23 Q And since the court reporter couldn't write
24 down what you were pointing to, you're pointing to

1 Exhibit 2083 as the --

2 A Sorry. Yeah, the Dayhoff matrix in the
3 Exhibit 2083.

4 Q Okay. So SIFT incorporated those kind of
5 matrixes --

6 A Right.

7 Q -- into its prediction --

8 A Right.

9 Q -- algorithm?

10 A Right.

11 Q And would SIFT be one way that a POSA could
12 have focused more narrowly on making the variants that
13 preserve function than just randomly changing every
14 amino acid by the 19 possible substitutions?

15 A It would have been one screen to apply.
16 You know, as I said, I would go through and residue by
17 residue decide the best candidates, but then one could
18 have at that time tested this algorithm to see what
19 prediction developed and perhaps thrown out some that
20 were predicted to be deleterious.

21 Q You cite Exhibit 2044 in that paragraph
22 when you describe SIFT.

23 Do you see that?

24 A Yeah.

1 Q So I'll show you Exhibit 2044.
2 Does this document look familiar?

3 A Yes.

4 Q Are you able to read it?

5 A I think so, yes.

6 Q I have a clearer copy if you would like.

7 A No. I think we're good.

8 Q So beginning at the bottom of Page 3812,
9 the first page, you see the section entitled "SIFT
10 Website?"

11 A Yes.

12 Q So have you ever seen used the SIFT
13 website?

14 A I have not, and it may not still be
15 available, but it was at that time.

16 Q So looking in the second paragraph of the
17 "SIFT website" section, it's the paragraph that begins
18 "For minimal involvement."

19 Do you see that?

20 A Yes.

21 Q So it says, "For minimal involvement, users
22 can simply submit their protein sequences and amino
23 acid substitutions. In its fully automated mode, SIFT
24 will search for protein sequences homologous to the

1 query protein and based on those sequences will
2 calculate probabilities for each amino acid change."

3 Do you see that?

4 A I do.

5 Q So if I'm understanding this, the way SIFT
6 works is that it tries to create an alignment, and
7 then it uses that alignment to calculate probabilities
8 for which amino acids are likely to be substituted.

9 Is that how you understand this?

10 MR. DEROO: Object to form.

11 A Well, not having used it in that fully
12 automated form or any other form, for that matter, but
13 I think this one is the one where there's the greatest
14 possibility for variation and what they did compared
15 to what I understand they did, but yes, it looks to me
16 like it will in its fully automated mode build
17 essentially what we've been referring to as Figure 2
18 and provide guidance in the same way that I was
19 walking through.

20 Q So in the next paragraph, it states,
21 "Although, SIFT can choose sequences automatically,
22 better prediction results may be obtained when all of
23 the sequences that are provided are orthologous to the
24 query protein."

1 Do you see that?

2 A Yes.

3 Q what does orthologous mean?

4 A It implies that the sequences that are
5 provided -- so here we're talking about protein
6 sequences -- are proteins that have the same function
7 in different organisms. That's what an ortholog is.

8 Q Are the five sequences in Figure 2 that we
9 have been looking at orthologous?

10 A Well, so not according to the strictest
11 definition of what orthologs are because we have
12 established that the five we're looking at -- I just
13 want to make sure I --

14 I'm going to have to be reminded again
15 which page? I'm sorry.

16 Q That's okay. I think it's the third page
17 of the patent right in front.

18 A Yeah. So TauD is not an ortholog. If you
19 want to debate whether the other four are, I think one
20 could -- in a just slightly more generous definition,
21 those four could be considered orthologs.

22 Q Okay. what I'm trying to figure out is
23 what a POSA in 2005 looking at SIFT would have done to
24 get the best results, and I'm wondering would they

1 have used all or some of the sequences shown in
2 Figure 2?

3 A Yeah. For sure, a POSA would have used the
4 first four, and I think it has been established since
5 then that these alignments of functionally related but
6 not strictly orthologous proteins helps in this, so
7 inclusion of TauD is not a bad choice.

8 Q Do you have a sense of how much -- well,
9 strike that.

10 Do you recall that Dr. Silverstone
11 calculated a number that was something like ten to the
12 106th power of possible variants?

13 A So I think I quoted that in my declaration.
14 Can I refer to that just to make sure I get it right?

15 Q Sure.

16 A Or we can look at Dr. Silverstone's
17 declaration.

18 Q You have it at -- Paragraph 140 is one
19 place, about the middle of the paragraph.

20 A Yeah.

21 Q So you recall that calculation, and you
22 disagree with that approach, right?

23 A I don't take issue with the mathematics,
24 but I don't see it as relevant to this case.

1 Q Because you're saying that a skilled
2 artisan would actually use these principles to narrow
3 the set of variants they would make.

4 Is that fair?

5 A I think -- it's based on my understanding
6 of the principles of what is needed. I mean, I'm not
7 a lawyer, so this has been explained to me, but in
8 this art, in my field, it would never be possible to
9 get every single possibility, and no one ever thinks
10 about doing so.

11 And so the calculations may be right, and
12 that number is astronomical, but it's not relevant
13 because given a functional sequence, a person of skill
14 in the art can make variants in huge numbers,
15 essentially, any reasonable number that one wants to
16 and get -- and maintain function. It's not a
17 difficult exercise.

18 So I thought -- or I have been told that
19 what is needed is, you know, there's a function to
20 find of the grade 2 classes of herbicides, and there's
21 a structure and a recipe for how to go from that
22 structure to get other members of the set that's
23 claimed, and that to me is what is more relevant.
24 It's not a theoretical number of, you know,

1 possibilities.

2 Q And so is it fair to say a program like the
3 SIFT website would be an example of a tool a POSA
4 could have used to focus on a much smaller subset of
5 the number that Dr. Silverstone identified?

6 A SIFT would have been one tool, but Figure 2
7 is a good tool, and, you know, I could also create
8 Figure 2 so -- but Figure 2 is in the patent, and I
9 look at that and get a ton of information. So SIFT
10 would be one way to, you know, maybe make choices just
11 a bit more intelligently, but I don't -- I don't think
12 it was necessary.

13 Q Do you have any sense of how much SIFT
14 would have reduced that number that Dr. Silverstone
15 calculated?

16 A I think back to the article that's
17 describing different -- different ways to apply it --
18 and I may not be on the right thing here. I think I'm
19 on the wrong thing. So one can provide orthologs.
20 One can have the program find those related sequences,
21 and I can ask about individual substitutions.

22 You know, it could exclude some number. I
23 don't know what number. I have not used the program.
24 I don't think it's available now, but it would be

1 additional information, and as you know, the people
2 doing directed evolution have been doing now since the
3 time this was filed in 2005/2006 incorporating
4 intelligent principles of selection.

5 Q So a POSA could have taken SIFT, gotten the
6 probabilities, set some kind of a filter --

7 A Right.

8 Q -- and picked a very narrow subset of what
9 Dr. Silverstone calculated.

10 Is that fair to say?

11 MR. DEROO: Object to the form.

12 A That would be one tool to apply. One could
13 design a whole bunch of possible substitutions based
14 on the principles I have outline. One could then
15 apply the screen and say if -- you know, if they're
16 predicted to be very deleterious, which I doubt
17 they're suggest that they're all going to work, but if
18 in the possibility that they were predicted to be
19 poor, one could discard those. I would have to look
20 at why.

21 Q Was this SIFT website expensive to use? Do
22 you know if you had to be a member?

23 A I don't know. I think it was free. My
24 understanding is it was free.

1 MR. RUTT: Let's take a break.

2 (Recess taken.)

3 BY MR. RUTT:

4 Q welcome back from your break,
5 Dr. Bollinger. During your break, did you discuss the
6 substance of your testimony with your counsel?

7 A No.

8 Q Turn to Paragraph 154 of your declaration.

9 A Okay.

10 Q So take a minute just to silently re-read
11 that for yourself, so you're familiar with it.

12 A Okay.

13 Q So the last sentence you say, "A skilled
14 artisan would have understood that the conserved
15 residues and fixed spacing of the AAD-12 motif
16 represent the active site and correlate to the claimed
17 dual activity."

18 Do you see that?

19 A I do.

20 Q I would like to understand what you mean by
21 correlate. What did you mean by correlate?

22 A So if one looks at the sequence alignment
23 in Figure 2 of the patent -- is that what we're
24 referring to here -- but also in my declaration, that

1 table. I need to find it.

2 I'm going to have this in front of me
3 because the numbers are written in red as opposed to
4 having a count. Okay. So I'm on -- I'm looking at
5 Paragraph 112 from the declaration and Figure 2 from
6 the patent simultaneously.

7 And so what I meant by that is that solely
8 AAD-12 has the exact motif specified by the characters
9 in the colored parts and the -- and within that set,
10 and only it has this dual activity toward the two
11 herbicides.

12 Q So do you think if you removed one of the
13 five motif residues, it would still have dual
14 activity?

15 A Removed it how?

16 Q I mean, not removed it. How about, say,
17 substitute it with something else?

18 A What is "something else?"

19 Q Any of them?

20 A Most would fail, but I could come up with
21 specific examples that might retain some activity.

22 Q And then looking at it, correlate it from
23 the other direction, would you expect most of the
24 variants that have the active site motif to have the

1 claimed functionality?

2 MR. DEROO: Object to form. Incomplete
3 hypothetical.

4 Q Strike that.

5 would you expect most of the variants that
6 are covered by Claim 1 to have the claimed dual
7 functionality?

8 MR. DEROO: Same objection.

9 A Two things, so Claim 1 deals with AAD-12.

10 Q Correct.

11 A And you're asking me whether most of the
12 variants that you said are covered by Claim 1 --

13 Q Yeah, and let's let me change it actually
14 and be more precise.

15 A Okay.

16 Q Most of the variants that have the
17 85 percent sequence identity --

18 A Yeah.

19 Q -- and that have the active site motif,
20 would they also have the claimed dual functionality?

21 A I'm answering that question because the
22 first question is inferred by Claim 1 as the
23 functional part of --

24 Q Right. So it's 100 percent, correct, by

1 definition?

2 A Right.

3 Q So changing it -- maybe I'll restate it, so
4 the record is clear.

5 A Okay.

6 Q So would a POSA expect that most of the
7 AAD-12 variants that have the claimed 85 percent
8 sequence identity, that have the claimed active site
9 motif, including the claimed spacing, also have the
10 claimed dual functionality?

11 MR. DEROO: Objection to form. The same
12 objections.

13 A Yes. As Dr. Silverstone calculated,
14 there's a lot of possible choices, a lot of
15 possibilities, and I wouldn't want to say, but I could
16 definitely look at a case-by-case basis and tell you
17 my expectation.

18 One thing that's important to note is I'm
19 quite certain I could kill this enzyme and it would
20 probably only take one substitution and it would still
21 have 85 percent identity and have that motif, and
22 I'm -- you know, I have to do the experiment to be
23 100 percent sure, but I'm, you know, as certain as is
24 possible to be that I could kill that enzyme.

1 Q with one substitution?

2 A with one substitution?

3 Q what would that substitution be?

4 A Put tryptophan in place of the glycine, and
5 that would do it.

6 Q And do you have a particular glycine in
7 mind or any glycine?

8 A Well, there are several that are strictly
9 conserved in the alignment. So somewhere around
10 70-something is a conserved glycine, and somewhere
11 around 157 and 158 are a pair of conserved glycines,
12 and I suspect that putting a bulky residue there would
13 be disastrous.

14 So the point is that a person of skill in
15 the art knows how to kill it and knows how not to kill
16 it, so just as a general principle, it's hard to say
17 most. I haven't done any calculations to say whether
18 it's more or less than 50 percent, but the well-chosen
19 ones would be well over 50 percent, so most of the
20 well-chosen ones would be active.

21 Q what about if you changed the R at the last
22 motif site, if you change that to something else, do
23 you think it would kill it, by "kill it," I mean
24 destroy the dual functionality?

1 MR. DEROO: Object to the form.

2 A The R in the motif?

3 Q Yeah.

4 A well, it wouldn't be -- it wouldn't qualify
5 here.

6 Q Right. But would it still have the dual
7 functionality or not?

8 A what do you want to change it to?

9 Q Say, A?

10 A Probably not.

11 Q why is that?

12 A well --

13 MR. DEROO: Object to form. Incomplete
14 hypothetical.

15 A It has been seen in other cases from where
16 structures are known that that arginine anchors the
17 part of the alpha-kg and sets up the active site for
18 proper function. without a positively charged group
19 to interact with that negatively charged group, it
20 would likely have very poor binding of alpha-
21 ketoglutarate and, even if it bound, poor reaction
22 with oxygen, so it would be compromised at multiple
23 levels.

24 Q So the R binds to alpha-kg and the T also

1 binds to alpha-kg?

2 A Right. It's sort of a bi-party
3 interaction --

4 Q So the same question --

5 A -- in some. It's not -- it's not
6 absolutely known here, but that's the --

7 Q So the same question for the T, what if you
8 substituted the T in the motif with -- and that's the
9 only change you made with some other amino acid, would
10 it still have the dual functionality?

11 A Well, again, I want to point out that would
12 not be, so it's a hypothetical outside the scope of
13 the patent --

14 Q That's right.

15 A -- as the previous one was, and again, it
16 would depend on what one would change it to. With the
17 R in place, I suspect you could get some activity with
18 the residue other than T.

19 Q What if you changed T to F?

20 A To F, probably not.

21 Q Why not?

22 A Too bulky.

23 Q I don't know the amino acids, so what does
24 F have one that could --

1 A Site G. It's got CH₂ and then a ring of
2 six with three double bonds, so it's aromatic. It's
3 like benzene, yeah.

4 Q Would that be even more likely to destroy
5 the dual functionality than the last hypothetical
6 where we changed the R to an A?

7 MR. DEROO: Objection to form.

8 A I think they would both be likely, but I
9 think they most likely abolish functionality, you
10 know, the reaction. There's always a possibility to
11 find an enzyme, like, with that kind of substitution
12 that loops along, but it's going to be bad.

13 Q So a similar question on the correlation
14 idea: Do you think AAD variants that are at least --
15 strike that.

16 Do you think that a POSA who makes AAD
17 variants that have the active site motif, that have
18 the claim spacers are more likely to have the dual
19 functionality the higher the sequence identity or does
20 it not matter?

21 MR. DEROO: Objection to form. Incomplete
22 hypothetical.

23 A So you're talking about AAD-12 specifically
24 variants?

1 Q Right, yeah. Variants that -- setting
2 aside functionality, variants that are otherwise in
3 the scope of the claim, I'm wondering is it more
4 likely that a variant with 99 percent sequence
5 identity has dual functionality compared to
6 85 sequence identity?

7 MR. DEROO: The same objections.

8 A So 99 percent, I'm finding 3 residues that
9 are different, right. It's a little less than, and
10 what was the other?

11 Q Eighty-five percent, the extreme other end
12 of the claim spectrum.

13 A At 85 percent, I think I am finding 42. I
14 think it's 42. It's different. And you're saying
15 that those --

16 How am I finding those proteins?

17 Q I'm just wondering what you mean by
18 correlate and whether you would expect correlation to
19 mean that the higher sequence identity, all of the
20 other things equal, the higher likelihood it has dual
21 activity?

22 MR. DEROO: Objection to form.

23 A Well, I think if a POSA makes this, there's
24 a high likelihood that they both would, but yes, the

1 probability exponentially approaches unity one for one
2 substitution or two or three, and it might be just
3 slightly lower for multiple substitutions.

4 Q So basically, the greater the sequence
5 identity, the better chance it will have dual
6 functionality.

7 Is that fair to say?

8 A I think, you know, all other things being
9 equal, because every deviation from 100 percent
10 identity represents a change, and the nature of that
11 change and the position where it occurs is not
12 unimportant. It's, in fact, quite important as we
13 have been mapping out here.

14 And so there's a non -- zero chance that an
15 additional change has a deleterious effect, but if
16 well chosen, that change is minimized.

17 Q So I was asking about dual functionality.
18 what if we just focus on just 2, 4-D or phenoxy
19 herbicides --

20 A Right.

21 Q -- do you think that a greater sequence
22 identity would mean greater activity against 2, 4-D?

23 MR. DEROO: Objection to the form and
24 relevance.

1 A Well, as I said, I did not look at
2 correlations of quantitative activity as we went
3 through with those tables and calculated, and I recall
4 from that analysis that TfdA was the most active of
5 the enzymes to 2, 4-D.

6 So if we're starting from that baseline and
7 changing residues, there's a chance the activity would
8 go up, but it's more likely it would go down, and so
9 in principle, I don't think it would be a smooth
10 correlation, but I take your point.

11 Q Another correlation question, so you need
12 to help me on my understanding of how amino acids
13 work.

14 There's a peptide backbone to an amino acid
15 chain, right?

16 A Right.

17 Q And there's a theoretical length to that
18 backbone for each amino acid, right?

19 A So what you're saying is if you stretched
20 it out, yes, there are bond lengths and -- yeah.

21 Q Are those bond lengths for the backbone
22 identical for all 20 amino acids or is there
23 variation?

24 A There's slight variation, but they're

1 modest. The backbone is relatively minimal, so they
2 do vary but not a lot.

3 Q Okay. What I'm thinking is that third
4 spacer where it's about 120, 130 residues --

5 Do you recall we did that calculation?

6 A Well, in AAD-12, it was exactly 126.

7 Q So take AAD-12 --

8 A Yeah.

9 Q -- and then suppose you made variants where
10 all of the changes were in that third spacer, is it
11 possible that would change the stretched out distance
12 between each edge of the third spacer based on the
13 composition of the intervening amino acids?

14 MR. DEROO: Objection to form.

15 A I don't think it would change -- it
16 wouldn't change much.

17 Q That's what I'm trying to get at --

18 A Yeah.

19 Q -- is what's the magnitude? You said
20 it's --

21 A It's very small.

22 Q -- very small distances.

23 A Well, you know, in the -- the peptide bonds
24 are probably identical to within a few hundredths of

1 an angstrom, which is in the percents range.

2 Q One? Two? Three percent?

3 A Yeah. But the question isn't -- yeah, it
4 wouldn't change much.

5 Q I asked about a third spacer because it has
6 so many amino acids, over --

7 A Right.

8 Q -- 100.

9 A Right.

10 Q So if you changed, say, 20 or 30 amino
11 acids, in that range from whatever the smallest ones
12 are --

13 A Right.

14 Q -- to whatever the biggest ones are --

15 A Right.

16 Q -- could it, you know, change the distance
17 by a percent or two?

18 MR. DEROO: Objection to form.

19 Hypothetical.

20 A That's a difficult one to answer. The
21 dogma in the field of protein structural biology is
22 that the linear geometry, so the length of the bonds
23 that make up the backbone are essentially constant,
24 not subject to variation, so the variation -- the wide

1 variation in protein structure that one could see
2 across different families of proteins --

3 I'm not talking about in this family
4 because it's narrow, but it emerges from other things.
5 The twist in trajectory of the backbone is important
6 and then the packing of the site, so it's not the
7 length, per se. It's more how the spaghetti goes.

8 Q Well, I'm asking this because my
9 understanding was that the spacing matters to the
10 AAD-12 --

11 A Right.

12 Q -- functionality.
13 Is that fair?

14 A The number of amino acids, because that
15 sets -- this sequence determines the fold or structure
16 determines function, and that's the bedrock principle
17 in the study of enzymes. So the number of amino acids
18 determines the contours of the active site by setting
19 the trajectory -- the number and the identity as well.

20 The identity even though the recognized
21 motif is denoted X, there can't be just anything
22 there, but a person skilled in the art knows what to
23 keep and what can be changed, so yeah, it's -- it's
24 the number and the trajectory setting the contours of

1 the active site. That's why that spacer length is
2 important.

3 Q And so on the third spacer, Claim 1 -- all
4 the claims require there to be a spacer with 126 amino
5 acids, right?

6 A Right.

7 Q So what if you took out one amino acid,
8 would a POSA expect that variant with only 125 amino
9 acids in the third spacer to retain the dual
10 functionality?

11 A No.

12 Q Do it the other way around, add an amino
13 acid so that it's 127 positions.

14 Would a POSA expect the variant to have the
15 dual functionality?

16 A No.

17 Q So in other words, it's quite -- the dual
18 functionality of the AAD-12 class is quite sensitive
19 to even the change of one amino acid in the spacers,
20 correct?

21 MR. DEROO: Object to the form.

22 A Yeah, I believe that to be the case. Now,
23 you could embark on an engineering project to try to
24 adjust the spacer length and control -- and maintain

1 the activity. Again, that's not a project I would
2 assign to a student of mine. That's complicated.

3 I'm not going to say it couldn't be done,
4 but I have yet to see any protein that doesn't conform
5 to that motif that has -- I don't think
6 Dr. Silverstone provided any example of protein that
7 violates or doesn't conform to that motif and has
8 activity, so as a person skilled in the art, I don't
9 think. I would expect not to find that activity in
10 such a protein.

11 Q Suppose you took out 40 amino acids from in
12 front of the first motif site, would that molecule be
13 expected to have the claimed functionality?

14 MR. DEROO: Objection to form.

15 A Yeah. I think you would need a more
16 refined hypothetical. Truncation proteins can be made
17 and they're sometimes functional, so if you chop 40
18 off the end terminus, you might be able to get a
19 protein that works.

20 Q What accounts for -- so I want to make sure
21 I understand this. If you took 1 amino acid out of 1
22 of the spacers, it wouldn't work, but if you took 40
23 out in front of the first spacer, it might still have
24 the claimed functionality; is that right?

1 A Yeah, that's my expectation.

2 Q What accounts for the --

3 A It's still more likely not to, but it's at
4 least possible.

5 Q Why is the dual functionality so sensitive
6 to changes in the spacers region but not sensitive to
7 changes in the first 107 amino acid sequences?

8 MR. DEROO: Objection to form.

9 A It has to do with the nature of proteins
10 adopting their tertiary structures and the fact that
11 core elements have a particular register, so a helix
12 has a certain turn -- yeah, a certain number of
13 residues per turn and inserting one or a few or taking
14 one out gets everything out of the register, so in
15 the --

16 It's characterized as cooperatives, so
17 there's a unfolded structure and elements begin to
18 form, and then they zip together in a way that's sort
19 of cooperative. And so disrupting a core element
20 would be usually disastrous, but peripheral elements
21 sometimes if they're not directing the folding
22 process, which they can sometimes, but they often
23 these things fold in modules and so that's why, you
24 know, the middle is bad, but you can often get rid of

1 cabbage on the ends.

2 Here, because the active site -- there is a
3 particular active site residue at the C terminal end,
4 I would be less inclined to truncate that site.

5 Q But there are secondary structures in front
6 of the first motif site, right?

7 A Yeah.

8 Q Like, there are beta strands and --

9 A Right. Right.

10 Q Do those beta strands have no involvement
11 in the active binding site or why is it that changes
12 in that region don't destroy the dual functionality?

13 MR. DEROO: Object to form.

14 A Well, I didn't say that. You asked about
15 the expectation of the POSA, and I'm not -- you know,
16 to explain that, I would like to have a more refined
17 hypothetical.

18 Q All right. Do you have Exhibit 1039, the
19 supplemental information to your paper?

20 A I do, and I'm also looking at Elkins.

21 Q So in Exhibit 1039, you have added
22 secondary structures in Figure 10 --

23 A Right.

24 Q -- to the -- among others, the AAD-12

1 sequence.

2 Do you see that?

3 A Yes.

4 Q And it looks like you have numbered
5 eight beta strands with the pink arrows.

6 Is that right?

7 A Yes.

8 Q And two of those eight beta strands are in
9 front of the first motif site residue, right?

10 A That is correct.

11 Q Do you know whether those two beta strands
12 are involved in the active binding site in the
13 alpha-kg enzymes?

14 A I didn't study --

15 MR. DEROO: Objection to form.

16 A I think we could dig through information
17 and find it, but I didn't study it, so I don't know
18 off the top of my head.

19 Q So I'll show you an exhibit marked as 2054
20 by your colleague, Hausinger.

21 Do you recognize this document?

22 A Yes.

23 Q So if you turn to Page 45, there is a
24 Figure 1 shown.

1 A I see it, yes.

2 Q Just read the caption and familiarize
3 yourself with the figure, and let me know when you're
4 ready.

5 A Okay.

6 Q So in Figure 1, you see there are
7 two images?

8 A Yes.

9 Q And on the left are the eight beta strands
10 that combine to form the core of all iron to alpha-kg
11 dioxygenases.

12 Do you see that?

13 A Yes.

14 Q Are those eight beta strands the same eight
15 beta strands you identified in your paper that we were
16 just looking at in Figure 10?

17 A I did not do this detailed comparison. I
18 didn't review this Exhibit 20534, so I can't -- I
19 can't say for sure.

20 Q Looking at the Hausinger Exhibit 2054, are
21 those eight beta strands important to the core of the
22 iron to alpha-kg dioxygenases?

23 MR. DEROO: Objection to the form and
24 foundation.

1 A What the figure legend says it's the
2 jellyroll fold -- that's one name. Cupid and beta
3 sandwich and others have been used -- found in all
4 iron alpha-ketoglutarate dependent dioxygenases, so
5 they're found in all. One would assume they're
6 somewhat important.

7 Q Do you have any reason to think that these
8 eight beta strands in Exhibit 2054 are different from
9 the eight beta strands you identified in Exhibit 1039?

10 MR. DEROO: Same objections.

11 A I just don't know. What I would want to do
12 is call up some structures and make sure. It seems
13 logical, but I can't attest to it.

14 Q How about Elkins Figure 5, take a look at
15 that.

16 A Okay. Yes.

17 Q Does that help you answer the question?

18 MR. DEROO: Objection to form and
19 foundation.

20 A Yeah, I think so. I don't think they
21 correlate, so beta 1 is not beta 1 here.

22 Q Because Elkins identified 16 or 17 beta
23 strands, right?

24 A Well, I see the last number in green is

1 beta 17, so yeah, it would seem unless they are doing
2 something weird with their -- I'm counting, and I see
3 17.

4 Q So going back to your figure in
5 Exhibit 1039, you don't know which, if any, of those
6 eight beta strands are relevant to the active binding
7 site of AAD-12; is that right?

8 MR. DEROO: Object to form.

9 A Can you ask the question again?

10 Q So you don't know -- you can't say whether
11 or not all eight of the beta strands identified in
12 Figure 10 of Exhibit 1039 are relevant to the active
13 binding site of AAD-12?

14 MR. DEROO: Object to form and relevance.

15 A Yeah. It's kind of a dicey question
16 because, you know, they have identified -- we have
17 identified eight core helixes. I strongly suspect
18 they're the same ones as in Hausinger, but they are
19 clearly different in terms of at least register
20 numbering from the Elkins.

21 Q Does this discussion change your opinion at
22 all about whether you could delete the residues
23 corresponding to the beta 2 and beta 2 in Figure 10
24 and still have dual activity for an AAD-12 variant?

1 MR. DEROO: Object to form and speculation.

2 A Sorry. One more time. I lost the thread
3 there.

4 Q Well, let me restart. We previously
5 discussed whether or not the removal of the first
6 two beta strands from an AAD-12 variant would destroy
7 the dual activity.

8 Does that ring a bell?

9 MR. DEROO: Object to form.

10 A No, I don't think so. You were asking me
11 about taking some number of amino acids off the end.

12 Q Right. So let's make -- Let's make the
13 hypothetical more specific then. Suppose you removed
14 the 13 amino acids or 15, however many it is that are
15 associated with beta 1 and beta 2, would you then
16 expect that AAD variant to have dual functionality?

17 A Well, beta 1 and beta 2 are well into the
18 protein, so we can't remove those without making it
19 eternal if we're removing that many amino acids,
20 right. The end terminus of AAD-12 is characterized in
21 Figure 10 as pre-A1 pre-B2, pre-B2 -- or pre-B1
22 pre-B2, pre-A2, pre-B3, pre-A3 and then beta 1, so
23 there's a lot of sequence that comes before beta 1.

24 Q So let's take that hypothetical then. If

1 you removed the 4 amino acids in beta 1 from AAD-12
2 and the 10 amino acids from the beta 2, would you
3 expect that AAD-12 variant to still have the claimed
4 dual functionality?

5 MR. DEROO: Object to form.

6 A Sorry. You said in that question beta 1
7 and beta 2.

8 Q That is correct.

9 A You're going to take amino acids from the
10 core beta strand out, just --

11 Q All of them.

12 A -- not have the beta of the core?

13 Q Correct, and shorten it by 14 amino acids.

14 A And reconnect the backbone?

15 Q That's right.

16 A Oh, boy. That's not something I thought
17 about. I sure don't think it would work, but I
18 haven't -- I haven't studied it.

19 Q That would be within the scope of Claim 1,
20 right?

21 MR. DEROO: Objection. Form. Foundation.
22 calls for legal conclusion.

23 A Well, I don't think it would be because if
24 I -- if it's not active, it definitely isn't, right.

1 Q Fair point. That would be within the
2 structural requirements of Claim 1, which are the
3 85 percent identity and the active site motif, right?

4 A I just want to make sure I have it, so
5 you're going to make a new protein and we're taking --
6 there's a red arrow labeled beta 1 that spans four
7 residues and another red arrow labeled beta 2 that
8 spans about ten residues and you're going to chop out
9 those two expanses, plus the residues between?

10 Q Sure. We can do that one. That's a few
11 more. That's an additional --

12 A Yeah. Or you just want to chop each one
13 out and reconnect the backbone missing those four and
14 those ten?

15 Q Let's do both.

16 A Okay.

17 Q Start with chopping out just the two red
18 arrows. Would it still have the claimed dual
19 functionality?

20 MR. DEROO: Object to form.

21 A I suspect, as a person skilled in the art,
22 that it's not something I would ever do, but if
23 someone forced me to do that, I would go into the
24 exercise expecting to have a dead protein.

1 Q And that would still meet the 85 percent
2 sequence identity, right?

3 MR. DEROO: Object to form.

4 A That's actually a slightly subtle actual
5 question. Well, sequence identity is established by
6 doing alignments, and so we take that sequence and we
7 align it, and the alignment program would find that
8 there's a -- you have introduced a gap there where we
9 had taken out residues and it would -- you know, with
10 only 14 plus 822, it would find it to be greater than
11 85 percent and still have that motif, but I'm saying
12 I'm not sure how it's relevant.

13 Q Well, it's an example of some variants that
14 you would not expect to have claimed functionality
15 even though they satisfied the structural
16 requirements, right?

17 MR. DEROO: Object to form.

18 A Right, but as I understand it, it's the
19 correlation of structure to function. Okay. And I
20 know that I can think as a person skilled in the art,
21 so I don't -- I guess I'm not sure what you're trying
22 to get at all.

23 Q I'm asking if -- it sounds like you're
24 saying you think there is a structure function

1 correlation for these two red strands now.

2 Is that right?

3 MR. DEROO: Objection to form.

4 A No. I'm saying in an experiment where you
5 have asked to delete out the core architecture.

6 That's not a distinguishing feature. That's a common
7 feature, so many enzymes in a given family, like, iron
8 alpha-kg dioxygenases, they share a common fold, if
9 you will, or core scaffold architecture, and that's
10 not what one correlates. That's the common thing.

11 The correlation is the special things,
12 right, and so your deleting out part of the common
13 thing is like saying if I take a car and chop off the
14 engine block, is it still a car?

15 Q What if you took out from an eight-cylinder
16 engine one of the cylinders, would it still work?

17 MR. DEROO: Objection to the form. Let the
18 record show --

19 A I don't know cars.

20 Q Going back to serious questions, what if
21 you only took out one of the amino acids of the four
22 amino acids in the beta 1 strand from AAD-12, would
23 you expect that molecule to still have the claimed
24 dual functionality?

1 MR. DEROO: Object to form.

2 A I would not.

3 Q So the removal of a single amino acid
4 within beta 1 would in your opinion be likely to
5 destroy the dual functionality?

6 A Absent some other sophisticated adaptation,
7 a more sophisticated plan, it would likely not work.

8 Q Did you identify this principle in your
9 declaration that you would not remove these amino
10 acids from these structures?

11 MR. DEROO: Object to form.

12 A Well, I talked about enzymes being linear
13 sequencing of amino acids and their folding. I did
14 not delve into what's known about protein folding. I
15 just didn't see that as central.

16 Q And so back to the beta strands, would your
17 answer be the same for beta strand 2 if one amino acid
18 was removed from beta strand two, would you expect it
19 to destroy the functionality?

20 A When you're saying "removed," you're, like,
21 making the protein one amino acid shorter --

22 Q That's right.

23 A -- by removing one from that region and
24 having nothing in its place?

1 Q That's right.

2 A I would not expect that to function.

3 Q What if you removed one amino acid from the
4 position immediately adjacent to the beta 2 strand,
5 then would you expect it to preserve the dual
6 functionality?

7 MR. DEROO: Object to form and foundation.

8 A In answering these hypotheticals, I'm
9 speaking to any kind of function because if it doesn't
10 fold, it's not going to function, and so I'm speaking
11 to the likelihood that that sort of change is going to
12 be tolerated in a protein that adopts the right
13 structure. And so if one does it right before the
14 core beta 2 --

15 Q That's right?

16 A -- it probably also would not.

17 Q How about two before the beta 2?

18 A Well, the issue is that beta 1 and beta 2
19 need to stay in some kind of register. There would be
20 a way to have a different type of linker between those
21 units to get it to fold and function. There would be
22 a way, but it wouldn't be simple to discover.

23 Q And you're talking about the importance of
24 preserving the distance between beta 1 and beta 2,

1 right?

2 A Preserving the possibility of the correct
3 folding trajectory is what I'm talking about.

4 Q So does the same principle hold true in the
5 region between beta 2 and beta 3?

6 MR. DEROO: Object to form. Foundation.

7 A Well, we see in different orthologs a lot
8 of variation, so I would think that -- the principles,
9 as I understand, a protein folding, there would be a
10 greater likelihood that something like that could
11 work.

12 Q And are you talking about the gaps that are
13 shown here between beta 2 and beta 3? Is that why you
14 think it's more likely to tolerate changes in that
15 region and still preserve the dual activity?

16 A Well, I'm saying only for orthologous in
17 the broader sense of enzymes, there are represented
18 three different spacer lengths there, and so it might
19 be possible. It's not nearly as easy as all of what
20 I'm just discussing in this case, which is a
21 functional protein, not killing it, right. You're
22 asking more sophisticated things, and it might be
23 possible.

24 Q Well, all of my questions were describing

1 variants that satisfied the 85 percent sequence
2 identity requirement and the active site motif
3 requirement, right?

4 A But widely violate known principles of
5 people skilled in the art, so I -- as I understand it,
6 I'm allowed to know the art, right, in thinking about
7 this correlation, so that's what my declaration is
8 based on.

9 Q And would your answers be the same if
10 instead of removing one amino acid between beta 1 and
11 beta 2, you added an amino acid?

12 MR. DEROO: Objection to form.

13 A Between beta 1 and beta 2?

14 Q Correct.

15 A Qualitatively, the same; quantitatively, a
16 little bit more couched in that. It might be possible
17 to included a -- probably not one, but a few amino
18 acids and still allow for folding.

19 Q Looking at the end of the sequence, you see
20 the beta 8 strand?

21 A Yes.

22 Q And that's beyond the active site -- the
23 last active site residue, right?

24 MR. DEROO: Objection to form to the extent

1 it mischaracterizes the document.

2 A Yeah, I don't think it's right. I don't
3 think your question is -- I think what you said is
4 wrong.

5 Q Okay. So are you saying it's because the R
6 that's shown at the beginning of the beta 8 is the
7 last active site residue?

8 A Yes.

9 Q So what if you removed one amino acid from
10 the -- I don't know how to say it -- far end of the
11 beta 8 strand that is closest the C terminus, would
12 you expect that to destroy the dual claimed
13 functionality?

14 MR. DEROO: Objection to form.

15 A Again, I'm speaking to function at all, and
16 I think if you took out that last residue -- and
17 again, are we removing it? Are we -- there's a chance
18 it would work.

19 Q What about the residue immediately adjacent
20 at G that is just beyond the beta 8 residue, if you
21 were --

22 A No.

23 Q -- to remove that residue from AAD-12,
24 would -- sorry. Strike that.

1 what about the residue A that's immediately
2 beyond the beta 8 strand, if that were removed, would
3 the AAD-12 still retain the claimed dual
4 functionality?

5 MR. DEROO: The same objection.

6 A It's -- you know, it's theoretically
7 possible. It's outside the core. It might still
8 function.

9 Q I give this as an example because you had
10 indicated earlier that changes towards the terminus
11 are more tolerated, right?

12 MR. DEROO: Objection to form.

13 A Well, when there's a core architecture, one
14 generally can't introduce changes that would
15 destabilize it or prevent it from forming in the first
16 place and have a functioning protein.

17 Q Right.

18 A So yeah, that's part of the reason why the
19 two ends tend to be more tolerant.

20 Q And so that's why I'm asking. This one is
21 maybe -- the A that we identified there is maybe 10 or
22 so positions from the C terminus in AAD-12, right?

23 A Yeah. Well, I mean, there's three As
24 toward the end, and I think you were pointing to the

1 one right before the G.

2 Q That's right.

3 A Yeah, so that is ten from the end.

4 Q So that's why I'm asking would that make a
5 difference, since we're only about 10 from the end, to
6 your opinion as to whether or not it would still have
7 the claimed dual functionality.

8 MR. DEROO: Objection to form. Incomplete
9 hypothetical.

10 A I'm answering whether I think it would fold
11 and be functional, and I think it's more likely than
12 something that was mucking with the core beta strands,
13 but it's not -- it's not a sure thing.

14 Q But it would be within -- it would
15 satisfy -- strike that.

16 An AAD-12 variant that removed the amino
17 acid from just beyond the beta strand would satisfy
18 the 85 percent sequence identity requirement of
19 Claim 1 and the active site motif requirement of
20 Claim 1, right?

21 MR. DEROO: Objection to the form to the
22 extent it calls for a legal conclusion.

23 You can answer.

24 A What I want to reiterate is there are lots

1 of things that fall within that that a person of skill
2 in the art doesn't do, and that's one of them, right,
3 so if I pretend I don't know anything, then maybe I
4 make that change and maybe I take your point, but I
5 just don't --

6 I don't see how the patent encourages me to
7 do that. The patent gives me guidance for things I
8 can do to this protein and retain function. That's
9 not one of the things that the patent instructs.

10 Q What if you added an extra amino acid to
11 the AAD-12 molecule at the 291st position, would that
12 have the claimed dual functionality?

13 A Adding one at the 291st position?

14 Q That's right.

15 A So I separate the L and V?

16 Q That is correct.

17 A And I put another amino acid in?

18 Q Correct.

19 MR. DEROO: Object to form. Incomplete
20 hypothetical.

21 A And you're asking does that have function
22 and does it retain the dual function?

23 Q That's right.

24 A It's -- I don't know. I don't know what I

1 would think for that. That would be an experiment,
2 but not one that I see any reason to do.

3 Q So it's the mirror image of what they did
4 on the other end of the AAD-12 sequence, right, when
5 they added the extra alanine at the second position?

6 A Right.

7 Q So why would it make a difference in
8 your opinion when you add the extra amino acid
9 two positions from the front of the chain or
10 two positions from the end of the chain?

11 A Well, it's just -- it doesn't necessarily
12 make a difference. It might work, but if I were going
13 to do that, I would verify its activity, as the
14 authors of the patent did, for the ones they report,
15 right, so I think it's less certain than what I'm
16 proposing to make variants keeping the number of amino
17 acids the same. I understand why they did. It was
18 for, you know, other technical issues, but they
19 verified that it was active, so that's -- I still
20 don't think I know where we're going.

21 Q Let's take a break.

22 A Let me just say one of the things in the
23 patent that the patent instructs is how to verify
24 activity, and when they needed to know if that one

1 was, they checked, and it was.

2 MR. RUTT: Let's take a break.

3 (Recess taken.)

4 BY MR. RUTT:

5 Q welcome back, Dr. Bollinger. During your
6 break, did you discuss the substance of your testimony
7 with your counsel?

8 A No.

9 Q I'm going to show you Exhibit 2035.
10 Do you recognize this document?

11 A Yes.

12 Q And I apologize to do this, but you cited
13 this document in Paragraph 56 of your declaration, so
14 why don't you just look at Paragraph 56 for a minute
15 to get the context for this?

16 A I recall this from before.

17 Q Yeah. And in your Principle No. 4, after
18 the first sentence, you cite Exhibit 2035. Do you see
19 that?

20 A Yes.

21 Q And you cite it in support of the sentence
22 that says, "Skilled artisans understood not to
23 introduce mutations that would change the enzyme's
24 overall surface charge or steric bulk."

1 Do you see that?

2 A I do.

3 Q And then in parenthesis --

4 A Let me say that's a little imprecise.

5 Q Okay.

6 A We're not -- we're trying not to change the
7 residue steric bulk or the enzyme's overall surface
8 charge. That's really referring to residues. I think
9 that may be -- I'm going to call it a typo that
10 slipped by.

11 Q Okay. So what should it say?

12 A Skilled artisans understood not to
13 introduce mutations that would change the enzyme's or
14 steric bulk, but it -- you know, it looks like one
15 that I half edited, and I characterize that as a
16 mistake.

17 Q Are there any residues in particular that
18 that the skilled artisan would not introduce mutations
19 to or is it any residues that you're talking about?

20 A Well, we went through the Dayhoff analysis
21 which gives some feel for which residues when you find
22 them are going to be less tolerant to substitution,
23 and a bulk changing substitution, for example, the
24 biggest is glycine to tryptophan. That goes from the

1 smallest possible sidechain to the biggest one, so
2 that's what is being referred to there.

3 Q And in the parenthetical that describes
4 Exhibit 2035, it says, "Suggesting restricting
5 mutation diversity where small amino acids can create
6 additional space in a binding pocket, whereas, large
7 amino acids can narrow the binding pocket."

8 Do you see that?

9 A Yes.

10 Q So were you referring to not changing the
11 amino acids in the binding pocket?

12 A It doesn't say that. It says restricting
13 mutation diversity, and that again goes with this
14 principle of not drastically changing the steric bulk
15 of the residue, especially, one in the binding pocket
16 according to this.

17 Q Okay. So turning back to Exhibit 2035, on
18 Page 184, there's a section titled, "1.2,
19 Considerations When Using Data-Driven Engineering."

20 Do you see that?

21 A Right.

22 Q And the first sentence there says that
23 "Targeted protein evolution first must begin with an
24 analysis of which portions of a protein are most

1 likely to impact the property of interest."

2 Do you agree with that statement?

3 MR. DEROO: Object to form.

4 A In general, yes. I mean, targeted protein
5 evolution implies we're changing a protein we have in
6 hand at some target, which is some novel or proved
7 property, and if you want to use the data that's
8 available, it's nice to know. It's helpful to know.
9 I don't know if I would go with "must," but it's
10 helpful to know which portions of a protein are most
11 likely to impact the property of interest.

12 Q And which portions of the AAD-12 sequence
13 are the ones that are most likely to impact the dual
14 functionality?

15 A Well, the motif is very likely --
16 100 percent likely because it contains the iron and
17 co-substrate interacting residues and then the spacers
18 that define the contour of the active site, so that's
19 the portion and -- yeah, that's the portion.

20 Q In Exhibit 2035, turn to Page 186 and look
21 at the right column. There's a section entitled
22 "Section 3: Further Restrictions to Limit Library
23 Size."

24 Do you see that?

1 A Yes.

2 Q And the second paragraph beings with the
3 phrase, "Restricting the diversity."

4 Do you see that?

5 A Yes.

6 Q Was this the sentence you had in mind when
7 you cited this exhibit in Paragraph 56 of your
8 declaration?

9 A That is asking sort of for an answer of my
10 thought process, which I don't recall, but I think so.

11 Q So do we -- do you know where the binding
12 pocket is in the AAD-12 motif -- or I'm sorry -- in
13 the AAD-12 sequence?

14 MR. DEROO: Objection to form.

15 A Where it is in the sequence?

16 Q Right. Do you know -- do you know, for
17 example, does the binding pocket -- is the binding
18 pocket formed by the five amino acids in the AAD-12
19 motif?

20 A Part of the active site pocket is formed by
21 these residues, yeah.

22 Q And other residues form other parts of the
23 binding pocket in the AAD-12 sequence?

24 A Well, you know, it's a big scaffold and

1 these enzymes bring together three substrates, so
2 there is going to be multiple residues involved in
3 those pockets.

4 Q Is there more than one pocket in AAD-12?

5 A There's an active site, but there are
6 contours in there, so I guess you could call them
7 subpockets.

8 Q So is there a subpocket for the phenoxy
9 auxin herbicide and another subpocket for the
10 pyridyloxy auxin herbicide and another subpocket for
11 the alpha-kg and another subpocket for the iron?

12 MR. DEROO: Objection. Form.

13 A Well, the iron sits between the three
14 specified motif residues. The alpha-kg interacts with
15 the iron and also those other matrixes. I would
16 presume that the peridoxy alkanoate and araloxy
17 alkanoate bind in a pocket that overlaps probably a
18 good bit mostly. Although, it's possible that they
19 contact different residues.

20 MR. RUTT: No further questions.

21 MR. DEROO: I'm going to have a few
22 questions. Why don't we take a short break?

23 (Recess taken.)

24 EXAMINATION

1 BY MR. DEROO:

2 Q Dr. Bollinger, do you remember earlier this
3 morning counsel asked you some questions about the
4 Chekan paper?

5 A Yes.

6 Q And that is Exhibit 1015. Do you have that
7 in front of you?

8 A Yes.

9 Q Would you please turn to Page 13300?

10 A Yes.

11 Q And then the right-hand column below
12 "Results and Discussions," there's a heading,
13 "Genome Context-based Identification of AAD Family
14 Members."

15 Do you see that?

16 A Yes.

17 Q And the first sentence begins, "We sought
18 to locate other candidate AADs."

19 Do you see that?

20 A Yes.

21 Q And during your cross-examination, I
22 believe you referred to the level of sequence identity
23 for the enzymes under consideration as being moderate
24 or low.

1 Do you recall that?

2 A Yes.

3 Q Within this section, a few lines down
4 there's a sentence beginning, "For example," and then
5 it mentions FtdA and AAD-1.

6 What level of sequence identities are
7 describe there?

8 A Thirty percent. TauD to FtdA is
9 30 percent, and what's described as an orthologous
10 AAD-1, similar substrate, the 28 percent sequence
11 identity to TfdA.

12 Q And would you or would you not consider
13 those identity levels as within the twilight zone of
14 sequence identity that you referred to in your
15 declaration?

16 A Yes. That is --

17 MR. RUTT: Objection. Scope.

18 A I think that's in the twilight zone,
19 meaning it's a relatively modest level where the
20 proteins might or might not be exact orthologs logs.

21 Q Okay. And the author is seeking to locate
22 other candidate AADs in the scope of this publication.
23 Did that have anything to do with making variants of
24 known AAD enzymes within 85 percent sequence identity?

1 MR. RUTT: Objection. Leading.

2 A Well, it's a different objective. In the
3 ladder objective, as you characterized it, there's a
4 working protein, a functional protein. It's known
5 what its activity is, and you're making changes for
6 the purposes of this case just not to screw up the
7 activity, so that's a completely different set of
8 considerations.

9 Q Were any AAD variants made and published as
10 part of this Chekan 2019 paper?

11 A Were any AAD -- which ones? Of any AAD?

12 Q Yeah. That was imprecise. Why don't we --
13 this section continues onto the next page.

14 A Right.

15 Q The bridging sentence says -- right above
16 the Figure 2, it says, "We found 59 putative AADs
17 encoded within genomic contexts," and it cites the
18 supplemental information appendix at Table S-1.

19 Do you see that?

20 A Yeah. It's at the very top. I'm going
21 into, "We found 59 putative AADs encoded within
22 genomic contexts that also include TfdB-like and TfdC-
23 like sequences." Yeah, so it's that genomic contexts
24 that suggests to us that these are actual AADs.

1 Q And would you please turn to Exhibit 1039,
2 which is the supplemental information?

3 A Yeah.

4 Q And would you confirm for me that on
5 Pages 17 and 18, that's the supplementary Table 1,
6 which is the list of the putative AADs?

7 A Yeah, I see that.

8 Q And can you tell me if these putative AADs
9 refer to sequences from various organisms or if they
10 are variants of a previously identified AAD enzyme,
11 like, AAD-1, AAD-2 or AAD-12?

12 MR. RUTT: Objection. Leading.

13 A They appear to be from different organisms.
14 Although, there's an uncultured bacterium and another
15 one that's delftia acidovorans, which I believe is
16 what AAD-12 comes from, so yeah, there are -- they
17 appear to be naturally occurring sequences found
18 within different organisms.

19 Q You also -- you can put both of those
20 aside.

21 Do you recall that counsel asked you some
22 questions today about the role of each of the five
23 amino acid residues in alpha-kG active site motifs?

24 A Yes.

1 Q And each alpha-kg enzyme, is the spacing of
2 the motif residues typically different or are they
3 typically the same?

4 A Well, they vary quite widely as one can
5 find in either the patent or my declaration. The
6 general motif sort of gives an idea of how much they
7 can vary, and so they do vary a lot.

8 Q Did counsel show you any enzyme sequences
9 today that have this specific AAD-12 motif but have a
10 different entomatic function?

11 A Not to my recollection.

12 Q And did counsel show you any enzyme
13 sequences today that have 85 percent sequence identity
14 to the AAD-12, but have a different entomatic
15 function?

16 A How does that question -- say it again. I
17 didn't understand --

18 Q Right.

19 A -- that question.

20 Q Yeah. Did counsel show you any enzyme
21 sequences today that have 85 percent sequence identity
22 to AAD-12, but have a different entomatic function?

23 A I thought that was the same as the last
24 question, but I would say no.

1 Q Okay. would you please turn to the Elkins
2 paper exhibit? I think it's 2022. It should be --

3 A It's under here.

4 Q It looks like you're on Figure 5?

5 A Uh-huh.

6 Q In view of the gaps in the alignments of
7 this sequences in Figure 5, do the ten enzymes here
8 have the same motif or different motifs with different
9 spacings?

10 MR. RUTT: Objection. Leading.

11 A They're definitely not all the same, but I
12 would have to count to make sure to see how many of
13 them -- how many different numbers are represented in
14 the spacers. It looks to be -- they may all be
15 different. The problem is to assure that there's not
16 a compensating -- you know, I can see different length
17 gaps, but then there could be a compensating gap
18 somewhere else.

19 Q well, I have an easier example.

20 A Okay.

21 Q Counsel showed you Exhibit 2054. Do you
22 have that in front of you?

23 A 2054 is this one.

24 Q That's Hausinger 2004, correct?

1 A Yes.

2 Q And would you please turn to Table 1 on
3 Page 22?

4 MR. RUTT: Objection. Scope.

5 A I see it.

6 Q In Table 1, there is a listing of different
7 enzymes with the variety of spaces and their specific
8 motifs, correct?

9 A Right.

10 Q And do these enzymes all have the same
11 function or do they have different functions --

12 MR. RUTT: Objection. Leading.

13 Q -- as you can tell based on their names?

14 MR. RUTT: Objection. Leading.

15 A I know most of these. They appear all to
16 have distinct different functions, and the spacing is
17 pretty widely variant from a low number in this -- in
18 this first spacing. This is between asparate and the
19 third ligand, histidine, and it's seems the low is 44
20 and the high is a whopping 146 if I scan through --
21 153. Sorry. So it varied by more than 100 amino
22 acids there.

23 Q would you please turn in your declaration
24 to Paragraph 140?

25 A Okay.

1 Q And this is the paragraph counsel directed
2 you to for where you addressed Dr. Silverstone's ten
3 to 106th power sequence calculation.

4 Do you recall that?

5 A Yes.

6 Q And stated in your declaration here, you
7 say, "Dr. Silverstone's enablement analysis fails to
8 account for a skilled person's background and
9 knowledge of entomology and protein engineering
10 principles. This is a critical deficiency because of
11 the purely mathematical ten to the 106th power
12 sequence calculation he repeatedly relies upon
13 incorrectly assumes that a skilled artisan would be
14 using no skill."

15 Do you see that?

16 A I do, and I would say it definitely implies
17 that, that we can't use the guidance of the art in
18 this, so that's why I characterize it as a
19 mathematical exercise.

20 Q And do you recall counsel asking you about
21 a series of hypothetical deletions, truncations and
22 other such changes to the AAD-12 sequence towards the
23 end of your deposition today?

24 A Yes.

25 Q And did those reflect a skilled artisan's

1 use of ordinary skill or closer to what you criticized
2 Dr. Silverstone of using no skill?

3 MR. RUTT: Objection. Leading.

4 A well, the way I would put it is they asked
5 about things that a skilled artisan wouldn't do if the
6 task was to make a whole bunch of AAD-12 variants that
7 were within the 85 percent sequence identity had
8 the -- all the motif residues and spacers and retain
9 the function because that's easy, and one doesn't have
10 to do the hard things, like, putting in insertions or
11 doing truncations of key structural elements, some of
12 which he asked me.

13 MR. DEROO: All right. No further
14 questions.

15 THE REPORTER: Copies?

16 MR. RUTT: Electronic.

17 MR. DEROO: Electronic as well and a rough
18 draft.

19 - - -

20 (Thereupon, at 5:34 o'clock p.m., the
21 deposition was concluded and signature was not
22 waived.)

23 - - -
24
25

CERTIFICATE

COMMONWEALTH OF PENNSYLVANIA,) SS:
)
COUNTY OF ALLEGHENY.)

I, Melissa L. Fenster, do hereby certify that before me, a Notary Public in and for the Commonwealth aforesaid, personally appeared J. MARTIN BOLLINGER, JR., Ph.D., who then was by me first duly cautioned and sworn to testify the truth, the whole truth, and nothing but the truth in the taking of his oral deposition in the cause aforesaid; that the testimony then given by him as above set forth was by me reduced to stenotypy in the presence of said witness, and afterwards transcribed by means of computer-aided transcription.

I do further certify that this deposition was taken at the time and place in the foregoing caption specified, and was completed without adjournment.

I do further certify that I am not a relative, counsel or attorney of either party, or otherwise interested in the event of this action.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my seal of office at Pittsburgh, Pennsylvania, on this _____ day of _____, 2024.

Melissa L. Fenster, Notary Public
My commission expires: January 21, 2027

- - -

COMMONWEALTH OF PENNSYLVANIA) E R R A T A
COUNTY OF ALLEGHENY) S H E E T

I, J. MARTIN BOLLINGER, JR., Ph.D., have read the foregoing pages of my deposition given and wish to make the following, if any, amendments, additions, deletions or corrections:

Page/Line	Should Read	Reason for Change
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In all other respects, the transcript is true and correct.

J. MARTIN BOLLINGER, JR., Ph.D.

Subscribed and sworn to before me this ____ day
of _____ 2024.

Notary Public

1 March 11, 2024

2 Finnegan, Henderson, Farabow, Garrett & Dunner, LLP:
3 901 New York Avenue, NW
4 Washington, DC 20001

5 ATTN: Pier DeRoo, Esquire:

6 NOTICE OF NON-WAIVER OF SIGNATURE

7 Please have the deponent read his deposition
8 transcript. All corrections are to be noted on the
9 preceding Errata Sheet.

10 Upon completion of the above, the deponent must affix
11 his signature, and it is to then be notarized.

12 Please forward the signed original of the Errata Sheet
13 to Mr. Eric Rutt, Esquire, for attachment to the
14 original transcript, which is in his possession,
15 copying all other counsel and myself.

16 As per the rules, if the witness does not sign the
17 signature page within 30 days after receipt of the
18 transcript, signature is deemed waived.

19
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22
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24
25

Melissa L. Fenster
Court Reporter

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