

In the Matter Of:

SAREPTA THERAPEUTICS vs

GENZYME

STEVEN BERKOWITZ, PH.D.

July 29, 2026



1 UNITED STATES PATENT AND TRADEMARK OFFICE

2

3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4

5 SAREPTA THERAPEUTICS, INC.

6

Petitioner

7

v.

8

GENZYME CORPORATION,

9

Patent Owner

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IPR2026-00150

12

U.S. Patent No. 12,031,894

13

14

VIDEOTAPED DEPOSITION of

15

STEVEN BERKOWITZ, Ph.D.

16

Wednesday, July 29, 2026

17

9:03 a.m.

18

Held at:

19

QUINN, EMANUEL, URQUHART & SULLIVAN LLP

111 Huntington Avenue

Boston, Massachusetts 02199

20

Judith McGovern Williams, CSR, CRR

21

Registered Professional Reporter

22

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13		homogeneity of	
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1 "Empty virions in AAV8
2 vector preparations
3 reduce transduction
4 efficiency and may
5 cause total viral
6 particle dose-limiting
7 side effects"

8 Exhibit 1041 Article entitled 131

9 "Analysis of Particle
10 Content of Recombinant
11 Adeno-Associated Virus
12 Serotype 8 Vectors by
13 Ion-Exchange
14 Chromatography"

15
16
17
18
19 (Original exhibits were marked by the
20 court reporter and distributed
electronically to all parties.)
21
22
23
24

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

2 - - -

3 THE VIDEOGRAPHER: We are now
4 recording and on the record. My name is
5 Jason Martin. I am a legal videographer
6 for Lexitas.

7 Today is July 29, 2026, and the
8 time is 9:03 a.m.

9 This is the deposition of Steven
10 Berkowitz, Ph.D., in the matter of Sarepta
11 Therapeutics, Inc., plaintiff, versus
12 Genzyme Corporation, respondent, in case
13 number IPR2026-0015, before the Patent
14 Trial and Appeal Board.

15 This deposition is being taken at
16 111 Huntington Avenue, Boston,
17 Massachusetts 02199.

18 The court reporter is Judith
19 Williams.

20 Counsel will state their
21 appearances, and the court reporter will
22 administer the oath.

23 ATTORNEY HACKMAN: I am Blaine
24 Hackman of Dechert LLP on behalf of

1 Genzyme.

2 ATTORNEY HELM: Katherine Helm on
3 behalf of Genzyme.

4 ATTORNEY WILSON: Robert Wilson
5 from Quinn Emanuel Urquhart & Sullivan on
6 behalf of Sarepta Therapeutics and the
7 witness.

8 - - -

9 STEVEN BERKOWITZ, Ph.D. , first
10 having been satisfactorily identified by
11 the production of his driver's license and
12 duly sworn by the Notary Public, testified
13 under oath as follows in answer to
14 examination by ATTORNEY HACKMAN:

15 Q. Good morning, Dr. Berkowitz. I
16 represent Genzyme Corporation in this
17 proceeding, and I am going to ask you some
18 questions today, and I would like to go
19 over before, a few ground rules before we
20 begin.

21 So, first, when I ask a question,
22 please let me finish asking the question
23 before you begin your answer, and I will
24 do the same for you?

1 The court reporter needs the
2 opportunity to take down the testimony, so
3 if we talk over each other, it is
4 difficult for her to do that.

5 Second is to please answer
6 verbally. Things like nods, head shakes,
7 can't be captured in your response on the
8 transcript, so we need verbal answers to
9 my questions.

10 Third, if you don't understand a
11 question, please say so, and I will try to
12 rephrase or clarify. If you answer a
13 question, I will assume that you
14 understood the question.

15 Is that fair?

16 A. Yes.

17 Q. Okay. And finally, your counsel
18 might object to some of my questions.
19 Unless you receive an express instruction
20 not to answer, you have to answer my
21 question --

22 A. Okay.

23 Q. -- to the best of your ability.

24 So have you ever been deposed

1 before?

2 A. No.

3 Q. And you do understand you are
4 under oath today, so just as if you were
5 testifying in a courtroom?

6 A. Correct.

7 Q. Is there any reason you cannot
8 provide truthful testimony today?

9 A. No.

10 Q. And one other thing actually I
11 forgot to mention. If you need a break at
12 any time, just let me know. The only
13 thing I ask is if there is a question
14 pending that you complete the answer to
15 the question, and then we can take a
16 break.

17 A. I have got it.

18 Q. So have you reviewed any
19 documents in preparation for your
20 deposition today?

21 A. Yes.

22 Q. And what documents did you
23 review?

24 ATTORNEY WILSON: Well, I am

1 going to object to that as calling for
2 work product and attorney-client
3 privileged information, and I will
4 instruct you not to answer.

5 BY ATTORNEY HACKMAN:

6 Q. Okay. So you did as part of
7 preparing your declaration, you reviewed
8 some documents?

9 A. Yes.

10 Q. And you identified those
11 documents in your declaration? Right?

12 A. Yes.

13 Q. And in preparing for the
14 deposition, did you review those documents
15 as well?

16 ATTORNEY WILSON: The same
17 objection.

18 I instruct you not to answer.

19 ATTORNEY HACKMAN: So, counsel, I
20 think that what I am trying to get at it
21 is not privileged. It is just to get to
22 the extent he is testifying today I want
23 to know what sort of documents he is
24 relying on.

1 ATTORNEY WILSON: Right. I mean
2 that there is a difference between what he
3 relied on in preparing his declaration and
4 the documents that he reviewed as part of
5 preparing for his deposition, and I am
6 objecting to your questions about the
7 specific documents that he reviewed in
8 preparing for the deposition as work
9 product and attorney-client privileged.

10 ATTORNEY HACKMAN: So let me ask
11 a little bit of a different question.

12 ATTORNEY WILSON: Okay.

13 BY ATTORNEY HACKMAN:

14 Q. Are there any documents that you
15 reviewed in preparing for your deposition
16 that are different than the documents that
17 you reviewed in preparing your
18 declaration?

19 A. No.

20 Q. Okay. So that the entire corpus
21 of documents that you have reviewed in
22 preparing your testimony for both the
23 declaration and deposition are the ones
24 that are listed --

1 A. Yes.

2 Q. -- in your declaration?

3 A. Yes.

4 Q. Okay.

5 ATTORNEY HACKMAN: With that, it
6 actually makes sense to mark Exhibit 1004.
7 This is Dr. Berkowitz's declaration.

8 ATTORNEY WILSON: Do you need
9 that separately marked by the court
10 reporter?

11 ATTORNEY HACKMAN: I don't know.
12 The exhibits are marked as part of the IPR
13 proceedings, but.

14 (Declaration of Steven
15 Berkowitz, PH.D. In support of
16 Petition for Inter Parties Review
17 of U.S. Patent No. 12,031,894
18 marked Exhibit 1004 for
19 identification.)

20 (Handing Exhibit 1004 to the
21 witness.)

22 BY ATTORNEY HACKMAN:

23 Q. So if you could just take a look
24 through your declaration and confirm that

1 this is indeed your declaration that you
2 submitted in the case?

3 (Pause.)

4 (Witness viewing Exhibit 1004.)

5 A. Yes.

6 Q. And that signature on page 116,
7 is that your signature?

8 A. Yes.

9 Q. And in preparation for today's
10 deposition, did you meet with anybody?

11 A. Today?

12 Q. Prior to your deposition.

13 A. I met with counsel.

14 Q. All right. And when did those
15 meetings occur?

16 A. Yesterday in person.

17 Q. And you said in person. Were
18 there other meetings as well?

19 A. Zoom meetings, yes.

20 Q. Okay. And approximately how long
21 did you spend preparing for your
22 deposition?

23 A. Maybe 20, 30 hours.

24 Q. Let's talk a little bit about

1 your professional background.

2 So you worked at Biogen --

3 A. Correct.

4 Q. -- prior to -- and I want to make
5 sure -- I know it is the natural course of
6 conversation you want to answer. Just
7 make sure I finish the question --

8 A. Sorry.

9 Q. -- just for her benefit.

10 A. Yes.

11 Q. Thanks.

12 So at Biogen, you said your work
13 involved analytical and biophysical
14 characterization, purification and
15 formulation and development of
16 biopharmaceutical products. That is a
17 reasonable characterization?

18 A. Yes.

19 Q. And did that work at Biogen
20 include virus-like particles and viral
21 vectors for gene therapy applications?

22 A. Yes.

23 Q. Since retiring you have worked as
24 a part-time consultant? Is that right?

1 A. Minimal consulting.

2 Q. And who have you consulted for?

3 A. Several biotech companies in
4 addition to, well, Biogen, my former
5 company.

6 Q. Are you able to disclose which
7 companies those are?

8 A. Yes.

9 Q. Okay. Can you please disclose
10 which companies you consulted for?

11 A. Hemology. There was -- I don't
12 know -- a number of these I don't remember
13 exactly the names. Addium. Spark.

14 I am trying to think.

15 (Pause.)

16 A. Is it PPD? I forget the name of
17 it. There were a couple of others. I
18 just don't remember the names.

19 Q. That is fine. Have these
20 consultancies been in a technical --

21 A. Yes.

22 Q. And you also have done expert
23 work for other companies, right, in patent
24 proceedings?

1 A. Have I done expert work for
2 patent?

3 Q. For example, have you prepared
4 expert declarations in other patent
5 proceedings?

6 A. No.

7 Q. I seem to recall Novartis, you
8 preparing a declaration. Do you recall
9 that?

10 A. Oh, excuse me. I correct myself.
11 Yes. Yes. Sorry.

12 Q. And that involved an analytical
13 ultracentrifugation patent that was owned
14 by Genzyme? Right?

15 A. Right.

16 Q. And that also involved -- I will
17 give you another word here --
18 adeno-associated viral particles?

19 A. Correct.

20 Q. Okay. How much of your work
21 since your retirement has focused on the
22 application of analytical
23 ultracentrifugation to gene therapy
24 products?

1 A. Most of it.

2 Q. And has that been -- actually I
3 withdraw that question.

4 What sort of viral particles have
5 you consulted on in that work?

6 A. Adeno-associated virus.

7 Q. And we can call that AAV?

8 A. Yes.

9 Q. Okay. And you have also done
10 work on adenoviruses as well?

11 A. Yes. While I was employed. Yes.

12 Q. So the work on adenoviruses was
13 during your course of employment?

14 A. Yes.

15 Q. And did you work on AAVs while
16 you were at Biogen?

17 A. No.

18 Q. Your AAV has started since your
19 retirement?

20 A. Correct.

21 Q. What year approximately did you
22 begin working on AAV?

23 A. Something on the order of '15,
24 '16, something like that, roughly

1 speaking. You know, it is an approximate
2 on my guess.

3 ATTORNEY HACKMAN: I am going to
4 mark another exhibit.

5 (Article entitled "Monitoring
6 the homogeneity of adenovirus
7 preparations (a gene therapy
8 delivery system) using analytical
9 ultracentrifugation" marked
10 Exhibit 1023 for identification.)

11 BY ATTORNEY HACKMAN:

12 Q. Dr. Berkowitz, I am handing you
13 Exhibit 1023.

14 (Handing Exhibit 1023 to
15 witness.)

16 Q. So, Dr. Berkowitz, I just want to
17 confirm. I have handed you your 2007
18 publication by Berkowitz and Philo. Is
19 that correct?

20 A. Correct.

21 Q. And in this publication, you
22 discuss analyses of adenovirus
23 preparations by analytical
24 ultracentrifugation? Correct?

1 A. Yes.

2 Q. Is it okay if I -- if I use AUC
3 when I am describing analytical
4 ultracentrifugation?

5 A. You can, but it can be very
6 confusing to some extent, because there
7 are various techniques that fall under
8 that.

9 Q. And the techniques that fall
10 under that you are referring to are
11 sedimentation equilibrium and
12 sedimentation velocity?

13 A. Even then there is some sort of
14 potential confusion, because there are
15 different types of equilibrium and
16 velocity. There is actually there are two
17 different types of velocity, there is
18 boundary and band sedimentation velocity,
19 and equilibrium very commonly is just
20 normal equilibrium, and then there is
21 density gradient equilibrium, typically
22 often referred to as cesium chloride
23 density gradient equilibrium, which also
24 has other names. But in terms of using

1 those kinds of abbreviations, it can get
2 confusing basically.

3 Q. All right. I will do my best to
4 describe what type of AUC that I am asking
5 a question about, and if you need
6 clarification, let me know. We will make
7 sure we are on the same page.

8 A. Absolutely. I get it. I mean I
9 do the same thing unfortunately. I will
10 say one thing and I will do the other.

11 Q. Understood. It is a lot of --
12 and it is a mouthful to say over and over
13 again. Okay.

14 So you are familiar with this
15 Exhibit 1023 that I handed you? Right?

16 A. Yes.

17 Q. And in this publication, you
18 studied adenovirus preparations by various
19 AUC techniques? Right?

20 A. Correct.

21 Q. And one of those techniques was
22 the banded sedimentation velocity AUC? Is
23 that right?

24 A. One of them. Yes.

1 Q. All right. And you said that is
2 one of them. What other techniques do you
3 remember applying to this?

4 A. Boundary. Boundary velocity
5 sedimentation AUC, ultracentrifugation.
6 So that is boundary sedimentation
7 velocity, analytical ultracentrifugation.

8 Q. So adenoviruses are structurally
9 different from AAV? Right?

10 A. Yes.

11 Q. And one of the structural
12 differences is that they are substantially
13 larger in size? Is that a reasonable
14 characterization?

15 A. Yes.

16 ATTORNEY WILSON: I object to
17 form.

18 BY ATTORNEY HACKMAN:

19 Q. Now you mentioned this paper. If
20 we go to page 18 of this publication.

21 I am referring to the number at
22 the top of the page, I think the way it
23 was numbered as an article not the way it
24 is numbered in the exhibit. I am going to

1 try to speak to that convention to avoid
2 confusion. I will refer to the article
3 numbering. Again if you have any
4 questions or confusion, please ask for
5 clarification.

6 A. Can I ask -- can I interject
7 something here?

8 Q. Sure.

9 A. In your previous questions, I
10 didn't fully answer it. You asked what
11 other techniques.

12 So in here there is in terms of
13 analytical ultracentrifugation, there is
14 cesium chloride density gradient
15 equilibrium, so.

16 Q. And for the cesium chloride
17 density gradient equilibrium, what was the
18 purpose of that study in terms of what you
19 were doing in this paper?

20 A. To assess microheterogenicity or
21 heterogenicity -- to assess heterogenicity
22 in the preparation in terms of buoyant
23 density.

24 Q. And by heterogenicity in terms of

1 buoyant density, you are trying to
2 identify the different particle species
3 that are in that composition?

4 ATTORNEY WILSON: I object to
5 form.

6 A. Correct.

7 BY ATTORNEY HACKMAN:

8 Q. And that technique that you are
9 describing with the cesium chloride
10 sedimentation equilibrium, that separates
11 particles based on their density? Right?

12 A. Buoyant density, right.

13 Q. Buoyant density, is that
14 different than just density?

15 A. It is -- there is a density form,
16 but it is related to the buoyant effect in
17 the analytical ultracentrifugation,
18 because there are three different types of
19 forces that are involved. There is, you
20 know, frictional forces; there is the
21 acceleration force from the rotation; and
22 then there is the mass effect basically.
23 So there is a buoyant effect and a mass
24 effect and a frictional effect.

1 Q. When you are using one of the
2 equilibrium techniques of AUC, does
3 particle friction vary depending on the
4 different species that are in the
5 composition?

6 ATTORNEY WILSON: Objection.

7 A. Some forms.

8 BY ATTORNEY HACKMAN:

9 Q. Does particle friction impact the
10 outcome of sedimentation equilibrium?

11 ATTORNEY WILSON: I object to
12 form.

13 A. Yes. It is in the Svedberg
14 equation, yes.

15 BY ATTORNEY HACKMAN:

16 Q. So the Svedberg equation I
17 thought relates to the rate of
18 sedimentation?

19 A. It relates-- it gives you the
20 velocity, but there is no -- you know, if
21 you reach forces that are balancing, then
22 there is no movement basically.

23 Q. Understood.

24 So that then in the sedimentation

1 equilibrium, where they -- where the
2 particles end up in the chamber --

3 A. Right.

4 Q. -- is determined in part by
5 friction?

6 A. No.

7 Q. Okay. So it is where the
8 particles end up in the chamber is
9 strictly determined by their buoyant
10 density?

11 A. Correct. Right. I mean the
12 Svedberg equation is the basis of all
13 analytical ultracentrifugation equations
14 basically. So the equilibrium will come
15 out from that eventually starting from
16 that type of equation.

17 Q. So friction impacts the rate, the
18 rate of sedimentation, but it doesn't
19 ultimately impact where once you reach
20 equilibrium the particles line up?

21 ATTORNEY WILSON: I object to
22 form.

23 A. Correct.

24 BY ATTORNEY HACKMAN:

1 Q. Okay. If I could go back to, I
2 think I referred you to page 18 --

3 A. Right.

4 Q. -- of your Exhibit 1023
5 publication.

6 If you go to the right column.

7 A. Right.

8 Q. We talk about the weight-average
9 translational frictional coefficient
10 ratio.

11 THE REPORTER: I need to go off
12 the record.

13 (Discussion off the record.)

14 THE VIDEOGRAPHER: The time is
15 9:21 a.m., and we are on the record.

16 ATTORNEY HACKMAN: Okay.

17 BY ATTORNEY HACKMAN:

18 Q. So, Dr. Berkowitz, I referred you
19 to page 18 of your Exhibit 1023
20 publication, and I was pointing to a
21 paragraph in the right column that refers
22 to the "weight-average translational
23 frictional coefficient ratio." Do you see
24 that?

1 A. Yes.

2 Q. So what is the weight average
3 translational frictional coefficient?

4 A. So, it basically -- the -- the --
5 the F without the naught under it, that
6 would be corresponding to the frictional
7 coefficient of the particle as it
8 naturally exists. And then it is being
9 ratioed to something of equivalent
10 molecular weight in a spherical form. The
11 naught refers to a sphere.

12 And so you are taking that ratio,
13 and then the concept of weight average, or
14 W , has to do with how the things are used
15 in the -- it is just an average of the
16 number. You are comparing a number or a
17 collection of particles, and you are
18 taking a weight average.

19 This ratio is actually used in
20 SEDFIT to do the deconvolution.

21 Q. And the F naught you are
22 referring to is this F with the subscript
23 zero?

24 A. Right.

1 Q. Or 0?

2 A. Yes.

3 Q. And the next part of it says:

4 "This weight average
5 translational frictional coefficient,
6 which provided optimum fits for the c(s)
7 distributions was 1.87 plus or minus 0.1"
8 -- excuse me -- "0.10 (SD)."

9 So what is this telling you about
10 the adenoviruses frictional coefficients
11 compared to the ideal spherical particle
12 that you have mentioned?

13 ATTORNEY WILSON: I object to
14 form.

15 A. It is basically less, analogous
16 to a sphere. Its shape is deviating away
17 from a sphere which would be one. The F
18 naught would for a sphere correspond to a
19 value of one.

20 BY ATTORNEY HACKMAN:

21 Q. Understood.

22 So the fact that you have
23 additional friction is caused by something
24 structural that is on the surface of the

1 particle that is causing it to behave in a
2 nonideal fashion? Is that reasonable?

3 ATTORNEY WILSON: I object to
4 form.

5 A. Yes. But it could be other
6 aspects of the whole -- the whole surface
7 -- not the surface -- but the whole
8 topology and shape of the particle is
9 deviating away from a spherical component.

10 BY ATTORNEY HACKMAN:

11 Q. In this case if we go a little
12 bit farther down this right column --

13 A. Yes.

14 Q. -- you have a sentence here that
15 says:

16 "This apparent discrepancy
17 between a highly symmetric, nearly
18 spherically shaped particle and the high
19 f/f naught ratio determined by boundary
20 sedimentation velocity in this work is
21 probably due in large part to the 12 spike
22 projections that extend about
23 30 nanometers beyond the adenovirus 90
24 nanometer diameter capsid shell."

1 Did I read that roughly
2 correctly?

3 A. Yes. That is correct.

4 Q. So with the adenoviruses, there
5 are things on the surface that are causing
6 there to be more friction than there would
7 be had the particle been closer to a
8 spherical shape? Is that right?

9 A. That's right.

10 ATTORNEY WILSON: I object to
11 form.

12 BY ATTORNEY HACKMAN:

13 Q. And so how did you identify the
14 presence of those spike projections?

15 A. By electron microscopy is one
16 approach.

17 Q. And in this particular
18 publication, was electron microscopy the
19 analytical technique that you used to
20 identify the spikes?

21 A. No, I didn't. No. Not in this
22 work.

23 Q. So you got the information about
24 the structures from somebody else's work?

1 A. It exists in the literature.

2 Q. And do you recall what analytical
3 techniques were described in the
4 literature for adenovirus particle shapes?

5 ATTORNEY WILSON: I object to
6 form.

7 A. Electromicroscopy in terms of
8 identifying the presence of fibers. I
9 wasn't involved in the work, but I, you
10 know, I have seen pictures of adenoviruses
11 in the literature which shows fibers
12 basically.

13 There might be other methods that
14 have been used. I'm just -- right off the
15 bat I don't -- I don't know for sure.

16 BY ATTORNEY HACKMAN:

17 Q. And the electron microscopy
18 methods, do they look specifically at
19 individual particles that were isolated
20 from the bulk composition?

21 ATTORNEY WILSON: Objection;
22 foundation.

23 A. You are looking at the grid.
24 They are individual particles basically on

1 the grid.

2 BY ATTORNEY HACKMAN:

3 Q. So adenoviruses are substantially
4 larger than AAV particles? Is that right?

5 ATTORNEY WILSON: I object to
6 form.

7 A. Can you repeat that question?

8 BY ATTORNEY HACKMAN:

9 Q. So adenovirus particles, their
10 diameters are substantially larger than
11 AAV particles? Right?

12 A. Correct. Yes.

13 Q. And that impacts the surface area
14 to volume of the particles? Right?

15 ATTORNEY WILSON: Objection.

16 ATTORNEY HACKMAN: Let me
17 withdraw that question.

18 BY ATTORNEY HACKMAN:

19 Q. So if a particle with a larger
20 diameter has a lower surface area to
21 volume ratio than a particle with a
22 smaller diameter, is that reasonable?

23 ATTORNEY WILSON: Objection;
24 foundation.

1 A. Can you repeat that again for me?

2 BY ATTORNEY HACKMAN:

3 Q. Sure.

4 So the surface area to volume of
5 a particle --

6 A. Yes.

7 Q. -- is determined by how much area
8 exists on the surface of the particle
9 versus the volume of what is contained
10 within the particle? Is that right?

11 ATTORNEY WILSON: Objection;
12 foundation.

13 A. It is -- there is more volume
14 obviously in a bigger particle than a
15 smaller particle of the same shape. Okay?
16 So are you asking me about the ratio of
17 the volume to the surface area?

18 BY ATTORNEY HACKMAN:

19 Q. Right.

20 A. I -- basically there is -- there
21 are relationships between a family of
22 particles. So you can understand there is
23 a progression that one can see in terms of
24 behavior that spheres follow a certain

1 type of, you know, relationship in terms
2 of various sedimentation properties.

3 Q. Has there again a documented
4 relationship between friction and surface
5 area to volume ratio?

6 ATTORNEY WILSON: Objection;
7 foundation.

8 A. There are, in terms of
9 sedimentation to mass, there are
10 relationships. Yes.

11 BY ATTORNEY HACKMAN:

12 Q. So mass, though, doesn't
13 necessarily impact the surface area of a
14 particle? Right?

15 A. There is more surface area -- you
16 know, there has to be more surface area on
17 a bigger particle than a smaller particle
18 in terms of both being spheres.

19 Q. But what I am getting at, I
20 guess, is when dealing with friction, does
21 having more surface area relative to the
22 volume of the particle make friction a
23 bigger factor for a smaller particle?

24 ATTORNEY WILSON: Objection;

1 foundation.

2 A. Well, if there is more -- if
3 there is more surface area, there is more
4 friction basically.

5 BY ATTORNEY HACKMAN:

6 Q. A really quick question.

7 So this paper that you worked on
8 with adenovirus, right, have you published
9 at all on AAV particle AUC?

10 A. Yes.

11 Q. Okay. When were those
12 publications?

13 A. '24, '25 -- 2024, 2025. There
14 may be one earlier, 2021, '22, that it
15 wasn't focused on the virus per se. It
16 was focused on the actual instrument and
17 existing possible problems with the
18 instrument.

19 Q. So you mentioned an existing
20 possible problem with the instrument?

21 A. Yes.

22 Q. Can you describe what that
23 problem was?

24 A. Yes. It was the design of the

1 temperature controller on the instrument.

2 Controlling temperature is a very
3 important attribute to getting stable
4 sedimentation.

5 Q. What -- if temperature is not
6 controlled, what sort of issues can arise?

7 A. Convection.

8 Q. And how does convection affect
9 the results?

10 A. Mixing.

11 Q. So describe what you mean by
12 mixing.

13 A. It gets stirred up basically.
14 You get vortexes formed. You get
15 inversion of the material, which basically
16 leads to mixing.

17 Q. And if you were to look at a
18 sedimentation distribution outcome, how
19 would that sort of issue, the mixing
20 issue, affect what you get out of that
21 sedimentation coefficient plot?

22 A. Okay.

23 ATTORNEY WILSON: Objection;
24 foundation.

1 A. Well, what would happen -- what
2 happens basically and what happened with
3 that instrument -- so this is the third
4 generation instrument that Beckman
5 designed, and I think it was released at
6 the very beginning of 2018.

7 And Biogen -- I was working with
8 people at Biogen. They bought one of the
9 first instruments, and it was installed in
10 their lab, and I was helping them do some
11 -- some work, and they were running
12 antibody at low speeds. They were
13 actually using the antibody as a reference
14 standard for their AAV work. So running
15 at roughly 16,000 RPM, they were getting
16 no sedimentation.

17 So what happens is that what we
18 basically pointed to is that there were
19 mixing effects, convection occurring in
20 the sedimentation.

21 So the effect of not controlling
22 temperature, getting mixing, when you look
23 at what you see in your -- by your
24 detector, instead of seeing an actual

1 sedimenting boundary pulling away from the
2 meniscus, you see nothing. You just see
3 the starting solution as it additionally
4 was put into the cell, because the
5 material is constantly being mixed by
6 thermal gradients that are induced during
7 the running of the instrument.

8 Q. Is this a common issue that was
9 observed to happen in instruments even
10 before the release of the 2018 Beckman
11 instrument?

12 A. It was actually very important in
13 terms of the design of the instrument
14 going back to Svedberg.

15 ATTORNEY HACKMAN: I just want to
16 mark another exhibit. This is
17 Exhibit 1005.

18 (Curriculum Vitae of Steven A.
19 Berkowitz, Ph.D. marked
20 Exhibit 1005 for identification.)

21 (Handing Exhibit 1005 to witness.

22 BY ATTORNEY HACKMAN:

23 Q. Dr. Berkowitz, this is a copy of
24 your CV that was filed with your

1 declaration? Right?

2 A. Yes.

3 Q. And you had mentioned that some
4 of these recent publications that you had
5 regarding the AUC instruments that we were
6 just discussing?

7 A. Yes.

8 Q. Can you identify where on your CV
9 those publications are?

10 A. So the one we're talking about
11 right now is one, two, three, four, five
12 -- going down, it is the fifth publication
13 with Tom Laue.

14 Q. Okay. And this work that you
15 were describing regarding the mixing, are
16 all of the publications that arose from
17 that work included in your CV?

18 A. Can you repeat that question?

19 Q. Yes.

20 So you mentioned that you had
21 some recent publications --

22 A. Yes.

23 Q. -- that you were studying AAV
24 particles?

1 A. Correct.

2 Q. Are all of those publications
3 listed in your CV?

4 A. Again could you just repeat? I
5 am sorry. I --

6 Q. That's okay.

7 So you had mentioned that you had
8 some recent publications that involved
9 work with AAV particles?

10 A. Right.

11 Q. So my question is whether you
12 could identify for us which of those --
13 which of these publications --

14 A. Oh.

15 Q. -- document that work that you --

16 A. Oh, okay.

17 Q. -- referred to.

18 A. Sorry. So the next one up
19 involved with Larson.

20 The one just below it, another
21 Berkowitz. I was lead author there with
22 Larson and Bou-Assaf and Tom Laue.

23 Then above that, Larson,
24 Bou-Assaf, Laue and myself.

1 And the top one was Bouch. That
2 is Spark Pharmaceutical. There is a list
3 of other authors.

4 And then just below, I didn't
5 mention it going up, Berkowitz, I was
6 asked to write an article. That doesn't
7 -- I did talk about analytical
8 understandings. It was sort of an insight
9 article for somebody to give some
10 perspective of the analytical tools that
11 dealt with characterizing virus particles.

12 Q. And the references you have
13 listed here on your CV --

14 A. Right.

15 Q. -- are these all of the
16 references that you published?

17 A. Yes.

18 Q. Okay. Let's go back. So you
19 have your Exhibit 1004, which is your
20 declaration.

21 (Witness complying.)

22 Q. And I would like for us to go to
23 paragraph 30 of that declaration, and in
24 fact, go ahead and review that, and then I

1 wanted to direct questions to this figure
2 that you have here on page 15.

3 A. Okay. Thank you.

4 Q. And I believe earlier when we
5 were discussing AUC and the abbreviation
6 generally, you had mentioned the various
7 types of AUC techniques? Right?

8 A. Correct.

9 Q. And is this figure a good summary
10 of the various AUC techniques to which you
11 were describing?

12 A. Yes.

13 Q. So there are two general classes
14 you have identified here: Sedimentation
15 velocity, SV; and sedimentation
16 equilibrium, SE? Right?

17 A. Correct.

18 Q. And is a key difference between
19 those two techniques the rotor speed which
20 controls the strength of the centrifugal
21 field as it is applied to the sample?

22 A. Yes.

23 Q. And in SV-AUC, sedimentation
24 velocity, the rotor then spins fast enough

1 to force the particles to migrate all the
2 way to the bottom of the cell? Right?

3 A. Correct.

4 Q. Where in SE-VOC the rotor spins
5 at a much lower speed, and that allows
6 each particle to settle into its own
7 static equilibrium? Is that right?

8 A. Correct.

9 Q. Now because of the differences in
10 these techniques, the forces that impact
11 the output of the studies are different?
12 Right?

13 ATTORNEY WILSON: I object to
14 form.

15 A. The same forces are applied, but
16 the resulting output leads to a different
17 behavior and migration or lack of
18 migration.

19 BY ATTORNEY HACKMAN:

20 Q. Right. And the sedimentation
21 rate broadly depends on three forces:
22 Centrifugal force, buoyant force, and
23 frictional force? Is that reasonable?

24 A. Yes.

1 Q. And the frictional force depends
2 on the frictional coefficient of the
3 particle? Right?

4 A. Yes.

5 Q. And the frictional coefficient is
6 affected by the overall size and shape of
7 the particle? Right?

8 A. Yes.

9 Q. Now in addition to size and
10 shape, are there other properties of a
11 particle that can impact the frictional
12 coefficient?

13 A. Other than -- can you -- can you
14 just repeat that question?

15 Q. Yes. Absolutely.

16 So you have mentioned size and
17 shape are one of the factors that will
18 determine the frictional coefficient for a
19 particle? Right?

20 A. Right.

21 Q. And so are there other properties
22 of a particle that could impact the
23 frictional coefficient?

24 ATTORNEY WILSON: I object to

1 form.

2 A. It is possible that the -- that
3 the chemical nature of the surface may
4 have some influence on -- on -- on some
5 bulk properties that go on in the
6 interaction with the bulk solvent
7 basically.

8 BY ATTORNEY HACKMAN:

9 Q. So you said the interaction with
10 the bulk solvent. Does that mean that
11 there is some sort of chemical interaction
12 that occurs between the particle and the
13 solvent?

14 ATTORNEY WILSON: I object to
15 form.

16 A. It is a chemical force. Yes.
17 Some kind of adhesion of some sort
18 basically that plays out in terms of
19 dragging additional solvent with the
20 particle as it migrates, which would
21 reflect some differences in frictional
22 coefficient.

23 BY ATTORNEY HACKMAN:

24 Q. And what chemical properties of a

1 particle would affect that chemical
2 adhesion that you are referring to?

3 ATTORNEY WILSON: I object to
4 form.

5 A. The chemical groups that are on
6 the -- on the surface basically.

7 BY ATTORNEY HACKMAN:

8 Q. Does charge affect the
9 interaction between the medium and the
10 particle?

11 A. It is possible.

12 Q. So if you had two particles that
13 were of identical size and shape but they
14 had different net charges on them, could
15 that lead to them having different
16 frictional coefficients?

17 ATTORNEY WILSON: Objection;
18 foundation.

19 A. It is possible.

20 BY ATTORNEY HACKMAN:

21 Q. How would you know whether those
22 chemical properties impact the frictional
23 coefficient?

24 A. Basically by looking at its

1 hydrodynamic properties.

2 Q. And how do you study hydrodynamic
3 properties?

4 A. Size exclusion chromatography is
5 one technique, and certainly
6 ultracentrifugation velocity,
7 sedimentation velocity,
8 ultracentrifugation.

9 Q. And so the only one to actually
10 determine whether there is hydrodynamic
11 forces that are affecting a particle would
12 be to actually do an SV-AUC experiment?

13 ATTORNEY WILSON: Objection;
14 form.

15 A. Can you repeat that again?

16 BY ATTORNEY HACKMAN:

17 Q. Sure. Actually I am going to ask
18 a little different question.

19 Just by looking at a particle on
20 an electron micrograph, can you detect
21 chemical differences between particles
22 that could impact these hydrodynamic
23 forces that you described?

24 ATTORNEY WILSON: Objection;

1 foundation.

2 A. Electromicroscopy typically looks
3 at the physical topology of the particle.
4 There are other forms that might more
5 advanced cryoEM may look at structural
6 effects that might lead to some
7 information that some changes have
8 occurred.

9 Q. So looking at a bulk electron
10 micrograph image can't tell you anything
11 -- everything --

12 ATTORNEY HACKMAN: Let me
13 withdraw that. I don't want to mess up
14 this one.

15 BY ATTORNEY HACKMAN:

16 Q. So looking at the bulk electron
17 micrograph image can't tell you everything
18 about the particle's frictional
19 properties? Right?

20 ATTORNEY WILSON: Objection;
21 foundation.

22 A. Yes. It can't tell you
23 everything about it, other than its
24 topology basically.

1 BY ATTORNEY HACKMAN:

2 Q. By topology, you mean the size
3 and shape --

4 A. Yes.

5 Q. -- of the particle?

6 So would you agree that friction
7 is a factor that complicates sedimentation
8 velocity in AUC analysis compared to
9 sedimentation equilibrium analysis?

10 A. Yes.

11 ATTORNEY WILSON: I object to
12 form.

13 A. The frictional coefficient plays
14 a role in sedimentation velocity. Yes. I
15 mean it is an active component.

16 BY ATTORNEY HACKMAN:

17 Q. And if you wanted to determine
18 whether there might be frictional
19 differences between two species of
20 particles that have otherwise the same
21 density, what would be the sort of
22 analytical techniques that you would use
23 to do that?

24 ATTORNEY WILSON: Objection;

1 foundation.

2 A. I have just mentioned the two:
3 size exclusion chromatography and
4 analytical velocity -- analytical
5 ultracentrifugation.

6 BY ATTORNEY HACKMAN:

7 Q. So size exclusion chromatography,
8 can you explain how that would analyze for
9 properties that would affect a particle's
10 friction?

11 A. It is basically looking at the --
12 the -- the -- it is concerned with the --
13 the volume -- the size of the particles,
14 which would encompass any hydration, you
15 know, aspects of the molecule. So you are
16 looking at its -- its bulk movement
17 through the various physical structures
18 which would reflect the size of the
19 particle basically.

20 Q. And you mentioned there was one
21 other analytical technique that you use to
22 analyze particle friction?

23 A. The analytical sedimentation --
24 sorry -- velocity -- sedimentation

1 velocity ultracentrifugation.

2 Q. If you wanted to get an idea of
3 how two species of particles differed in
4 terms of their frictional coefficient
5 before doing sedimentation velocity AUC
6 experiment, would you say size exclusion
7 would be the best technique to use?

8 ATTORNEY WILSON: I object to
9 form.

10 A. I would think it would be
11 analogous to what you would get with, you
12 know, with -- with velocity sedimentation.
13 I think both techniques could give you
14 basically equivalent information.

15 I should also mention -- and I
16 didn't mention -- that you could look at
17 diffusion coefficient measurements
18 basically to get information -- rough
19 information to get solutions size
20 information.

21 But by and large, size exclusion
22 chromatography and analytical --
23 sedimentation velocity ultracentrifugation
24 are some of the best tools to really use.

1 You could, as I just mentioned, which I
2 forgot to mention, is looking at dynamic
3 light scattering, which measures
4 diffusion, it is also good, but it has a
5 lot of complicating effects of making sure
6 you get rid of other contaminants
7 basically. It is not necessarily the best
8 technique to use. Of these three, I would
9 put the two that I mentioned initially,
10 size exclusion chromatography and velocity
11 -- sedimentation velocity analytical
12 ultracentrifugation as sort of comparable
13 techniques.

14 Q. So I am going to ask a slightly
15 different question.

16 If you had a particle and you
17 don't know what its molecular weight was,
18 which of the AUC techniques would a person
19 of ordinary skill in the art find as most
20 useful for determining the molecular
21 weight of that particle?

22 ATTORNEY WILSON: Objection;
23 foundation.

24 A. Equilibrium tends to be the best.

1 BY ATTORNEY HACKMAN:

2 Q. And is equilibrium the best
3 technique because you don't have to
4 concern yourself with the friction that
5 different particles would experience?

6 A. Yes.

7 ATTORNEY WILSON: Objection;
8 foundation.

9 BY ATTORNEY HACKMAN:

10 Q. I want to go back to your
11 declaration, Exhibit 1004.

12 (Witness complying.)

13 Q. If you would go to paragraph 48.
14 I think it is on page 24.

15 A. Oh, excuse me. I went to
16 paragraph twenty -- excuse me -- on
17 paragraph 48 on 28?

18 Q. Page 24.

19 A. Okay. My numbers. Page 24,
20 paragraph 48?

21 Q. Yes.

22 A. Right.

23 Q. And there is a figure on this
24 page that is a -- you referred to as a

1 sedimentation coefficient profile
2 generated by the SEDFIT program for SV-AUC
3 data for a sample with two species.

4 Right?

5 A. Right.

6 Q. So this is intended to be a
7 representative example of what a
8 sedimentation coefficient distribution
9 profile looks like? Right?

10 A. Yes.

11 Q. So each of these peaks that are
12 in this image you have here correspond to
13 a species of particles having particular
14 sedimentation coefficients? Right?

15 A. Yes.

16 Q. And if you have a heterogenous
17 mixture of particles like this where you
18 have different particle species, the
19 usefulness of sedimentation velocity AUC
20 depends on the ability to resolve these
21 distinct peaks for each species? Right?

22 A. Right.

23 ATTORNEY WILSON: Objection to
24 form.

1 THE WITNESS: Sorry. Can you
2 repeat that again?

3 ATTORNEY HACKMAN: Could you just
4 read my question back.

5 (The pending question and
6 objection were then read.)

7 THE WITNESS: I believe so.

8 BY ATTORNEY HACKMAN:

9 Q. And if these peaks start to
10 overlap, can it become more difficult to
11 determine the presence of multiple
12 species?

13 ATTORNEY WILSON: I object to
14 form.

15 A. Yes. If they start overlapping,
16 yes, they can. They would.

17 BY ATTORNEY HACKMAN:

18 Q. And so it is important to be able
19 to have separate peaks when you are
20 looking at a sedimentation coefficient
21 distribution?

22 ATTORNEY WILSON: I object to
23 form.

24 A. You always want to be able to --

1 in terms of characterizing your material,
2 you want to know what is in there. You
3 want to be able to separate it, you know,
4 whatever really is in there. So if for
5 some reason they overlap, you are missing
6 information. So you are looking for
7 techniques that if different things are
8 present you want to separate them out.

9 Q. And what could be some of the
10 causes for peaks that overlap in a
11 sedimentation coefficient distribution?

12 ATTORNEY WILSON: Objection;
13 foundation.

14 A. They have the same sedimentation
15 coefficient and --

16 BY ATTORNEY HACKMAN:

17 Q. What if the species have
18 different sed sedimentation coefficients
19 but their peaks are in some way
20 overlapping with each other?

21 ATTORNEY WILSON: Objection;
22 foundation.

23 A. They overlap? Can you -- sorry
24 -- can you --

1 BY ATTORNEY HACKMAN:

2 Q. Why don't we go to -- I think
3 there are examples in your report that we
4 can go to.

5 Just bear with me for a second.

6 (Pause.)

7 Q. If you go to paragraph 108 in
8 your declaration, the paragraph 108 is on
9 page 54 of your declaration.

10 (Witness complying.)

11 A. Yes.

12 Q. These are two figures that you
13 took from the Le Bec reference? Right?

14 A. Right.

15 Q. Let's focus on the bottom figure,
16 figure 3. Do you see that, Dr. Berkowitz?

17 A. Yes. The bottom figure?

18 Q. And in this figure, if we look --
19 we will look at the lines that are in --
20 that are not dotted -- the solid lines.

21 A. Right.

22 Q. There looks like there is this
23 shoulder on the bigger peak. Do you see
24 that?

1 A. Yes.

2 Q. So is it your view that there are
3 multiple species that are in this
4 collection of peaks here?

5 A. Yes. There is the most dominant
6 peak at something close to 100, and what
7 you call I guess is the shoulder, around
8 -- I can't read it -- something like 90,
9 90S basically you would assign its peak.

10 Q. So it is a little difficult to
11 identify where the peak is, right, because
12 of the way that the peaks are overlapping?

13 ATTORNEY WILSON: I object to
14 form.

15 A. It is. You can see that the peak
16 maximum basically, and you can -- you
17 know, you can see -- you can use -- call
18 out that maximum with the S value.

19 I am having a little -- trying to
20 look up, from the bottom up, I can't read
21 the scale that well on the bottom. But it
22 looks like something on the order of 90,
23 something in that ballpark. There is a
24 slight shift in these three shoulders.

1 Sometime the shoulders are a little more
2 resolved than others.

3 ATTORNEY HACKMAN: For the
4 convenience of being able to read the
5 figure, why don't I mark a different
6 exhibit. This is Exhibit 1006. This is
7 the Le Bec reference.

8 THE WITNESS: Yes.

9 (International Publication
10 Number WO 2014/125101 A1 marked
11 Exhibit 1006 for identification.)

12 (Handing Exhibit 1006 to
13 witness.)

14 BY ATTORNEY HACKMAN:

15 Q. And if you go to -- here is the
16 one instance where I -- the one instance I
17 am going to refer to the exhibit number
18 for convenience. At the bottom of the
19 page, if you go to page 25.

20 A. Yes.

21 Q. You are already there?

22 A. Yes.

23 Q. There are the two figures that we
24 were discussing in your report? Right?

1 A. Right.

2 Q. And so we will look at figure 3
3 here, and we were talking about the
4 shouldering on these?

5 A. On the bottom, figure 3?

6 Q. Yes.

7 A. Right.

8 Q. And so this -- the fact that
9 there is the shoulder in this overlap,
10 does that impede the person of ordinary
11 skill in the arts ability to derive
12 certain information from this
13 sedimentation distribution plot?

14 ATTORNEY WILSON: I object to
15 form.

16 A. You can assign a sedimentation
17 coefficient. Just, you know, they are
18 close by.

19 Actually looking more clearly, to
20 some extent it -- you know, you can call
21 it a shoulder, but it is two peaks, sort
22 of resolved. I tend to -- if it is
23 shoulder, it is hard to even see the peak
24 maximum basically. Here you have two

1 peaks. You can call out -- using the
2 maximum of each peak, you can call out
3 clearly the peak maximum. You can assign
4 the sedimentation coefficient to each peak
5 maximum.

6 BY ATTORNEY HACKMAN:

7 Q. So it looks like the collection
8 of peaks that we're discussing here runs
9 from somewhere between 60 and 80 S to
10 about 110 S? Am I in the ballpark?

11 A. Yes. It looks like about -- if
12 you -- are you going to -- you don't want
13 to include what they call the empty?
14 Correct? You want to leave that out?

15 Q. Well, here I have a question
16 then.

17 So does this what you call the
18 empty peak, is that peak fully resolved in
19 your opinion from these other peaks?

20 ATTORNEY WILSON: I object to
21 form.

22 A. You can see that. I mean you get
23 -- certainly the dotted is fully resolved.
24 Right?

1 The other two are very low in
2 amount. Yet you could make out a maximum
3 that you could assign there.

4 BY ATTORNEY HACKMAN:

5 Q. If you have an AAV species at a
6 very low concentration in a composition,
7 can it be difficult to identify that
8 species using sedimentation velocity AUC?

9 ATTORNEY WILSON: I object to
10 form.

11 A. It all depends on, you know, it
12 makes -- it all depends what you are
13 seeing. When you say low, I think it is a
14 matter of looking at what you are talking
15 about as opposed to making a general
16 statement saying low.

17 BY ATTORNEY HACKMAN:

18 Q. Now under this complex of peaks
19 in figure 3, is it possible that there are
20 other species that are present that we
21 don't see separate peaks for?

22 ATTORNEY WILSON: Objection;
23 foundation.

24 A. That is possible.

1 BY ATTORNEY HACKMAN:

2 Q. And what causes peaks to broaden
3 out like this?

4 ATTORNEY WILSON: Objection;
5 foundation.

6 A. They have different sedimentation
7 properties.

8 BY ATTORNEY HACKMAN:

9 Q. Is there a way for an ordinary
10 person skilled in the art could try to
11 make the peaks sharper?

12 A. I mean there are limitations to
13 what the technique can resolve. One of
14 the things that you might be able to do is
15 actually do these experiments at higher
16 speed. And actually I have been recently
17 working with several people -- actually
18 there are several -- some publications,
19 most recent publications, that point to
20 running the centrifuge at high speeds.

21 And this has been known since the
22 very beginning. Svedberg pointed out the
23 higher the speed, the rotational speed,
24 the better the opportunity for obtaining

1 higher resolution.

2 Q. Are there downsides to running
3 the experiment at higher speeds?

4 ATTORNEY WILSON: I object to
5 form.

6 A. You have less data. You just get
7 -- well, you don't get as many scans
8 potentially in a given run. That is
9 certainly one limitation.

10 But that -- as long as you get
11 enough scans, I wouldn't call that
12 necessarily a limitation.

13 BY ATTORNEY HACKMAN:

14 Q. So you get fewer scans, because
15 the particles are sedimenting faster
16 through the chamber?

17 A. Right.

18 Q. So there is less time to take
19 scans?

20 A. Right. Correct. And that
21 actually could be a benefit, because the
22 experiment is very short.

23 Q. So Le Bec here, however, filed a
24 patent, and they have this broad

1 collection of peaks.

2 Do you -- can you surmise a
3 reason that they would not have tried to
4 make these peaks sharper?

5 ATTORNEY WILSON: Objection;
6 foundation.

7 A. That wasn't their main objective
8 in this patent. They were working on
9 utilizing their gene -- the various types
10 of gene vectors to try -- I am assuming to
11 try to get optimum performance in terms of
12 reducing the amount of empty capsids.

13 BY ATTORNEY HACKMAN:

14 Q. So the goal of the Le Bec patent
15 was to compare the number of empty capsids
16 to species that contained some genomic
17 DNA? Right?

18 ATTORNEY WILSON: I object to
19 form.

20 A. I think their main purpose was to
21 get more production out of the vector
22 basically. So it was very common that
23 with AAV that they produce virus vectors,
24 a lot of them are empty basically, and

1 they found -- they demonstrate that this
2 type of a construct in cells that they are
3 using leads to productions that basically
4 you say maximizes the production of
5 complete AAVs basically. And certainly in
6 terms of the empty, that is very dramatic.

7 BY ATTORNEY HACKMAN:

8 Q. So their interest was more
9 focused on being able to track the empty
10 particles then?

11 ATTORNEY WILSON: I object to
12 form.

13 A. Not necessarily. I think at the
14 time most people were -- were interested
15 in empty/full by and large.

16 BY ATTORNEY HACKMAN:

17 Q. By at the time meaning in when
18 this came out in 2014?

19 A. Right.

20 Q. Under the heading of full, I will
21 focus on figure 3 again, not all of the
22 peaks correspond to particles having full
23 sets of genomic DNA? Right?

24 A. Yes. And actually the definition

1 of full is kind of, you know, from my
2 perspective, it is kind of sort of
3 misleading. It is a collection of virus
4 particles.

5 Q. It is a collection of virus
6 particles? What do you mean by a
7 collection of virus particles?

8 A. Well, you can see the different
9 peaks correspond to different
10 adeno-associated virus particles, and they
11 basically assigned the fastest sedimenting
12 peak, their complementary form, and the
13 most common aberrant form would be half
14 that basically, because it is missing the
15 complementary form. So they assign I
16 think the 90S material corresponding to
17 their incomplete -- one of their
18 incomplete forms.

19 Q. Incomplete form being that not
20 all of the genomic DNA --

21 A. Yes.

22 Q. -- has made it into the AAV?

23 A. Yes. Correct.

24 Q. Make sure to give time for her --

1 I don't want to get in trouble. I can see
2 her stewing over here. All right.

3 Okay. So we were talking about
4 there are some particles in here that have
5 -- that don't contain the full genomic --

6 A. The target, yes. The target
7 genome that they are trying to make.

8 Q. Now one of the things you can do
9 in sedimentation velocity AUC is to
10 measure the area below the peak? Right?

11 A. The area of the peak?

12 Q. Yes. That's right?

13 A. Right.

14 Q. And that is part of what needs to
15 be done in order to determine the
16 concentration of the particle species that
17 show up in that?

18 ATTORNEY WILSON: I object to
19 form.

20 A. Yes.

21 ATTORNEY WILSON: Sorry.

22 A. That is one of the -- yes.
23 Assuming -- yes.

24 BY ATTORNEY HACKMAN:

1 Q. So would an issue like the peaks
2 overlapping that you see in figure 3,
3 would that impact the accuracy by which a
4 person of ordinary skill in the art could
5 determine the concentration of the
6 different species?

7 ATTORNEY WILSON: Objection.

8 A. Yes.

9 ATTORNEY WILSON: Foundation.

10 Go ahead.

11 A. It is like chromatography. If
12 you have peaks overlapping, it is more
13 challenging. If it is really a side
14 shoulder and you can't even see the
15 maximum, it is really very difficult to
16 quantitate.

17 BY ATTORNEY HACKMAN:

18 Q. So would you say a prerequisite
19 to getting an accurate determination of
20 the quantity of an AAV particle species
21 would be to have well resolved peaks?

22 ATTORNEY WILSON: I object to
23 form.

24 A. Yes. Sure.

1 ATTORNEY HACKMAN: So I have
2 marked --

3 I can pause here if you need a
4 break, or we can keep going.

5 THE WITNESS: We can keep going.

6 ATTORNEY HACKMAN: Okay.

7 ATTORNEY WILSON: Do you have
8 enough water?

9 THE WITNESS: Yes. I am dry.

10 ATTORNEY HACKMAN: I am going to
11 mark or submit Exhibit 1024.

12 (Characterizing
13 Biopharmaceuticals using Analytical
14 Ultracentrifugation marked
15 Exhibit 1024 for identification.)

16 (Handing Exhibit 1024 to the
17 witness.)

18 BY ATTORNEY HACKMAN:

19 Q. Dr. Berkowitz, this is your
20 publication with John Philo from 2015?
21 Right?

22 A. Yes.

23 Q. So we were talking about in the
24 Le Bec reference we have these peaks that

1 overlap. Is that a product of something
2 that you have referred to in your
3 publication as diffusional broadening?

4 ATTORNEY WILSON: Objection;
5 foundation.

6 A. Can you repeat the question
7 again? Sorry.

8 BY ATTORNEY HACKMAN:

9 Q. Sure.

10 Let's actually go -- let's do a
11 little bit something different.

12 So let's go to page 230 of your
13 Exhibit 1024.

14 (Witness complying.)

15 A. Yes.

16 Q. Page 230.

17 A. 230.

18 Q. It looks like you are there.

19 A. 230.

20 Q. If we go back to the bottom
21 paragraph that is still complete?

22 A. Yes.

23 Q. Do you see that?

24 A. Still --

1 Q. I will start. It says "For
2 both."

3 A. Yes.

4 Q. I'm not exactly sure how to even
5 describe these annotations here.

6 A. Yes. I understand it. Yes. I
7 am sorry. Yes. But yes.

8 Q. Does the $ls_g(s)$ analysis and
9 $g(s)$ analysis?

10 A. Yes.

11 Q. Am I close enough --

12 A. Yes.

13 Q. -- in describing?

14 A. Yes.

15 Q. "For both $^{\wedge}ls_g(s)$ analysis and
16 $g(s)$ analysis the peaks from a single
17 species are, for the most common sized
18 protein drugs, fairly broad."

19 A. Correct.

20 Q. Did I read that correctly?

21 A. Yes.

22 Q. And then you go on to say:

23 "... even though the species has
24 a unique sedimentation coefficient, it

1 appears to have a spread of values."

2 Is that describing the phenomenon
3 we are seeing in the Le Bec figures where
4 there is a spreading of the peak?

5 ATTORNEY WILSON: I object to
6 form.

7 A. Yes. This -- with these
8 modalities, you are not deconvoluting the
9 confusion of the data, so they tend to be
10 broad basically. When you use SEDFIT, it
11 is basically trying to take into account
12 for the broadness of these peaks that you
13 see by sedimentation velocity. So it is
14 trying to figure out the diffusion.

15 And when it does that, it
16 tightens up the peak obviously, because it
17 is mathematically accounting for the
18 diffusion effect, which is very commonly,
19 prior to 2000, the development of SEDFIT,
20 the diffusion was not really taken
21 advantage of. So all of the results were
22 they always had the effect of diffusion in
23 these peaks. So they are broad.
24 Absolutely.

1 So now you have SEDFIT which
2 basically tries to mathematically
3 deconvolute out the diffusioning effects,
4 the broadening from the diffusion. They
5 get better resolution.

6 Needless to say, there are
7 limits. There could be other components
8 present. So it is -- that -- that becomes
9 a more prominent effect moving over to the
10 more modern modalities of velocity
11 sedimentation using, for example, SEDFIT.

12 There could be other species
13 present that account for the broadening
14 that you see.

15 Q. So if we can go back to Le Bec --

16 A. Right.

17 Q. -- to Exhibit 1006, and I need to
18 get back there myself.

19 (Witness complying.)

20 Q. Okay. I am just, for the clarity
21 of the record, I am back. We are talking
22 now again about page 25 of the Le Bec
23 reference, figures 2 and 3.

24 So we talked about SEDFIT, and

1 you mentioned that that allows for some of
2 the deconvolution of diffusion? Right?

3 A. Right. Correct.

4 Q. And you mentioned one of the
5 causes of or one of the limitations of
6 SEDFIT would be if there is a lot of
7 species that have similar sedimentation
8 coefficients?

9 A. Yes.

10 Q. So based on both -- let's start
11 with figure 2.

12 Based on figure 2, is it possible
13 that there are some species that are
14 underneath these peaks that we're not able
15 to see in this sedimentation distribution?

16 ATTORNEY WILSON: I object to
17 form.

18 A. It is conceivable. Even there is
19 a possibility that on a microlevel there
20 could be heterogenicity even in a peak
21 that looks symmetrical.

22 Q. So in order to have confidence in
23 using a sedimentation distribution to
24 quantify the species in a composition, the

1 sharper the peak, the more confidence you
2 would have?

3 ATTORNEY WILSON: I object to
4 form.

5 A. By and large, yes.

6 BY ATTORNEY HACKMAN:

7 Q. And you mentioned earlier that
8 what Le Bec was really trying to do here
9 was differentiate particles that had
10 genomic DNA contained within from those
11 that were empty? Right?

12 A. Right.

13 Q. And so for the purposes of
14 Le Bec's experiment, it wasn't so
15 important to be able to deconvolute the
16 peaks? Right?

17 ATTORNEY WILSON: I object to
18 form.

19 A. Well, they -- they want to see
20 what is in this preparation basically, and
21 this technique offers a way of
22 characterizing what heterogeneity is
23 present in the preparation.

24 BY ATTORNEY HACKMAN:

1 Q. But they didn't quantify the --
2 all of the peaks? Right?

3 ATTORNEY WILSON: I object to
4 form.

5 A. They didn't quantify all, but
6 their quantification was simply based on
7 signal.

8 BY ATTORNEY HACKMAN:

9 Q. Based on signal? What do you
10 mean by that?

11 A. Just looking at the signal
12 output. You integrate the area under that
13 peak basically, assuming everything has
14 the same response.

15 Q. A few other questions just
16 generally about particles and the use of
17 SV, sedimentation velocity, SV.

18 If you have particles that have a
19 tendency to aggregate, would that
20 potentially impact the ability to
21 accurately identify their sedimentation
22 coefficient?

23 ATTORNEY WILSON: Objection;
24 foundation.

1 A. If they aggregate, that basically
2 changes their sedimentation coefficient.

3 BY ATTORNEY HACKMAN:

4 Q. And so that the aggregates would
5 have -- well, how do aggregates change the
6 sedimentation coefficient?

7 A. They change them by mass
8 predominantly and then also frictional
9 coefficient. You have got a different --
10 you have a different shaped particle.

11 Q. Could the tendency of particles
12 to aggregate cause peaks to broaden?

13 ATTORNEY WILSON: Objection;
14 foundation.

15 A. No. They -- they would basically
16 create their own peaks by and large.

17 BY ATTORNEY HACKMAN:

18 Q. All right. I just wanted to ask
19 you a few questions about your declaration
20 again. We can go to paragraph 52.

21 (Witness complying.)

22 Q. It is on page 26.

23 A. Okay.

24 Q. Are you there, Dr. Berkowitz?

1 A. Yes.

2 Q. Great.

3 So in these paragraphs, you are
4 discussing the research of Dr. Barrie
5 Carter's laboratory? Right?

6 A. Yes.

7 Q. And your declaration cites
8 several publications that were authored or
9 co-authored by Dr. Carter? Right?

10 A. Right.

11 Q. So have you ever met Dr. Carter
12 personally?

13 A. No.

14 Q. Have you ever communicated at all
15 in any way with Dr. Carter?

16 A. No.

17 Q. Have you ever attended a
18 conference presentation by Dr. Carter?

19 A. No.

20 Q. So before your work in preparing
21 your declaration, had you previously read
22 any of the Carter publications that you
23 cited in your declaration?

24 A. No. I made light of them

1 basically due to a lot of this work.

2 Q. So do you recall whether you in
3 the past incidentally read any of Carter's
4 publications?

5 A. No. I mean -- no.

6 Q. Would you consider the references
7 that you have cited in your declaration
8 from Dr. Carter's laboratory as being
9 foundational prior art for AAV assembly?

10 A. Yes.

11 Q. And were the Carter laboratories'
12 publications foundational for your
13 conclusion that the claims of the '894
14 patent were obvious?

15 ATTORNEY WILSON: I object to
16 form.

17 A. That they fall into a category
18 that, yes, they are obvious, yes.

19 BY ATTORNEY HACKMAN:

20 Q. And that was based in part on
21 your reading of the Carter laboratory
22 publications?

23 A. Yes. Realizing that they fall
24 into this category.

1 Q. What do you mean by category?

2 A. Basically that you have formed
3 these AAV particles from a preformed
4 capsid, and then the DNA is inserted,
5 which would imply that while all of these
6 particles basically have the same shape,
7 okay, and with the same shape you would
8 look at the Svedberg equation, and they
9 all basically have the same frictional
10 coefficient. It is the mass, actually the
11 buoyant mass that changes, which drives
12 the sedimentation.

13 Q. You mentioned earlier, though,
14 that shape and size of a particle are not
15 the only factors that determine friction?
16 Right?

17 ATTORNEY WILSON: I object to
18 form.

19 A. Shape? Excuse me. Could you
20 repeat that?

21 BY ATTORNEY HACKMAN:

22 Q. Sure. Sure.

23 So you just mentioned that one of
24 your reasons for determining the claimed

1 method to have been obvious was your
2 opinion that the way that the AAV
3 particles are assembled via inserting DNA
4 into a preformed capsule makes it so that
5 there is no frictional differences between
6 different particles? Is that correct?

7 A. That's correct. Yes.

8 Q. And so my question was -- it may
9 be a different question.

10 Could there be other --

11 ATTORNEY HACKMAN: Or excuse me.

12 Let me withdraw that.

13 BY ATTORNEY HACKMAN:

14 Q. You had mentioned earlier so size
15 and shape are not the only properties of a
16 particle that affect its frictional
17 coefficient? Right?

18 ATTORNEY WILSON: Objection to
19 form.

20 A. Yes. Buoyant mass. The amount
21 of actual material present.

22 BY ATTORNEY HACKMAN:

23 Q. You also mentioned some things
24 like hydration? Right?

1 ATTORNEY WILSON: I object to
2 form.

3 A. Yes.

4 BY ATTORNEY HACKMAN:

5 Q. And that hydration can be
6 impacted by chemical properties? Right?

7 A. It is conceivable. Yes.

8 Q. And does the, in your opinion,
9 the assembly method of these particles
10 mean that they all have the same chemical
11 properties with respect to hydration?

12 A. Unless something significantly
13 changes. If they -- basically you have an
14 assembled capsid consisting of the same
15 protein units, basically they should be
16 the same and should give you the same
17 hydration basically.

18 Q. So the different amount of
19 capsidated, so DNA that has been input
20 into the capsid, that would not in your
21 opinion impact any of the chemical
22 properties that affect the frictional
23 coefficient of the particles?

24 A. That -- the -- certainly it is

1 all that material is on the internal. So
2 whatever interactions the inside are not
3 necessarily being implemented on the
4 outside.

5 Q. I think you mentioned that charge
6 could be a factor in frictional
7 coefficient?

8 ATTORNEY WILSON: I object to the
9 form.

10 A. It is potential. If it is on the
11 surface, it could influence the hydration
12 basically.

13 BY ATTORNEY HACKMAN:

14 Q. So your scientific conclusion is
15 that a person of ordinary skill in the art
16 would not have considered the amount of
17 DNA within the capsid to impact the
18 external charge of the particle?

19 ATTORNEY WILSON: Objection;
20 foundation.

21 A. Can you repeat that?

22 BY ATTORNEY HACKMAN:

23 Q. Sure.

24 So DNA has a charge? Right?

1 A. Right.

2 Q. And so if different amounts of
3 DNA are inserted into a capsid, would a
4 person of ordinary skill in the art
5 consider that potentially the overall
6 charge of the particles was different?

7 ATTORNEY WILSON: Objection;
8 foundation.

9 A. It is possible, but these -- you
10 know, these particles by size exclusion
11 don't separate out. So you have
12 information that basically reflects the
13 hydrations of these particles are the
14 same. But it is conceivable.

15 BY ATTORNEY HACKMAN:

16 Q. So you mentioned size exclusion?

17 A. Yes.

18 Q. Could you point out where in your
19 declaration that you discuss the size
20 exclusion?

21 A. I don't have it in there. No.

22 Q. Okay. So when did you develop
23 this opinion on the size exclusion issue?

24 ATTORNEY WILSON: I object to

1 form.

2 A. In seeing Karen Fleming's
3 deposition.

4 BY ATTORNEY HACKMAN:

5 Q. Her declaration?

6 A. Declaration. Excuse me.

7 Q. Okay.

8 A. Sorry.

9 Q. And can you recall what it was in
10 her declaration that led you to this?

11 A. Well, she invoked hydration as a
12 factor leading to differences in size.

13 Q. And hydration was not something
14 that you addressed in your declaration?
15 Correct?

16 ATTORNEY WILSON: I object to
17 form.

18 A. That's correct.

19 BY ATTORNEY HACKMAN:

20 Q. And so in her invocation of
21 hydration, do you recall what specifically
22 she said that made you consider the issue
23 of size exclusion chromatography?

24 ATTORNEY WILSON: I object to

1 form.

2 A. She was talking about external
3 surface pop changes.

4 BY ATTORNEY HACKMAN:

5 Q. Do you recall whether there was
6 any particular reference that she cited in
7 that discussion?

8 ATTORNEY WILSON: The same
9 objection.

10 A. She might have, but I just don't
11 recall that.

12 ATTORNEY HACKMAN: Why don't we
13 go -- are you good with a break?

14 THE WITNESS: I'm fine.

15 ATTORNEY WILSON: I could use a
16 break to tell you the truth, so if we
17 could go off the record.

18 ATTORNEY HACKMAN: This maybe is
19 a good place to pause.

20 THE VIDEOGRAPHER: The time is
21 10:28 a.m., and we are off the record.

22 (Recess taken at 10:28 a.m.)

23 (Recess ended at 10:41 a.m.)

24 THE VIDEOGRAPHER: The time is

1 10:41 a.m., and we are on the record.

2 BY ATTORNEY HACKMAN:

3 Q. All right. Dr. Berkowitz, did
4 you discuss any of your testimony with
5 counsel during the break?

6 A. No.

7 Q. Thank you.

8 So I want to go to paragraph 38
9 of your declaration.

10 (Witness complying.)

11 A. Am I -- did you say page --

12 Q. Paragraph 38.

13 A. Paragraph 38. I am looking over
14 at you.

15 ATTORNEY WILSON: I am doing the
16 same thing.

17 BY ATTORNEY HACKMAN:

18 Q. It is on page 19. Are you there?

19 A. (No audible response.)

20 Q. You are there, Dr. Berkowitz?

21 A. Yes.

22 Q. Thank you.

23 So the equation that you give in
24 paragraph 38, is that the Svedberg

1 equation?

2 A. Yes.

3 Q. And in the numerator of the
4 Svedberg equation, does that account --
5 actually let me just ask the question.

6 So what does the numerator of the
7 Svedberg equation address?

8 A. The frictional effect.

9 Q. Not the denominator. The
10 numerator?

11 A. The buoyancy effects.

12 Q. And the buoyancy effects would
13 include the mass of the particle? Right?

14 A. Correct.

15 Q. And it would include the density
16 of the particle? Right?

17 A. The V bar.

18 Q. The V bar is the density?

19 A. It is the amount displaced by the
20 particle relative to its mass.

21 Q. Sedimentation then is
22 proportional as to the buoyant density of
23 the particle?

24 A. The buoyant density. Yes.

1 Q. I want to make sure we don't talk
2 over each other for the benefit of the
3 reporter.

4 A. Sorry.

5 Q. No worries.

6 And then the denominator, that --
7 why don't you just explain what the
8 denominator of the Svedberg equation
9 accounts for.

10 A. That is the friction.

11 Q. And so the Svedberg equation --
12 or excuse me -- the coefficient S value --

13 A. Right.

14 Q. -- is inversely proportionate to
15 friction? Right?

16 A. Correct.

17 Q. So if you have a situation with
18 two particle species, one of them is a
19 more dense or denser particle, and the
20 other particle is less dense --

21 A. Right.

22 Q. -- and the less dense particle
23 has a higher S value, what does that tell
24 you about the friction?

1 ATTORNEY WILSON: Objection;
2 foundation.

3 A. It is less.

4 BY ATTORNEY HACKMAN:

5 Q. If the denser particle has a
6 lower S value, that means that then -- a
7 less dense particle, that means that it
8 must have a higher frictional coefficient?

9 ATTORNEY WILSON: Objection.

10 A. Yes.

11 ATTORNEY WILSON: Foundation.

12 BY ATTORNEY HACKMAN:

13 Q. And so in a comparison of like
14 that --

15 ATTORNEY HACKMAN: Let me
16 withdraw that question.

17 BY ATTORNEY HACKMAN:

18 Q. So in a situation where the
19 denser particle sediments more slowly than
20 a less dense particle, that is telling us
21 something about the surface of the denser
22 particle having a higher friction?

23 ATTORNEY WILSON: I object to
24 form.

1 A. No. Not necessarily.

2 BY ATTORNEY HACKMAN:

3 Q. Okay. So what could be the cause
4 of a more dense particle sedimenting
5 slower than a less dense particle?

6 ATTORNEY WILSON: I object to
7 form.

8 A. A more dense particle sedimenting
9 slower? It has a higher frictional
10 coefficient.

11 ATTORNEY HACKMAN: I'm going to
12 mark as another exhibit, Exhibit 1007.

13 (Replication of Mammalian
14 Parvoviruses marked Exhibit 1007
15 for identification.)

16 (Handing Exhibit 1007 to
17 witness.)

18 BY ATTORNEY HACKMAN:

19 Q. And Dr. Berkowitz, you are
20 familiar --

21 A. Yes.

22 Q. -- with the reference that I just
23 handed you?

24 A. Yes. Sorry.

1 Q. And I believe you referred to
2 Exhibit 1007 in your declaration as the
3 de la Maza publication?

4 A. Yes.

5 Q. Let me know when you are ready --

6 A. Yes.

7 Q. -- to answer questions.

8 A. I am.

9 Q. Great.

10 So in the de la Maza paper,
11 Exhibit 1007, fractionated AAV particles
12 were subjected to equilibrium density
13 centrifugation in a cesium chloride
14 density gradient? Right?

15 A. Correct.

16 Q. And this is a form of
17 sedimentation equilibrium? Right?

18 A. Correct.

19 Q. And so the sedimentation
20 equilibrium AUC, the result is not
21 affected by the particle friction? Right?

22 A. Correct.

23 Q. So the particles are separated
24 solely by their density? Right?

1 ATTORNEY WILSON: Objection --

2 A. Buoyant density.

3 ATTORNEY WILSON: -- to form.

4 BY ATTORNEY HACKMAN:

5 Q. The particles are separated by
6 their buoyant density? Right?

7 A. Right.

8 Q. So let's go to, on page 195 of
9 Exhibit 1007.

10 (Witness complying.)

11 Q. Do you see table 1,
12 Dr. Berkowitz?

13 A. Where are we?

14 Q. I am sorry. This is the de la
15 Maza paper.

16 A. Right.

17 Q. It is the -- it has Ward and
18 Tattersall as editors on the front. And
19 we look at page 195 of the publication
20 itself. Do you see that?

21 A. The article is indicating 195
22 page.

23 Q. That's right?

24 A. Correct.

1 Q. And you see table 1 there?

2 A. Yes.

3 Q. And the density -- the column
4 that corresponds to the density of the
5 virion -- is that how you pronounce it?

6 A. Virion.

7 Q. Virion. I apologize.

8 -- in grams per centimeter
9 cubed --

10 A. Yes.

11 Q. -- that is this leftmost column?
12 Right?

13 A. Correct.

14 Q. And it shows three, on the DNA
15 column on the farthest left, there is
16 intact Type 1 and Type 2 DNA? Right?

17 A. On intact, yes. Your DNA column.
18 Correct. I have got it.

19 Q. And would you understand these
20 three types of DNA to be different from
21 each other?

22 ATTORNEY WILSON: I object to
23 form.

24 A. So your question is would the DNA

1 from the -- oh -- the DNA? Yes. Okay.

2 So that is the DNA from these buoyant

3 particles, AAV particles? Right? I

4 guess. Yes. Okay. Okay.

5 BY ATTORNEY HACKMAN:

6 Q. Right. Actually I am going to
7 back up a little step in this discussion
8 of the paper.

9 So the de la Maza paper, this
10 Exhibit 1007, the authors did not conduct
11 any sedimentation velocity AUC with an
12 intact AAV particle? Right?

13 A. Yes. That's correct.

14 Q. So that the sedimentation
15 velocity AUC experiments were done
16 strictly with DNA that had been released
17 from those particles? Correct?

18 A. Correct.

19 Q. And after releasing the DNA from
20 the particles, the authors used
21 sedimentation velocity AUC to determine
22 the sedimentation coefficients for the
23 DNA --

24 A. Correct.

1 Q. -- that had been released?

2 A. Correct.

3 Q. So in this case the sedimentation
4 coefficients for each of the types of DNA
5 correspond to the naked DNA itself?
6 Right?

7 A. Correct.

8 Q. I am sorry. What was that?

9 A. Correct.

10 Q. Thank you. Sorry. I just
11 couldn't hear. Okay.

12 So we have on the farthest level
13 column we have intact Type 1 and Type 2
14 DNA? Right?

15 A. Correct.

16 Q. And in the next column, we have
17 the density of the virion as 1.41 for the
18 intact Type 1 and Type 2 DNA? Right?

19 A. Correct.

20 Q. So would you understand this
21 table would be saying that these DNA are
22 the DNA that have been released from the
23 1.41 density virion particles? Right?

24 A. Yes.

1 Q. Now it appears in the initial --
2 in the first alkaline sucrose experiment
3 that the S values for the intact and
4 Type 1 DNA have the same sedimentation
5 coefficients? Right?

6 A. Correct.

7 Q. But the Type 2 DNA has a
8 different sedimentation coefficient?
9 Right?

10 A. That's right.

11 Q. And the authors concluded that
12 the sedimentation coefficients for the
13 Type 2 DNA indicates that this has a lower
14 molecular weight than the other DNA? Is
15 that right?

16 A. That's correct.

17 Q. So would you agree,
18 Dr. Berkowitz, that the authors have shown
19 that the 1.41 density particle can
20 intercalate different sizes --

21 ATTORNEY HACKMAN: Actually let
22 me withdraw that question.

23 BY ATTORNEY HACKMAN:

24 Q. Can you tell from the paper and

1 the data in table one that the 1.41
2 density virion particles contain different
3 amounts of DNA?

4 ATTORNEY WILSON: I object to
5 form.

6 A. That is what it seems to
7 indicate. Yes.

8 BY ATTORNEY HACKMAN:

9 Q. So the three particles
10 corresponding to the intact Type 1 and
11 Type 2 all have identical density? Right?

12 A. Right.

13 Q. But they have different amounts
14 of genome that has been encapsidated in
15 size? Right?

16 ATTORNEY WILSON: I object to
17 form.

18 A. That's correct.

19 BY ATTORNEY HACKMAN:

20 Q. So from this, would this data
21 tend to indicate that the density of an
22 AAV particle is not solely determined by
23 the size of the genome inside?

24 ATTORNEY WILSON: I object to

1 form.

2 A. It would look like that's the
3 case. Yes.

4 BY ATTORNEY HACKMAN:

5 Q. I want to go back to your
6 declaration. This is Exhibit 1004.

7 (Witness complying.)

8 A. Sorry.

9 Q. And let's go to paragraph 58.
10 Actually, let's go to paragraph 168.
11 Sorry.

12 So paragraph 168 is on page 80 of
13 your declaration.

14 A. 158?

15 Q. 168. Paragraph 168.

16 A. Oh, excuse me.

17 (Witness complying.)

18 Q. So at the very bottom of that
19 paper, you quote a different de la Maza
20 paper, Exhibit 1008, and say that, and you
21 quote it saying the:

22 "... particle density has an
23 approximately direct linear relationship
24 to the [DNA] strand length."

1 Right?

2 A. Right.

3 Q. So the data in the exhibit that
4 we were just discussing doesn't seem to
5 indicate a direct linear relationship
6 between density and DNA strand length?
7 Right?

8 ATTORNEY WILSON: I object to
9 form.

10 A. I guess you would have to say
11 that basically. Yes.

12 ATTORNEY HACKMAN: Let's mark
13 Exhibit 1008.

14 (Article entitled "Molecular
15 Structure of Adeno-associated Virus
16 Variant DNA" marked Exhibit 1008
17 for identification.)

18 (Handing Exhibit 1008 to
19 witness.)

20 BY ATTORNEY HACKMAN:

21 Q. So this publication is another
22 publication from the Carter lab? Right?

23 A. Yes.

24 Q. And this was another publication

1 that you cited in your declaration?

2 Right?

3 A. Correct.

4 Q. And in fact, this Exhibit 1008 is
5 the reference that you quoted in your
6 declaration at paragraph 168? Right?

7 A. Right.

8 Q. So this is -- this is the
9 publication where the quote that you say
10 "... particle density has an approximately
11 direct linear relationship to the DNA
12 strand length," this is the publication?
13 Right?

14 A. Correct. Which comes later.
15 Correct? Than --

16 Q. Yes. This is in April of 1980.

17 A. As opposed to 2078 in the Cold
18 Spring Harbor.

19 Q. 1978. Yes.

20 A. Okay.

21 Q. So can you go to page 3202 of
22 Exhibit 1008?

23 (Witness complying.)

24 A. 3202?

1 Q. That's right. Yes.

2 A. Okay.

3 Q. And you see there is a

4 "Discussion" section --

5 A. Yes.

6 Q. -- on 3202?

7 And if we go to the second
8 sentence, I will just read it:

9 "These molecules appear to be
10 encapsidated in AAV virions with usually
11 only one stand per particle; thus, the
12 particle density has an approximately
13 direct linear relationship to the strand
14 length."

15 A. Right.

16 Q. Did I read that right?

17 A. Yes.

18 Q. And it has a footnote here?

19 Right?

20 A. Yes.

21 Q. The 3. And if we go down to the
22 bottom of the column on the left side of
23 32, it refers to the sentence coming from
24 unpublished observations? Right?

1 A. Can you -- so you -- you said the
2 footnote?

3 Q. That's right.

4 A. Yes. So that appears after
5 strand length, that number 3?

6 Q. That's right.

7 A. And we go down to the bottom.
8 That is a reference.

9 Q. Right. And it refers to this as
10 unpublished observations? Right?

11 A. Right.

12 Q. So would a person of ordinary
13 skill in the art reading this article
14 understand that this statement that "the
15 particle density has an approximately
16 direct linear relationship to the strand
17 length" be derived from these unpublished
18 results that are cited in the paper?

19 ATTORNEY WILSON: I object to
20 form.

21 A. Right.

22 BY ATTORNEY HACKMAN:

23 Q. Sorry?

24 A. Correct. Sorry.

1 Q. Correct.

2 So you haven't seen this
3 unpublished data? Right?

4 A. That's correct. I believe yes.

5 Q. And --

6 A. Yes.

7 Q. And when we were talking just
8 about the data that was in table one of
9 the 1978 de la Maza publication, which is
10 Exhibit 1007 --

11 A. Correct.

12 Q. -- you had mentioned that that
13 data was inconsistent with a direct linear
14 relationship? Right?

15 ATTORNEY WILSON: I object to the
16 form.

17 A. Yes. Apparently yes.

18 BY ATTORNEY HACKMAN:

19 Q. So we at least know that there
20 are exceptions to this statement that is
21 relating to unpublished data? Right?

22 ATTORNEY WILSON: I object to
23 form.

24 A. It could be. Yes. In general.

1 BY ATTORNEY HACKMAN:

2 Q. And so we don't know how often
3 this approximate linear relationship holds
4 for AAV particles? Right?

5 ATTORNEY WILSON: I object to
6 form.

7 A. That's -- that's true. That is
8 one of the reasons I pointed out that this
9 is a later publication. Correct.

10 BY ATTORNEY HACKMAN:

11 Q. Are you aware of whether the
12 Carter laboratory did eventually publish
13 this data?

14 A. I'm not aware. No.

15 Although -- can I add something
16 here?

17 I mean they have repeatedly said
18 in their public indications that that they
19 find particles between full and empty, you
20 know, existing across the whole board
21 basically, and there is this progression
22 that the linear density follows with the
23 size of the DNA.

24 Q. So the goals of the de la Maza

1 and Carter publications, though, was
2 focused on ascertaining the mechanism by
3 which AAV particles were assembled?
4 Right?

5 ATTORNEY WILSON: I object to
6 form.

7 A. That is one of the things they
8 brought out. Yes.

9 BY ATTORNEY HACKMAN:

10 Q. So is it possible that this
11 general observation that supports their
12 theory? Right?

13 A. Right.

14 Q. But isn't it possible also that
15 there are often exceptions to this direct
16 strand length -- excuse me -- this direct
17 linear relationship?

18 ATTORNEY WILSON: I object to
19 form.

20 A. It is conceivable, yes.

21 ATTORNEY HACKMAN: Okay. I am
22 going to bring out another publication,
23 another exhibit. All right. This is
24 Exhibit 1013.

1 (Article entitled "Heavy and
2 Light Particles of Adeno-Associated
3 Virus" marked Exhibit 1013 for
4 identification.)

5 (Handing Exhibit 1013 to
6 witness.)

7 BY ATTORNEY HACKMAN:

8 Q. And this is another reference
9 that was authored by de la Maza and
10 Carter? Right?

11 A. Yes.

12 Q. And this was another reference
13 that you cited in your declaration?
14 Right?

15 A. Yes.

16 Q. So let's turn to page 1129 of
17 this Exhibit 1013.

18 (Witness complying.)

19 Q. And I think that is the front
20 page. Have you had an opportunity to
21 review the publication adequately?

22 A. Yes.

23 Q. So do you recall that this
24 publication discusses there being two AAV

1 particles having different densities, 1.45
2 grams per centimeter cubed and 1.41 grams
3 per centimeter cubed?

4 A. Yes.

5 Q. And in fact they mention these
6 two particles in the abstract? Right?

7 A. Correct.

8 Q. And these were densities that
9 were determined by this sedimentation
10 equilibrium using cesium chloride? Right?

11 A. Correct.

12 Q. Now in the earlier de la Maza
13 publication that was from 1978, that
14 publication did not use sedimentation
15 velocity AUC to study its particles?
16 Right?

17 A. Correct.

18 Q. But now this March 1980
19 publication of de la Maza and Carter, they
20 do use sedimentation velocity AUC to study
21 AAV particles? Right?

22 A. Correct.

23 Q. And so I am just going to -- we
24 will use the abstract. It says:

1 "The main component from this
2 band" --

3 And I am understanding first that
4 "this band" is referring to the 1.45 gram
5 per centimeter cubed band? Is that
6 reasonable?

7 A. Yes.

8 Q. So it says:

9 "The main component from this
10 band had a smaller S value (109) than the
11 main component from the 1.41 band (111S),
12 although both had the same DNA/protein
13 ratio and the same density in metrizamide
14 gradients."

15 A. Yes. Right.

16 Q. Okay. Let's unpack this in
17 pieces here.

18 So we have two particles with
19 identical -- with different densities?
20 Right?

21 A. Right.

22 Q. Would you agree that these two
23 particles have the identical DNA
24 content --

1 A. Sure.

2 Q. -- of encapsidated inside?

3 ATTORNEY WILSON: I object to
4 form.

5 A. Yes.

6 BY ATTORNEY HACKMAN:

7 Q. And would you agree that from
8 what we can tell in this publication that
9 they had the same amount of capsid protein
10 present?

11 ATTORNEY WILSON: I object to
12 form.

13 A. In that -- there is -- there
14 might be some element of questioning.
15 They do say that it has the same -- do
16 they say the same protein? -- the same
17 DNA-to-protein ratio? Right?

18 BY ATTORNEY HACKMAN:

19 Q. That's right.

20 A. Right.

21 Q. Can you think of another way that
22 a DNA-to-protein ratio would be -- would
23 indicate a different amount of capsid
24 protein?

1 ATTORNEY WILSON: I object to
2 form.

3 A. No.

4 BY ATTORNEY HACKMAN:

5 Q. Okay. So would you agree that
6 the denser component sediments at a slower
7 rate than the less dense component in this
8 composition?

9 A. That is what they're saying.
10 Yes.

11 Q. What did that tell you about each
12 particle's frictional coefficient?

13 ATTORNEY WILSON: I object to
14 form.

15 A. It indicated that there is some
16 potential difference basically.

17 BY ATTORNEY HACKMAN:

18 Q. Do you have -- actually let's go
19 -- let's go to another page of this
20 publication.

21 So if we go to page 1136 of
22 Exhibit 1008 -- excuse me -- 1013,
23 page 1136 of Exhibit 1013.

24 ATTORNEY WILSON: Which page

1 again? I am sorry.

2 ATTORNEY HACKMAN: 1136.

3 (Witness complying.)

4 THE WITNESS: Yes.

5 BY ATTORNEY HACKMAN:

6 Q. And if you look in the right
7 column, do you see the sentence that says:

8 "We found that the 1.41 component
9 has a slightly higher S value (111) than
10 the 1.45 particle (109)"?

11 Do you see that?

12 A. Yes.

13 Q. And a couple of sentences down,
14 it says:

15 "This difference in sedimentation
16 value corresponds with the reported
17 smaller diameter of the 1.45 band when
18 compared by the electron microscope with
19 the 1.41 region."

20 Do you see that?

21 A. Yes.

22 Q. So just to start, these two
23 particles having the same DNA content and
24 same DNA-to-protein ratio have different

1 diameters? Right?

2 ATTORNEY WILSON: I object to
3 form.

4 A. That's what they are saying.
5 Yes.

6 BY ATTORNEY HACKMAN:

7 Q. And would the difference of
8 diameters in your opinion be a factor for
9 why the one of the particles is denser
10 than the other?

11 ATTORNEY WILSON: Objection;
12 lacks foundation.

13 A. Yes.

14 BY ATTORNEY HACKMAN:

15 Q. And so maybe you can expound. Is
16 a smaller diameter particle would be
17 expected to be more dense? Right?

18 ATTORNEY WILSON: Lacks
19 foundation.

20 A. Yes.

21 BY ATTORNEY HACKMAN:

22 Q. So would this indicate to you
23 that AAV particles having identity --
24 identical genome compositions can have

1 different size and shape?

2 ATTORNEY WILSON: I object to
3 form.

4 A. That is basically what it is --
5 what it implies.

6 BY ATTORNEY HACKMAN:

7 Q. Does it imply it or does it just
8 teach that?

9 ATTORNEY WILSON: I object to
10 form.

11 A. It implies that basically.

12 BY ATTORNEY HACKMAN:

13 Q. What do you mean by "imply"?

14 A. That would be a conclusion
15 basically.

16 Q. Does that tell us anything about
17 differences in structural confirmation
18 between the two particles?

19 ATTORNEY WILSON: I object to
20 form.

21 A. Yes.

22 BY ATTORNEY HACKMAN:

23 Q. So can we go back to
24 paragraph 168 of your declaration on

1 page 80?

2 (Witness complying.)

3 A. 158?

4 Q. Page 80, paragraph 168.

5 A. Paragraph?

6 Q. I am sorry. Page 80,
7 paragraph 168.

8 A. Oh, 80? 80?

9 (Witness complying.)

10 A. Oh, 168?

11 Q. 168.

12 A. Oh, 168. Sorry. Okay.

13 Q. Now you say in this first
14 sentence:

15 "Because AAV assembly occurs via
16 packaging of DNA into preformed capsids, a
17 POSA would understand that empty AAV
18 particles, particles containing fragmented
19 genomes, and particles containing complete
20 genomes are all approximately the same
21 size and shape."

22 A. Correct.

23 Q. Now we just discussed this
24 Exhibit 1013 of de la Maza and Carter,

1 showing that particles appear like they
2 can have different sizes and shape?
3 Right?

4 ATTORNEY WILSON: I object to
5 form.

6 A. That appears to be the case.
7 Yes.

8 BY ATTORNEY HACKMAN:

9 Q. And this Exhibit 1013 actually is
10 later in time in terms of its publication
11 date than the Exhibit 1007 that you cite
12 for de la Maza --

13 A. Yes.

14 Q. -- and Carter? Right?

15 A. Yes.

16 Q. Would you agree that maybe this
17 understanding of a POSA of genomes of
18 being approximately all the same size and
19 shape may not actually be what a person of
20 ordinary skill in the art would understand
21 about these particles?

22 ATTORNEY WILSON: Object to form
23 and foundation.

24 A. There is overall data. I mean

1 you have a lot of data, and there is this
2 trend, but there could be defective
3 particles or something that they had that
4 may cause a particle to undergo some
5 change that they're just, you know, they
6 are not aware of, and yet they
7 characterize it, and, yes, it falls out of
8 that progression.

9 BY ATTORNEY HACKMAN:

10 Q. Now another observation that
11 Exhibit 1013 had was that the particles
12 exhibited -- the particles having the
13 1.45 grams per centimeter cubed and the
14 1.41 grams per centimeter cubed had
15 different infectivities? Right?

16 A. That's correct.

17 Q. And would you agree that in gene
18 therapy you would want to -- you would be
19 concerned -- a person of ordinary skill in
20 the art would be concerned about particles
21 having different infectivity in a gene
22 therapy composition? Right?

23 ATTORNEY WILSON: I object to
24 form.

1 A. Right.

2 BY ATTORNEY HACKMAN:

3 Q. And so in terms of characterizing
4 a gene therapy composition, if there is an
5 error in the calculation of impurities --

6 ATTORNEY HACKMAN: Actually let
7 me withdraw that.

8 BY ATTORNEY HACKMAN:

9 Q. In characterizing a gene therapy
10 composition, if there is an error in the
11 analysis of the amounts of different
12 species present, that could impact the
13 infectivity of that composition? Right?

14 ATTORNEY WILSON: I object to
15 form.

16 A. Right.

17 BY ATTORNEY HACKMAN:

18 Q. And infectivity would be a
19 concern for the efficacy of that
20 composition? Right?

21 A. Yes.

22 Q. And infectivity could also be a
23 concern for the safety of that
24 composition? Right?

1 A. Yes.

2 Q. So would you agree that the
3 stakes of analyzing an AAV composition
4 accurately are high for its efficacy and
5 safety?

6 ATTORNEY WILSON: Object to form.

7 A. Absolutely. Yes.

8 ATTORNEY HACKMAN: I am going to
9 go -- bear with me for just a minute.

10 (Pause.)

11 ATTORNEY HACKMAN: Okay. I am
12 going to mark another exhibit.

13 This is Exhibit 1026.

14 (Article entitled "Empty
15 virions in AAV8 vector preparations
16 reduce transduction efficiency and
17 may cause total viral particle
18 dose-limiting side effects" marked
19 Exhibit 1026 for identification.)

20 (Handing Exhibit 1026 to
21 witness.)

22 BY ATTORNEY HACKMAN:

23 Q. And, Dr. Berkowitz, are you
24 familiar with this --

1 A. Yes.

2 Q. -- exhibit?

3 A. Yes.

4 Q. And just let me know when you are
5 ready to answer questions.

6 A. Yes.

7 Q. Okay. Just to confirm, if we
8 could go back to your 168 -- paragraph 168
9 of your declaration.

10 A. Correct.

11 Q. This is the same publication of
12 Gao, Exhibit 1026, that you are referring
13 to in your declaration here?

14 A. That's correct.

15 Q. So let's go to page 2 of Gao,
16 which is what you cite in this paragraph.

17 (Witness complying.)

18 Q. So would you agree that Gao is
19 analyzing completely empty and partially
20 empty AAV8 particles?

21 A. Yes.

22 Q. And this figure 1A, which shows
23 these electron micrograph images, are
24 showing both collection of AAV8 particles?

1 A. Yes.

2 Q. And from this image, you say that
3 these images show full and empty AAV
4 particles with the same size and shape?

5 A. Well, yes.

6 Q. So to confirm, however, that you
7 did not conduct any quantitative analysis
8 of these figures?

9 A. They didn't. No.

10 Q. The Gao authors do not --

11 A. Right.

12 Q. -- conduct any quantitative
13 analysis?

14 A. Right.

15 Q. In your declaration, you also did
16 not conduct any quantitative analysis?

17 A. That's correct.

18 Q. And your reliance on these images
19 was to determine whether there were
20 differences in particle shape and size
21 that would be impactful on the particle
22 frictional coefficient? Right?

23 ATTORNEY WILSON: I object to
24 form.

1 A. Yes.

2 BY ATTORNEY HACKMAN:

3 Q. Are these the types of images
4 that a person of ordinary skill in the art
5 would look at to ascertain whether or not
6 two different species of AAV particles
7 would have different frictional
8 coefficients?

9 ATTORNEY WILSON: I object to
10 form.

11 A. They are representative.

12 BY ATTORNEY HACKMAN:

13 Q. So in your opinion, there is
14 sufficient resolution at the surface level
15 to see differences in particle shape or
16 size that would impact frictional
17 coefficients?

18 A. Qualitatively, yes.

19 Q. Is frictional coefficient
20 qualitative, though?

21 ATTORNEY WILSON: I object to
22 form.

23 A. No. It can be quantitative. So
24 could these pictures. You could

1 quantitate these.

2 BY ATTORNEY HACKMAN:

3 Q. You did not quantitate these?

4 A. No, I did not.

5 Q. And the authors did not
6 quantitate these?

7 A. That's correct.

8 Q. So if we go to page 6 of Gao.

9 (Witness complying.)

10 Q. We will start on the right-hand
11 column of Exhibit 1026, page 6. And it
12 says, it is kind of the middle of the
13 column there, it says:

14 "One of the caveats with our
15 study is the use of EM" --

16 And EM is electron microscope?
17 Sorry?

18 A. Where are we exactly in that
19 paragraph?

20 Q. To orient yourself, it is the
21 paragraph that starts with "One of the
22 caveats."

23 A. That is in the middle. Right.

24 Q. Just for the purpose of clarity

1 for the record, EM is electron microscopy?

2 Right?

3 A. Yes.

4 Q. And it says:

5 "One of the caveats with our
6 study is the use of EM for
7 semiquantitative analysis for the ratios
8 of empty AAV virions in viral
9 preparations. EM technology is very
10 useful and informative for qualitatively
11 setting the structures of virions but not
12 ideal for precise quantitative assessment
13 of empty and full virions in a viral
14 preparation. In addition, EM cannot
15 distinguish full virions packaged with
16 full-length genomes from those with
17 partial viral genomes."

18 So would you agree that Gao is
19 stating here that it wasn't possible to
20 accurately distinguish whether or not you
21 had a particle with a fully intact DNA
22 genome from those that have a partial DNA
23 genome?

24 A. Yes. It was difficult. Yes.

1 Q. And would the inability to
2 distinguish between which particle was
3 which hinder the confirmation of whether
4 or not these particles actually were all
5 identical sizes?

6 ATTORNEY WILSON: I object to
7 form.

8 A. It is a general -- it is a
9 general statement within its limitations
10 basically.

11 BY ATTORNEY HACKMAN:

12 Q. So Gao is saying that electron
13 microscope is limited application in terms
14 of assessing the composition of a mixture,
15 heterogeneous mixture of AAV particles?

16 ATTORNEY WILSON: I object to
17 form.

18 A. For its time. I mean at this
19 given date, yes.

20 BY ATTORNEY HACKMAN:

21 Q. And I want to go on -- we can
22 keep going in the same column.

23 A. Yes.

24 Q. There is another sentence that

1 says:

2 "These PE particles" --

3 And just to confirm, a PE
4 particle in Gao is partially empty?

5 A. Yes.

6 Q. Is that right?

7 A. Yes. That's correct.

8 Q. So partially empty also means the
9 same thing as a partial genome that has
10 been encapsidated?

11 A. Yes.

12 Q. Right?

13 A. Yes.

14 Q. "These PE particles with partial
15 viral genomes may also contribute to the
16 side effects of the PE virions due to
17 their different capsid conformations as
18 compared with CE particles."

19 And to confirm, CE is the
20 completely empty particles? Right?

21 A. That's correct.

22 Q. So what -- do you understand Gao
23 to be indicating here that there are
24 structural differences between AAV

1 particle species?

2 ATTORNEY WILSON: I object to
3 form.

4 A. Yes. There is structural
5 differences. But, you know, they could be
6 -- they would be contained to this, you
7 know, the various areas that don't
8 necessarily influence the overall size of
9 the virus particle.

10 BY ATTORNEY HACKMAN:

11 Q. But Gao doesn't draw a conclusion
12 about the size of the virus particle?
13 Right?

14 ATTORNEY WILSON: Objection to
15 form.

16 A. Other than the fact that they
17 seem to be the same, empty and full. It
18 is hard to distinguish partials basically.

19 Q. Could conformational changes,
20 though, impact the frictional coefficient
21 of an AAV particle in a sedimentation
22 velocity AUC experiment?

23 ATTORNEY WILSON: Objection to
24 form.

1 A. It is potential if you change
2 the, you know, the outside diameter or
3 somehow change the hydration basically.

4 BY ATTORNEY HACKMAN:

5 Q. And even changes that don't
6 impact the diameter can still affect
7 friction? Right?

8 ATTORNEY WILSON: I object to
9 form.

10 A. If you don't change the bulk
11 product basically, the entire virus
12 particle from its outside, and if you
13 don't change its mass, you -- you
14 shouldn't have a change basically.

15 The change from a sedimentation
16 velocity has limitations of picking up
17 things, and it is dependent on its
18 frictional impact and mass.

19 BY ATTORNEY HACKMAN:

20 Q. But would a change in capsid
21 formation potentially change how the
22 particle interacting chemically with the
23 environment?

24 ATTORNEY WILSON: I object to

1 form.

2 A. Then you are speaking of
3 hydration of some sort or solvation
4 effects.

5 Q. And hydration and solvation
6 effects do matter for frictional
7 coefficients? Right?

8 ATTORNEY WILSON: I object to
9 form.

10 A. Yes, they could.

11 BY ATTORNEY HACKMAN:

12 Q. And just to clarify, do you -- in
13 your declaration did you do any analysis
14 of differences between -- differences in
15 AAV particle species with respect to their
16 hydration?

17 A. No, I did not.

18 Q. So you would agree that your
19 opinions are based on your conclusion that
20 they have approximately the same size and
21 shape regardless of genome content?

22 A. That is just --

23 ATTORNEY WILSON: I object to
24 form.

1 A. That is correct.

2 ATTORNEY HACKMAN: All right. I
3 am going to mark another exhibit. All
4 right. This is Exhibit 1041, the Lock
5 reference.

6 (Article entitled "Analysis of
7 Particle Content of Recombinant
8 Adeno-Associated Virus Serotype 8
9 Vectors by Ion-Exchange
10 Chromatography" marked Exhibit 1041
11 for identification.)

12 (Handing Exhibit 1041 to
13 witness.)

14 BY ATTORNEY HACKMAN:

15 Q. Let me know when you are ready --

16 A. Yes.

17 Q. -- Dr. Berkowitz.

18 A. Yes.

19 Q. Okay. So Exhibit 1041 is another
20 reference that you cited in your
21 declaration? Right?

22 A. Correct.

23 Q. And in your paragraph 168, the
24 Lock -- of your declaration -- Lock is one

1 of the references you cite in support of
2 your conclusion that genomes are
3 approximately -- excuse me -- all
4 particles are approximately the same size?

5 A. Correct.

6 Q. So you cite figure 2. So let's
7 go to figure 2 in Lock.

8 (Witness complying.)

9 Q. So these -- figure 2 on page 59
10 of Exhibit 1041, these are the images that
11 you are relying on to support your
12 conclusion that the particles are
13 approximately the same size and shape?
14 Right?

15 A. Correct.

16 Q. So this figure in Lock does not
17 address the presence of partial genomes?
18 Right?

19 ATTORNEY WILSON: I object to
20 form.

21 A. Yes.

22 BY ATTORNEY HACKMAN:

23 Q. So all of the particles according
24 to Lock in this figure are either full or

1 empty? Right?

2 A. Basically yes.

3 Q. So how can you draw the
4 conclusion that partially full particles
5 would be approximately the same --

6 ATTORNEY HACKMAN: Excuse me.

7 Let me withdraw that.

8 BY ATTORNEY HACKMAN:

9 Q. How can you draw the conclusion
10 that AAV particles with partial genomes
11 are the same size and shape as those that
12 are empty and those with full genomes if
13 the figure doesn't show partial particles?

14 ATTORNEY WILSON: I object to
15 form.

16 A. It is not scientifically shown
17 basically, but it is implied, given the
18 preparation has all of these components
19 typically present in them, and this is a
20 general field, you would imply that, you
21 know, you are seeing all of the materials,
22 the various features that are in there.
23 But granted, there is limitations. Right?
24 We are not quantitating all of this. And

1 it is true you can't -- it is difficult to
2 quantitate partials.

3 BY ATTORNEY HACKMAN:

4 Q. And in addition to not being able
5 to quantitate size and shape --

6 ATTORNEY HACKMAN: Actually let
7 me withdraw that question.

8 BY ATTORNEY HACKMAN:

9 Q. When you say difficult to
10 quantitate, are you referring to size and
11 shape of particles?

12 ATTORNEY WILSON: I object to
13 form.

14 A. Yes.

15 BY ATTORNEY HACKMAN:

16 Q. And in addition to difficulty
17 with quantitating size and shape, it is
18 not possible from visual inspection to
19 determine differences in chemical
20 properties? Right?

21 A. That's correct.

22 Q. And one of those chemical
23 properties would be hydration? Right?

24 A. That's correct.

1 Q. And hydration is a factor in --

2 A. Yes.

3 Q. -- friction coefficients?

4 A. Potentially, yes.

5 ATTORNEY WILSON: I object to
6 form.

7 Let him finish the question.

8 THE WITNESS: Sorry.

9 ATTORNEY WILSON: We are getting
10 all --

11 THE WITNESS: I'm sorry. Yes.

12 ATTORNEY HACKMAN: Okay.

13 BY ATTORNEY HACKMAN:

14 Q. So we have been discussing
15 electron microscopy for analyzing particle
16 size and shape. Are there other
17 techniques that a person of ordinary skill
18 in the art would use to assess the surface
19 properties of an AAV particle?

20 ATTORNEY WILSON: I object to
21 form.

22 A. Just focusing on the surface?

23 BY ATTORNEY HACKMAN:

24 Q. Let's --

1 ATTORNEY HACKMAN: I will ask the
2 question a little bit differently.

3 BY ATTORNEY HACKMAN:

4 Q. So looking at the structure of an
5 AAV particle, what are some other
6 techniques that a person of ordinary skill
7 in the art would use for structural
8 analysis?

9 ATTORNEY WILSON: I object to
10 form.

11 A. When you say structure, what
12 exactly do you mean by structure?

13 BY ATTORNEY HACKMAN:

14 Q. Well, for example, we discussed
15 earlier your studies on adenovirus?
16 Right?

17 A. Right.

18 Q. And we noticed that adenovirus
19 have these fiber spikes? Right?

20 A. (The witness nodding his head.)

21 Q. Let's make sure it is verbal.

22 A. Yes.

23 Q. And you mentioned that electron
24 microscopy could be one type of analysis

1 for those particles?

2 A. Correct. At a -- at a certain
3 level in terms of what it is capable of
4 seeing. Right.

5 Q. And, for example, when we were
6 talking about the Lock and Gao electron
7 microscopy images, were those the type of
8 images that would allow you to see a
9 surface feature like a fiber spike in a
10 particle?

11 A. We have already gone through
12 that. I mentioned that you could see --
13 potentially see these fibers by electron
14 microscopy.

15 Q. Are there other methods that
16 would provide a clear image of the size
17 and shape of a particle?

18 A. Size and shape, from size
19 exclusion chromatography, it would look at
20 its overall structure.

21 Q. Is Xray crystallography a
22 potential method to analyze size and shape
23 of a particle?

24 A. Yes.

1 Q. Is that a method that you have
2 ever relied on for understanding the size
3 and shape of a particle?

4 A. It -- yes.

5 Q. And does Xray crystallography
6 give a more detailed image of a particle's
7 size and shape?

8 A. You are getting the atomic
9 structure of the entity that you are
10 studying.

11 Q. So getting the atomic structure
12 is more detailed than --

13 A. Yes.

14 Q. Just make sure to give it time.

15 A. Yes.

16 Q. In terms of ensuring a reliable
17 image of a particle, do some --

18 ATTORNEY HACKMAN: Let me
19 withdraw that.

20 BY ATTORNEY HACKMAN:

21 Q. Would a person of ordinary skill
22 in the art rely on multiple different
23 analytical methods to ensure that they get
24 the most accurate image of a particle

1 shape and size?

2 ATTORNEY WILSON: I object to
3 form.

4 A. In principle, you would. But you
5 could take it to various levels. If you
6 want to know more and more, yes, you want
7 to get more and more high resolving
8 techniques.

9 BY ATTORNEY HACKMAN:

10 Q. I think you mentioned earlier
11 cryoelectron microscopy?

12 A. Yes.

13 Q. And what is cryoelectron
14 microscopy?

15 A. Basically the material is
16 embedded in ice, and you are looking at
17 more native of a picture as opposed to
18 negative stain, where you dehydrate the
19 structure and stain it.

20 Q. So when you do negative staining,
21 you said you dehydrate the structure?
22 Right?

23 A. Yes. The processing, the sample
24 processing, potentially involves this.

1 Q. And would dehydrating the
2 structure impact its size and shape?

3 ATTORNEY WILSON: I object to
4 form.

5 A. It is possible.

6 BY ATTORNEY HACKMAN:

7 Q. And the Lock and Gao electron
8 microscopy images that you looked at,
9 those were done through the negative
10 staining technique that you are referring
11 to?

12 A. Yes.

13 Q. So it is possible that the
14 particles are not the same size and shape
15 that they would be in a sedimentation
16 velocity AUC experiment?

17 ATTORNEY WILSON: I object to
18 form.

19 A. It is possible, yes, because they
20 are not in their native environment.

21 BY ATTORNEY HACKMAN:

22 Q. So a cryoelectron microscopy
23 experiment would potentially give you a
24 better image of the particle size and

1 shape?

2 A. In a native, yes, an aqueous type
3 of solution. In this case it is ice. But
4 certainly less sample -- having less --
5 less of an influence potentially on the
6 material.

7 Q. And is cryoEM allow --
8 cryoelectron microscopy -- does that allow
9 the experimenter to see individual
10 structures, individual particle
11 structures?

12 ATTORNEY WILSON: I object to
13 form.

14 A. You can see the three-dimensional
15 -- you can get three-dimensional structure
16 somewhat equivalent to Xray defraction,
17 certain forms of the cryoEM.

18 BY ATTORNEY HACKMAN:

19 Q. Did you look at cryoEM images of
20 recombinant AAV particles as part of your
21 analysis in your declaration?

22 A. I have seen in the pictures
23 cryoEM. Yes.

24 Q. And do you recall whether any of

1 those pictures compared particles having
2 different genome sizes encapsidated?

3 A. I don't think that was, you know,
4 determined in those type of pictures.

5 Q. Are you aware of any studies that
6 compared /TP-Z the particle images of an
7 AAV particle ^ with an empty versus a full
8 genome?

9 A. I think there has been in the
10 literature. Yes.

11 Q. But you didn't cite any of
12 those --

13 A. No.

14 Q. -- to your awareness in your
15 declaration?

16 A. No. Those are all more recent --
17 I think they were more recent, prior to
18 the patent.

19 Q. Okay. So there was nothing
20 available in the art, the prior art,
21 before 2015 --

22 A. Much more limited.

23 ATTORNEY WILSON: You have to let
24 him finish the question --

1 THE WITNESS: Okay.

2 ATTORNEY WILSON: -- because we
3 don't know what he is asking you.

4 THE WITNESS: All right.

5 BY ATTORNEY HACKMAN:

6 Q. So there are no publications
7 before the time frame of about 2015 that
8 we are dealing with here that you are
9 aware of of cryoEM structures of AAV
10 particles having different genome --
11 genomes encapsidated inside?

12 ATTORNEY WILSON: I object to
13 form.

14 A. They were looking at the entire
15 preparation, so I would assume, you know,
16 that it would be present in there.

17 BY ATTORNEY HACKMAN:

18 Q. Okay. So entire preparations,
19 meaning like --

20 A. Yes.

21 Q. -- Gao and Lock?

22 A. Yes.

23 Q. Actually I want to just return
24 briefly to the Le Bec reference,

1 Exhibit 1006.

2 (Witness complying.)

3 Q. And we can go back to page 25 of
4 that reference. That is labeled in the
5 exhibit number, 1006, page 25.

6 A. Yes.

7 Q. So these are the two figures that
8 we discussed earlier, and is your
9 understanding that in Le Bec they used
10 absorbance detection with UV light?

11 A. Yes, they did.

12 Q. And you mentioned that in the
13 Le Bec publication they were determining
14 the areas of the peak? Right?

15 A. Correct.

16 Q. And they were doing that to
17 qualitatively compare the number of empty
18 versus full AAV viral --

19 A. Yes.

20 Q. -- particles?

21 A. Yes.

22 Q. But that wasn't their
23 quantitative experiment? Right?

24 ATTORNEY WILSON: Objection.

1 A. To that level in terms of signal
2 response. Right.

3 BY ATTORNEY HACKMAN:

4 Q. And one of the things that a
5 person of ordinary skill in the art would
6 need to quantify concentration accurately
7 would be the extinction coefficients of
8 the different viral particle species?
9 Right?

10 A. Yes.

11 Q. And in order to determine an
12 extinction coefficient, one of ordinary
13 skill in the art would need to know how
14 much genome is encapsidated within a
15 particle? Right?

16 A. Yes.

17 Q. And knowing that would require
18 knowing the molecular weight of that
19 genome? Right?

20 A. It would help you get it. Yes.

21 Q. I think you mentioned earlier
22 that for determining molecular weight of a
23 genome --

24 ATTORNEY HACKMAN: Actually, let

1 me back up.

2 BY ATTORNEY HACKMAN:

3 Q. So just generally in AUC
4 analyses, determining the molecular weight
5 of a particle is -- was generally done
6 using sedimentation equilibrium AUC?
7 Right?

8 ATTORNEY WILSON: I object to
9 form.

10 A. Yes. That made it easier.

11 BY ATTORNEY HACKMAN:

12 Q. Yes. And Le Bec doesn't go to
13 that step of determining the molecular
14 weight? Right?

15 A. Correct.

16 Q. I want to go to -- I am sorry to
17 keep going back and forth.

18 Let's go back to your
19 declaration, and we will go to
20 paragraph 190.

21 (Witness complying.)

22 A. Right.

23 Q. So I am looking at the table in
24 190, and you have -- in the rightmost

1 column you have the "Number of
2 nucleotides"?

3 A. Yes.

4 Q. Where did you get these values
5 from?

6 A. They are hypothetical based on
7 what a full AAV would contain. I think in
8 the literature, it is commonly said that a
9 full wild AAV will hold 4,700 nucleotide
10 pieces of DNA.

11 Q. Okay. So Le Bec doesn't give you
12 this data then?

13 A. No.

14 Q. And this is approximated on the
15 viral genome being the maximum size?

16 A. Typical.

17 Q. Typical? Sorry. Typical?

18 A. Yes. Because you can overfill
19 these.

20 Q. Okay. Would overfilling an AAV
21 particle potentially impact its size and
22 shape?

23 ATTORNEY WILSON: I object to
24 form.

1 A. It is possible.

2 BY ATTORNEY HACKMAN:

3 Q. And would empty space within a
4 capsid potentially lead to distortions of
5 the particle surface?

6 ATTORNEY WILSON: I object to
7 form.

8 A. I don't know what you mean by --
9 I mean there is empty space in partials?
10 Correct?

11 BY ATTORNEY HACKMAN:

12 Q. Right.

13 A. Okay.

14 Q. Could that impact the size and
15 shape of the particle?

16 ATTORNEY WILSON: Objection to
17 form.

18 A. Empty space? Not necessarily.
19 No.

20 BY ATTORNEY HACKMAN:

21 Q. And then the 2,300 -- you have
22 the 4,700. You said that that is the
23 theoretical maximum or typical -- let me
24 back up.

1 You said the 4,700 is the typical
2 genome size for a fully impact particle?
3 Right?

4 A. That is what is found in the
5 nature wild.

6 Q. The 2,300, how do you derive that
7 number?

8 A. They are trying to make a
9 complementary piece of DNA, and if you
10 lose one of the complementary pieces, it
11 is half the molecular weight.

12 Q. Okay. So you relied on Le Bec's
13 statement that it was a single strand
14 particle?

15 A. Yes.

16 ATTORNEY HACKMAN: Oh, I know
17 what I want to do. Are you okay on a
18 break? Good?

19 ATTORNEY WILSON: Are you okay?

20 THE WITNESS: I am okay.

21 ATTORNEY HACKMAN: Okay.

22 Let me go to another exhibit
23 here. We are going to mark Exhibit 1012.

24 (Article entitled "Assembly of

1 Adeno-Associated Virus" marked
2 Exhibit 1012 for identification.)

3 (Handing Exhibit 1012 to
4 witness.)

5 BY ATTORNEY HACKMAN:

6 Q. Okay. Dr. Berkowitz, are you
7 familiar with this exhibit?

8 A. Yes.

9 Q. And this was another publication
10 that you cited in your declaration?
11 Right?

12 A. Right.

13 Q. So Exhibit 1013 is another
14 publication that came from Dr. Carter's
15 group?

16 A. Correct.

17 Q. So this is also referred to as
18 the Myers publication.

19 So this is another example where
20 they observed the AAV 1.45 and AAV 1.41
21 particles, which both contained intact
22 genomes? Right?

23 ATTORNEY WILSON: I object to
24 form.

1 A. Yes.

2 BY ATTORNEY HACKMAN:

3 Q. And one of the goals of this
4 publication was to analyze the assembly
5 process of AAV particles?

6 A. Yes.

7 Q. And so your analysis is that --

8 ATTORNEY HACKMAN: Actually this
9 is a question, I will withdraw that.

10 BY ATTORNEY HACKMAN:

11 Q. Does your analysis assume that
12 the insertion of the DNA into a preformed
13 capsid is a single-step process?

14 ATTORNEY WILSON: I object to
15 form.

16 A. Within the limitations of
17 knowledge, yes. It is, yes.

18 BY ATTORNEY HACKMAN:

19 Q. Have you seen anything in the
20 literature that indicates that there may
21 be additional steps in which intermediate
22 particles convert to the final product?

23 ATTORNEY WILSON: I object to
24 form.

1 A. Not to my knowledge per se,
2 although there could be speculations in
3 the attempts to look for that. I am sure
4 that is where the things that they are
5 trying to do is to assess, within their
6 limitation and capability, especially at
7 this time, you know, which is 1980.

8 BY ATTORNEY HACKMAN:

9 Q. Right. And did you see any
10 references since the Carter group
11 references that you cite in your report of
12 where they discussed the assembly -- the
13 assembly of viral particles more recently
14 than these publications?

15 A. I haven't pursued that
16 extensively. So I am assuming, you know,
17 there might very well be, you know, more
18 literature for sure.

19 Q. But you have relied on these --

20 A. Yes.

21 Q. Sorry. Let me finish the
22 question.

23 A. I'm sorry.

24 Q. You relied on these publications

1 for the purposes of presenting your
2 opinion in your declaration? Right?

3 A. Yes.

4 Q. If we go to paragraph -- excuse
5 me -- page 81 of the Exhibit 1012.

6 (Witness complying.)

7 Q. And in the right column, starting
8 with the sentence "Also it does not appear
9 to arise" from the particles. Starting
10 there. There is a little passage. I will
11 just let you read that.

12 ATTORNEY WILSON: Where are you
13 again?

14 ATTORNEY HACKMAN: On page 81.

15 ATTORNEY WILSON: Right.

16 ATTORNEY HACKMAN: Then on the
17 right column starting at the top of the
18 column and just start -- you can actually
19 start at the paragraph, sorry, the
20 leftmost paragraph.

21 THE WITNESS: Okay.

22 ATTORNEY HACKMAN: The bottommost
23 paragraph on the left side, and then it
24 continues on to the right side.

1 THE WITNESS: Yes. I am sorry.

2 I wasn't following that.

3 ATTORNEY HACKMAN: That's okay.

4 I mucked it up pretty badly.

5 BY ATTORNEY HACKMAN:

6 Q. So we start -- it is the last

7 paragraph of the left column.

8 A. The last paragraph?

9 Q. It starts with "The AVV (SP)
10 component."

11 A. This is on page 1012?

12 Q. Sorry. Exhibit 1012, page 81.

13 A. Oh, 81? Yes, I am on 81. Which
14 side? Left? Right?

15 Q. At the bottom -- the paragraph
16 that starts at the bottom.

17 A. "The AAV(SP)"?

18 Q. Yes.

19 A. All right.

20 Q. I am just going to let you read
21 this paragraph.

22 A. Okay.

23 Q. And then we can go to specific
24 parts of it and request questions.

1 (Pause.)

2 (The witness viewing

3 Exhibit 1012.)

4 A. Yes.

5 Q. So a theory that they were
6 providing in this paragraph regarding AAV
7 assembly was that the denser 1.45 particle
8 was a precursor to the 1.41 particle?
9 Right?

10 ATTORNEY WILSON: I object to the
11 form.

12 A. They speculate. Yes.

13 BY ATTORNEY HACKMAN:

14 Q. And you recall that the
15 1.45 particle had a smaller diameter than
16 the 1.41? Right?

17 A. From its sedimentation is
18 implying that; right? And I guess there
19 was a side reference that seemed to
20 indicate that that was the case.

21 Q. Right. And so this suggests that
22 one possibility is that the smaller 1.45
23 particle was a precursor to the
24 1.41 particle? Right?

1 A. That is what they are trying to
2 find out. Yes.

3 Q. And that would be -- that would
4 -- that would contradict the assembly
5 process being a single step? Right?

6 ATTORNEY WILSON: I object to
7 form.

8 A. If true, yes.

9 BY ATTORNEY HACKMAN:

10 Q. The other possibility could be
11 that not all preformed capsids are the
12 same size? Right?

13 ATTORNEY WILSON: I object to
14 form.

15 A. Hmm. If it was true, yes.

16 BY ATTORNEY HACKMAN:

17 Q. What do you mean "if it was
18 true"?

19 A. You are saying that -- can you
20 just repeat that again --

21 Q. Sure.

22 A. -- so that I can --

23 Q. Sure. We will go back a step
24 here.

1 A. Yes.

2 Q. We know we have two populations
3 of AAV species that have different
4 densities --

5 A. Yes.

6 Q. -- and different diameters?
7 Right?

8 A. Yes.

9 Q. And these two species have the
10 same amount of DNA content?

11 A. Yes.

12 Q. Right?

13 A. Right.

14 Q. And we also know that these two
15 species have the same DNA-to-protein
16 ratio? Right?

17 A. That's correct.

18 Q. So would this -- is one possible
19 theory for how we got to having these two
20 species of particles be that the preformed
21 capsids were different for each species of
22 particle?

23 ATTORNEY WILSON: I object to
24 form.

1 A. I mean they speculate it could be
2 a dead end for the process. So this is
3 not -- this does not necessarily lead to
4 the final finished product. It is a
5 pathway. It is an alternative pathway
6 that leads to they don't know. They call
7 it a dead end? Right?

8 BY ATTORNEY HACKMAN:

9 Q. Right. If it is a dead-end
10 process that means it is possible to end
11 up with heterogeneous AAV particle
12 composition where there are particles of
13 different shapes and sizes containing the
14 same genomic DNA? Right?

15 ATTORNEY WILSON: I object to
16 form.

17 A. I guess so. Yes.

18 BY ATTORNEY HACKMAN:

19 Q. And the other alternative is that
20 there is a multistep process? Right?

21 A. Possibly, yes.

22 Q. Okay.

23 A. I don't think they ruled out
24 degradation. They talk about that in this

1 paragraph, I think, where does it say it?
2 Because of the -- "also it does not appear
3 to arise from disruption."

4 That is an interesting statement
5 that you make there. I mean there could
6 be something -- this may not have nothing
7 necessarily to do with the assembly
8 process, but it could actually be some
9 degradation of these preformed capsids.

10 Q. And if there is a degradation
11 product, that would be something a person
12 of ordinary skill in the art would want to
13 characterize --

14 A. Yes.

15 ATTORNEY WILSON: Object to form.

16 Let him finish the question.

17 BY ATTORNEY HACKMAN:

18 Q. If there is a degradation
19 product, it would be something that
20 somebody -- a person of ordinary skill in
21 the art would want to characterize in the
22 composition? Right?

23 A. Yes.

24 ATTORNEY HACKMAN: If it is okay,

1 we take a little break here.

2 THE WITNESS: Sure.

3 ATTORNEY HACKMAN: I don't know
4 if we want to do -- what the lunch plan
5 is.

6 ATTORNEY WILSON: Let's go off
7 the record first.

8 THE VIDEOGRAPHER: The time is
9 12:00 p.m. We are off the record.

10 (Luncheon recess taken at
11 12:00 p.m.)

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1 A F T E R N O O N S E S S I O N

2 1 2 : 4 3 P. M.

3 - - -

4 THE VIDEOGRAPHER: The time is
5 12:43 p.m., and we are on the record.

6 BY ATTORNEY HACKMAN:

7 Q. Dr. Berkowitz, during the lunch
8 break, did you have any discussions with
9 counsel regarding your testimony today?

10 A. No.

11 Q. Thank you.

12 So AUC in general has been
13 available to scientists for several
14 decades? Right?

15 A. A century.

16 Q. How long in that period has
17 sedimentation velocity AUC been an
18 available technique?

19 ATTORNEY WILSON: I object to
20 form.

21 A. It has been available during that
22 time.

23 BY ATTORNEY HACKMAN:

24 Q. So your testimony then is that it

1 has been about a century that
2 sedimentation velocity AUC has been
3 available?

4 ATTORNEY WILSON: I object to
5 form.

6 A. Yes.

7 BY ATTORNEY HACKMAN:

8 Q. And we understand that from the
9 Carter references, as you say, there had
10 been work to characterize the structure of
11 AAV particles starting back at least in
12 the 1970s? Right?

13 A. Correct.

14 Q. And in that time one of the
15 techniques that was used to characterize
16 AAV particles was AUC? Right?

17 A. Yes.

18 Q. Are you surprised based on this
19 knowledge that it took several decades for
20 researchers to develop a method to use
21 sedimentation velocity AUC to determine
22 the size of encapsidated genomes?

23 ATTORNEY WILSON: I object to
24 form.

1 A. No. I mean you have to -- I mean
2 what we have been talking about in terms
3 of Carter's lab is -- in terms of you
4 would call analytical ultracentrifugation,
5 that has all been done preparatively, and
6 we still call it analytical, I guess some
7 people call it analytical, but in reality
8 you could sort of use the reference
9 preparative.

10 Analytical ultracentrifuge
11 basically is a very precise device that is
12 made to follow the movement of particles.
13 Its whole objective is to analytically
14 look at these materials. And so what we
15 are dealing with here is predominantly --
16 I shouldn't say predominantly -- all the
17 stuff that is being reported by Carter's
18 lab are preparatory-type analytical
19 ultracentrifugation basically, where one
20 of your main objectives is to fractionate
21 all of these materials to get these
22 materials to do virtually other
23 experiments. It is used to characterize.
24 But you are also getting materials to do

1 follow-on experiments.

2 In terms of all of these years in
3 terms of sedimentation velocity, you have
4 got to look at, until we get around the
5 year 2000, where Peter Schuck basically
6 develops this program SEDFIT where you can
7 really do a lot of detailed analytical
8 analysis on sedimentation velocity, the
9 capability of the analytical tool.

10 Again here when I say analytical,
11 I am talking about a special
12 ultracentrifuge that is basically focused
13 on analytically characterizing and
14 utilizing these tools. Around 2000 this
15 program comes out and gives you a
16 tremendous amount of capability of
17 improving the separations basically.

18 So that is sort of a point where
19 centrifugation would start being applied
20 to, particularly in terms of the
21 commercial area, and biotechnology is --
22 obviously wasn't, you know, around as it
23 is today.

24 So as an analytical tool and the

1 capability of that, this analytical tool,
2 you have to look at the year 2000 as sort
3 of a starting point where people basically
4 realized the capability of this technique
5 and really take advantage of it.

6 So at that time also then you
7 also have to keep in mind that gene
8 therapy was a low-level activity prior to
9 going back to the '70s, '80s, '90s, and
10 then in 2000, around, it took a big hit.
11 Gene therapy wasn't really a big area for
12 doing a lot of analytical work. A lot of
13 businesses was trying to get this
14 technology off the ground.

15 Then when they had this big
16 problem occur, it took a nose dive.
17 Meanwhile, centrifugation, analytical
18 centrifugation was being propagated you
19 might say. People were realizing its
20 capability.

21 I wrote a paper in 2006 with the
22 key purpose of highlighting, you know,
23 this technique. It sort of went asleep
24 basically and needed to have a little

1 reawakening. And then people -- it took
2 time for people to realize the capability
3 of programs like Peter Schuck.

4 So you talk about the delay. I
5 think in the context of what I have been
6 telling you, it is not by any means
7 unusual that what we're seeing, that there
8 wasn't much, you know, earlier activity in
9 developing this to where it is today. It
10 has taken a long time to materialize.

11 And people were pursuing a lot of
12 other techniques to characterize, you
13 know. Mass spectrometry was making a big
14 realization, and people were turning to
15 that, to do some things that to some
16 extent you could do with analytical
17 centrifugation, particularly in terms of
18 molecular weight and gels and
19 high-performance chromatography were
20 appearing on the scene.

21 So this technique fell asleep you
22 might say. Even the instrument companies,
23 it took quite a bit of prodding by what
24 few researchers that were left in the

1 field to make a second generation machine,
2 which appears in the '90s, mid '90s,
3 around that time.

4 And, like I said, the development
5 of Peter Schuck that followed, that really
6 put impetus, but, you know, it takes time
7 to get people doing things, and gene
8 therapy needed a recovery period of some
9 sort.

10 Certainly after the 2000 sort of
11 debacle around that time that occurred
12 with Wilson, who was a pioneer. I don't
13 remember his last name. But there was a
14 death, and it really took a -- you know,
15 whatever was going on took a big hit. So
16 even that field sort of fell asleep.

17 And the work of AAV to try to get
18 around all of these problems of side
19 effects from delivering these -- these --
20 these types of drugs, adenovirus, you
21 know, adenovirus still being somewhat
22 pursued. AAV now has come sort of come to
23 the forefront. So it has taken all of
24 these things for things to fall into

1 place.

2 So from my perspective, this is
3 not surprising.

4 BY ATTORNEY HACKMAN:

5 Q. So I think you mentioned -- may
6 have mentioned Beckman Coulter. Beckman
7 Coulter?

8 A. Yes. Beckman Coulter, right.

9 Q. And Beckman Coulter publicizes
10 the work of AUC researchers? Right?

11 A. Yes. Sure.

12 Q. And you have been one of those
13 researchers that have spoken at Beckman
14 Coulter --

15 A. Yes. Right.

16 ATTORNEY WILSON: Let him finish
17 the question. You are kind of jumping the
18 gun a little bit.

19 THE WITNESS: Sorry. I -- it is
20 a fault of mine.

21 ATTORNEY HACKMAN: It is a --
22 depositions are a different environment
23 than we are accustomed to.

24 THE WITNESS: I am new to it. It

1 is not a good idea to talk over people
2 obviously.

3 BY ATTORNEY HACKMAN:

4 Q. So would you consider Beckman
5 Coulter influential in the field of
6 analytical ultracentrifugation?

7 ATTORNEY WILSON: I object to
8 form.

9 A. They are the only ones that makes
10 the instrument. So if they are -- they
11 have a monopoly on the whole thing.

12 BY ATTORNEY HACKMAN:

13 Q. So do practitioners often consult
14 with Beckman Coulter as part of their work
15 in AUC?

16 ATTORNEY WILSON: I object to
17 form.

18 A. There are some probably
19 collaboration. I don't know if they are
20 that big on it. I think a lot of their
21 collaboration is more or less to get
22 exposure, right, from the advertisement
23 standpoint.

24 BY ATTORNEY HACKMAN:

1 Q. And so, for example, how did it
2 come about that you have given lectures
3 sponsored by Beckman Coulter?

4 A. Because I was pretty influential
5 -- I would like to think I was pretty
6 influential in getting people to pay
7 attention to the technique.

8 Q. So Beckman Coulter discussed
9 having you present on the AUC topic
10 because they were trying to get visibility
11 within the industry of the value of the
12 technique? Right?

13 A. Yes.

14 ATTORNEY WILSON: I object to
15 form.

16 BY ATTORNEY HACKMAN:

17 Q. And do the users of AUC
18 instruments look to Beckman Coulter for
19 guidance as to how to design AUC
20 experiments?

21 ATTORNEY WILSON: I object to
22 form.

23 A. To some extent, yes.

24 BY ATTORNEY HACKMAN:

1 Q. What sort of guidance does the
2 user seek from Beckman Coulter in your
3 experience?

4 ATTORNEY WILSON: I object to
5 form.

6 A. In terms of the operation of the
7 instrument.

8 BY ATTORNEY HACKMAN:

9 Q. What about in terms of the
10 capabilities of what type of assays that
11 can be done using the instrument?

12 ATTORNEY WILSON: I object to
13 form.

14 A. I don't know how much that --
15 that goes on per se. I mean they have
16 probably a very limited capability of on
17 their own developing methodology, you
18 might say. It is a small part of their
19 business.

20 BY ATTORNEY HACKMAN:

21 Q. I want to go back to an exhibit
22 that we have already marked, which is
23 Exhibit 1013.

24 A. What is the authors on that?

1 Q. This is also a de la Maza and
2 Carter publication.

3 A. Okay.

4 Q. This is the one from March 1980.

5 A. March of 2080?

6 Q. 1980.

7 A. 1980, the Journal of Virology?

8 Q. That is right. If you look at
9 the bottom 1013 is the exhibit number.

10 A. Oh, yes. Yes.

11 Q. And so previously, to orient
12 ourselves, in this publication de la Maza
13 and Carter describe these two AAV
14 particles having different density but the
15 same DNA content and same DNA protein
16 ratio? Right?

17 ATTORNEY WILSON: I object to
18 form.

19 A. Right.

20 BY ATTORNEY HACKMAN:

21 Q. And they did use sedimentation
22 velocity AUC in analyzing these two
23 particles? Right?

24 ATTORNEY WILSON: I object to

1 form.

2 A. Yes. Again this is a preparative
3 investigation, analytical preparative
4 investigation.

5 BY ATTORNEY HACKMAN:

6 Q. My understanding of preparative
7 analytical ultracentrifugation is that its
8 purpose is to be able to isolate separate
9 particles? Right?

10 A. Right.

11 Q. But here if we look at, for
12 example -- well, the easy place to find is
13 the abstract at --

14 A. Yes.

15 Q. -- the top of page 1129.

16 A. Yes.

17 Q. They also discuss sedimentation
18 velocity? Correct?

19 A. Yes.

20 Q. And that is what these 109 and
21 111 numbers are? Right?

22 A. Yes. Those are -- yes. Those
23 are sedimentation coefficients. Right.

24 Q. So sedimentation velocity AUC is

1 not a preparative method? Right?

2 ATTORNEY WILSON: I object to the
3 form.

4 A. It could be carried out in a
5 modality of what I would call preparative.
6 You could measure -- you certainly can
7 measure numerically the sedimentation
8 coefficients from the peaks, but you don't
9 need it typically as you would use an
10 analytical -- a defined special instrument
11 that is made to really look very carefully
12 at what is sedimenting here under --
13 under, you know, very controlled optimum
14 conditions you might say.

15 BY ATTORNEY HACKMAN:

16 Q. So if you recall we had the
17 1.45 density and the 1.41 density AAV
18 particles? Right?

19 A. Yes.

20 Q. The 1.45 particle is a denser
21 particle than the 1.41? Right?

22 A. Right.

23 Q. Now the denser particle, however,
24 sediments at a lower rate than the less

1 dense particle? Right?

2 ATTORNEY WILSON: I object to
3 form.

4 A. Right. That's right.

5 BY ATTORNEY HACKMAN:

6 Q. And doesn't this provide some
7 evidence that friction can be
8 unpredictable in sedimentation velocity
9 AUC?

10 ATTORNEY WILSON: I object to
11 form.

12 A. You are referring to the nature
13 of there was a structure basically.
14 Whatever gives rise to that friction, it
15 is -- it is -- it is indicative of the
16 surprise in the particle basically. It is
17 -- the particle structure.

18 BY ATTORNEY HACKMAN:

19 Q. What do you mean -- I'm sorry?

20 A. Yes. It's -- maybe if you just
21 repeat the question for me again. Maybe I
22 can --

23 Q. That's okay.

24 So I asked whether the fact that

1 the denser particle sediments at a lower
2 rate than the less dense particle --

3 A. Right.

4 Q. -- is an indicator that there is
5 unpredictable friction in AAV particles?

6 ATTORNEY WILSON: I object to
7 form.

8 A. It is unpredictable structure of
9 the particle, how it is behaving. It
10 plays out in terms of whatever the
11 particle structure is there, then that
12 reflects the physical properties
13 basically.

14 So I am sort of maybe getting --
15 when you say unpredictability about
16 friction, you are talking about the
17 unpredictability of the structure.

18 BY ATTORNEY HACKMAN:

19 Q. I see. So the structure of
20 particles produced in an AAV composition
21 appears to have some unpredictability in
22 terms of its surface properties?

23 ATTORNEY WILSON: I object to
24 form.

1 A. In terms of the structure. In
2 terms of what would normally be -- normal
3 anticipated behavior based on other
4 knowledge, yes. It falls out like this is
5 an outlier. Right?

6 Q. Understood.

7 ATTORNEY HACKMAN: I am going to
8 pause here. I think I am actually near
9 wrapping up. I just want to evaluate to
10 see if there are any other final
11 questions.

12 ATTORNEY WILSON: Let's go off
13 the record.

14 THE VIDEOGRAPHER: The time is
15 1:00 p.m. We are off the record.

16 (Recess taken at 1:00 p.m.)

17 (Recess ended at 1:10 p.m.)

18 THE VIDEOGRAPHER: The time is
19 1:10 p.m., and we are on the record.

20 ATTORNEY HACKMAN: Thank you.

21 BY ATTORNEY HACKMAN:

22 Q. So during the break, did you
23 discuss any aspect of your testimony with
24 counsel?

1 A. No.

2 ATTORNEY HACKMAN: So I just want
3 to thank you, Dr. Berkowitz. I am
4 complete with these questions, with the
5 reservation if there is any redirect
6 testimony, an opportunity to cross you on
7 that.

8 THE WITNESS: Okay.

9 ATTORNEY WILSON: I don't have
10 any questions for Dr. Berkowitz.

11 ATTORNEY HACKMAN: One final
12 thing. Thank you very much for your time
13 today, Dr. Berkowitz. We appreciate it.

14 THE WITNESS: Thank you.

15 THE VIDEOGRAPHER: The time is
16 1:10 p.m. The deposition is concluded and
17 we are off the record.

18 (Whereupon, at 1:10 p.m., the
19 deposition was adjourned.)
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When the Errata Sheet has been
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ATTACH TO DEPOSITION OF
STEVEN BERKOWITZ, Ph.D.

CASE: SAREPTA THERAPEUTICS, INC. v. GENZYME
CORPORATION

DATE TAKEN: July 29, 2026

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I have read the foregoing transcript of
my deposition and except for any corrections
or changes noted above, I hereby subscribe to
the transcript as an accurate record of the
statements made by me.

Executed this ____ day of
_____, 2026.

STEVEN BERKOWITZ, Ph.D.

CERTIFICATE

Commonwealth of Massachusetts

Plymouth, ss.

I, Judith McGovern Williams, a
Notary Public in and for the Commonwealth of
Massachusetts, do hereby certify:

That STEVEN BERKOWITZ, Ph.D. , the
witness whose deposition is hereinbefore set
forth, was duly sworn by me and that such
deposition is a true record of the testimony
given by the said witness.

IN WITNESS WHEREOF, I have hereunto
set my hand this 30th day of July, 2026.

Judith McGovern Williams

Judith McGovern Williams
Registered Professional Reporter
Certified Realtime Reporter
Certified Shorthand Reporter No. 130993

My Commission expires:

April 19, 2031

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