

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

THE TRUSTEES OF THE UNIVERSITY
OF PENNSYLVANIA and REGENXBIO
INC.,

Plaintiff,

v.

SAREPTA THERAPEUTICS, INC. and
SAREPTA THERAPEUTICS THREE, LLC,

Defendant.

C.A. No. 20-1226 (RGA)

JURY TRIAL DEMAND

EXPERT REBUTTAL REPORT OF MICHAEL METZKER

Dated: May 26, 2023

By: _____

Michael Metzker

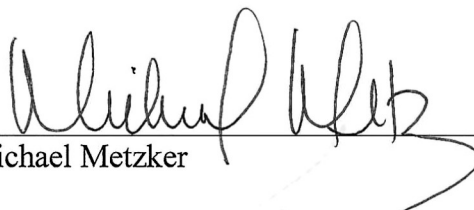
A handwritten signature in black ink, appearing to read 'Michael Metzker', is written over a horizontal line. The signature is stylized with large, flowing loops.

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I. QUALIFICATIONS, FEES AND PREVIOUS EXPERT TESTIMONY

1. I described my qualifications and prior testimony in my Opening Report in this case, which was submitted on April 28, 2023.¹

II. MATERIALS CONSIDERED FOR THIS REPORT

2. In formulating by analysis and writing this Report, I have reviewed portions of the materials listed in Exhibit A. I reserve the right to rely on additional materials produced in this litigation after the submission of my Report, and to respond to any additional expert reports submitted by Sarepta.

3. My opinions expressed in this Report are based on those materials as well as my general knowledge, education, and experience.

III. RELEVANT CLAIM CONSTRUCTION

4. I understand the parties disputed the proper claim construction for two terms that appear in the '617 Patent claims, one of which was the term “at least 95% identical.”

5. I understand that the Court has construed “at least 95% identical” as follows: “at least 95% identical” in the context of nucleic acid or amino acid sequences refers to the percentage of residues which are the same over the full length of the referenced sequence when aligned for maximum correspondence.²

6. I understand that the Court gave additional guidance on that term during the Markman hearing in this case, and I have reviewed that transcript and the guidance of the Court. I agree that the language of the specification and the claims of the '617 Patent³ requires that to

¹ See *Opening Expert Report of Michael Metzker*, dated April 28, 2023 (“Metzker Op. Report”).

² See Markman hearing transcript at 63:6-19.

³ See Gao *et al.*, *Method of detecting and/or identifying adeno-associated virus (AAV) sequences and isolating novel sequences identified thereby*, U.S. Patent No. 10,526,617 (the “'617 Patent”).

determine infringement, a test sequence should be compared against the sequence referenced in the claims, and that the length of the sequence described in the Asserted Claims should be used as the denominator in calculating percent identity. I have accounted for that in performing my analysis.

IV. PERSON OF SKILL IN THE ART

7. Throughout this report, I have discussed what a person of skill in the art (called a “POSA” or “POSITA”)⁴ would have known or understood from the various alignment tools. I understand that Dr. Leone has offered the following definition of one of ordinary skill in the art:

a person of ordinary skill in the art related to the '617 patent would include a scientist with a degree in biochemistry, molecular biology, genetics, or a related field, and practical knowledge of the theory and practice of gene therapy, including AAV gene therapy. This person could have a Ph.D. or Master's degree, along with approximately five years of experience in the field of gene therapy, with a lower level degree requiring more experience in order to be considered a person of ordinary skill.⁵

8. I further understand that Sarepta's experts have offered similar, but slightly different definitions of the person of skill in the art:

a person of ordinary skill in the art for the '617 patent would have at least a Ph.D. in biochemistry, molecular biology, or a related field and between one and four years of post-doctoral experience in the field of gene therapy. Alternatively, a person of ordinary skill in the art have at least a Master's Degree in biochemistry, molecular biology, or a related field and between four and six years of experience in the field of gene therapy. Alternatively, a person of ordinary skill in the art would have at least a Bachelor's Degree in biochemistry, molecular biology, or a related field and between six and eight years of experience in the field of gene therapy.⁶

⁴ Throughout this Report, I also refer to a POSA as one of ordinary skill in the art.

⁵ Leone Op. Report at ¶ 24.

⁶ Kay Op. Report at ¶ 118.

a person of ordinary skill (“POSA”) in the art relevant to the ’617 patent would have a Ph.D. in biochemistry, molecular biology, genetics, or a related field and at least one year of either academic or industry experience in the field of gene therapy.⁷

9. While I do not meet the actual work experience of one of ordinary skill in the art, I regularly work with people with this skill level and provide assistance to them using various tools for sequence analysis. I base my conclusions on how one of ordinary skill in the art, in my experience, would approach the various alignment tools on that experience, and on the assistance that I have provided on these matters to those with that skill level.

V. DR. QUACKENBUSH’S SEQUENCE ALIGNMENTS

10. I reviewed the sequence alignments presented in the Appendices to the Quackenbush Op. Report.⁸ In my opinion, these alignments are flawed and unreliable for numerous reasons. These reasons include, for example, Dr. Quackenbush’s manipulation of the claimed sequences to create hypothetical sequences using the ’617 Patent as a starting point, Dr. Quackenbush’s ignoring of gap regions in his hypothetical sequences to obtain skewed percent identities, and Dr. Quackenbush’s use of the incorrect denominator (e.g., using the length of the test sequence as a denominator) in numerous of his percent identity calculations. In my opinion, Dr. Quackenbush’s approach is inconsistent with how one of ordinary skill in the art would have performed sequence alignments in the context of the ’617 Patent.

A. Alignment Programs Used

11. As an initial matter, Dr. Quackenbush used seven different alignment programs in his report. Of the seven, five of those programs—BLAST, Needle, Stretcher, Water, and

⁷ Rubanyi Op. Report at ¶ 62.

⁸ See *Opening Expert Report of John Quackenbush, Ph.D.*, dated April 28, 2023 (“Quackenbush Op. Report”).

VI. DR. KAY'S IMPROPER ANALYSIS

303. I also reviewed the Kay Op. Report,³⁵⁸ and specifically the sections where Dr. Kay claims the '617 Patent encompasses “an incomprehensibly large number of possible sequences.”³⁵⁹ I disagree with Dr. Kay's opinions and do not believe Dr. Kay did a proper analysis that one of ordinary skill in the art would have conducted.

304. Dr. Kay claims to have estimated “the total number of sequences encompassed by the Asserted Claims of the '617 Patent” by taking into account “the random distribution of substitutions within the recited sequences.”³⁶⁰ In my opinion, this is a purely hypothetical exercise and does not reflect how one of ordinary skill in the art would have understood the scope of the invention of the '617 Patent. No skilled artisan would completely randomize mutations throughout a known sequence in order to assess the scope of sequences that were within 95% identity, as claimed. On the contrary, one of ordinary skill in the art at the time of the invention would have used available tools and known principles to put practical boundaries on the type and location of mutagenesis carried out in the sequence.

305. For example, in my opinion, one of ordinary skill in the art at the time of the '617 Patent would have consulted known related sequences, such as the sequences of other known AAVs, to identify conserved regions across those sequences. Because one of ordinary skill in the art would have understood that mutating residues within a conserved region could destroy structure or cause a significant change in function, one of ordinary skill in the art would have known not to mutate residues in those regions. Consulting with related sequences would allow one of ordinary skill in the art to have created directed libraries by which they could introduce

³⁵⁸ See *Opening Expert Report of Mark Kay, M.D., Ph.D.*, April 28, 2023 (“Kay Op. Report”).

³⁵⁹ See, e.g., Kay Op. Report Section IX.

³⁶⁰ *Id.* at ¶ 206.

targeted mutations and consult with other sequences as a guide as to where to introduce those mutations.

306. Further, one of ordinary skill in the art would have consulted known crystal structures of related sequences to guide where to introduce mutations to a sequence. For example, I understand that “a hypothetical model of the AAV2 capsid three-dimensional structure” had been developed and was known as the time of the ’617 Patent.³⁶¹ One of ordinary skill in the art would have consulted this hypothetical model such as for the AAV2 capsid protein to inform where mutations could and could not be introduced to a sequence while not disturbing protein folding and structure. In fact, several research groups such as Ried, Shi, Judd, and Warrington did just that. One of ordinary skill in the art would not have, as Dr. Kay suggests, blindly introduced randomized mutations to any region of a sequence.

³⁶¹ See Ex. 58 to Quackenbush Op. Report, Girod at 1052.