

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD,
Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK,
Patent Owner.

Case No. IPR2024-00313
Patent No. RE47,045

REPLY DECLARATION OF F. PETER GUENGERICH, PH. D.

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I, F. Peter Guengerich, declare as follows:

I. INTRODUCTION

1. I previously submitted a declaration in this case (EX1002) and was deposed by counsel for the Patent Owner (EX2103). I previously submitted my CV (EX1003) and discussed my qualifications.

2. I have been asked by Counsel for Gene Company Pty Ltd (Gene Company) to review the Declaration of Dr. Prestwich (EX2052), the materials cited therein, the transcripts of Drs. Del Priore's (EX1069) and Prestwich's Depositions (EX1070), and the Patent Owner's brief to provide my reply opinion in response thereto. My opinions are based on my skills, knowledge, training, education, and experience, and my examination of the materials.

3. I understand I will be compensated for the time I spend on this matter, but my compensation in no way depends on the opinions that I offer or the outcome of the proceeding.

II. DEUTERIUM-SUBSTITUTION WAS PART OF A POSA'S TOOLKIT

4. Dr. Prestwich testified that obviousness must be assessed before the patent was filed (September 12, 2007) from the perspective of a POSA who is presumed to have knowledge of all relevant prior art references. EX2052, ¶¶24-25. During his deposition, Dr. Prestwich testified that the relevant field is chemistry, biochemistry, pharmaceutical science, medicine, or a related field. EX1070, 37:3-

10. I agree. This is consistent with what Dr. Prestwich identifies as Gene Co.'s definition of a POSA. EX2052, ¶26.

5. Dr. Prestwich states that the Patent Owner has proposed that a POSA may have an advanced degree in “a related field with at least three years of experience researching biosynthesis and structure of naturally-occurring terpenoids (e.g., retinoids and bis-retinoids such as lipofuscin pigments, carotenoids, steroids) and/or methods to slow lipofuscin formation or accumulation to treat an ophthalmologic disorder, such as AMD or Stargardt’s disease.” EX2052, ¶28. Dr. Prestwich further testified that the ’045 Patent presumes that “a POSA has specialized skill with respect to the biosynthesis and structure of related natural products and mechanisms of retinal degeneration.” EX2052, ¶27.

6. During his deposition, Dr. Prestwich testified that he has never published any work about slowing or limiting the accumulation of lipofuscin, A2E, or all-*trans*-retinal (ATR)-dimer, on retinoid biosynthesis, or the mechanisms of retinal degeneration. EX1070, 24:8-12, 25:2-15, 38:1-16, 39:5-15, 41:22-42:5. Though Dr. Prestwich states that he has satisfied both Gene Company’s and the Patent Owner’s definitions of a POSA “since 1974,” which is the year his CV says he received his Ph.D., he says that Patent Owner’s definition of a POSA makes no difference to his opinion “unless stated otherwise.” EX2052, ¶¶33-34, EX2053. In

reviewing Dr. Prestwich's testimony, I did not find any place where he identified any way in which Patent Owner's definition would make any difference.

7. Dr. Prestwich's lifetime research achievement is centered on the chemistry, biology and biochemistry of *insect chemical communication*. EX2052, ¶17; EX1070, 30:9-31:1. Dr. Prestwich emphasizes work he did as a post-graduate student in Kenya isolating and purifying diterpenes from *termite soldiers*. EX2052, ¶30; EX1070, 17:7-18:20. He also identifies work he later published with Marcus Boehm placing iodine or tritium labels on *insect* juvenile hormone analogs. EX2053; EX1070, 31:2-33:6. He clarified during his deposition, however, that he did not work with any members of Dr. Nakanishi's team on their (much later) retinoid synthesis papers, and did not collaborate with Marcus Boehm on his retinoid work. EX1070, 16:12-17:6, 20:22-21:22, 35:5-36:5.

8. Furthermore, Dr. Prestwich's reliance on his terpene chemistry work to justify his status as a POSA is at odds with his testimony that he has satisfied the Patent Owner's definition "since 1974." EX2052, ¶33. This is the year his CV says he received his Ph.D. EX2053. According to Dr. Prestwich's own testimony, he completed three years of insect terpene structural characterization several years **after** 1974. EX2052, ¶¶30-31. His subsequent terpene work was even later. It is thus unclear whether Dr. Prestwich ultimately satisfied Patent Owner's identified pre-requisites by 1974 as Dr. Prestwich asserted.

9. Patent Owner's definition of a POSA also eliminates certain important knowledge that a POSA would have had by September 2007. Specifically, Patent Owner's definition removes all mention of a POSA having had practical knowledge about, among other things, the deuterium isotope effect. EX2052, ¶¶26, 28. In my opinion, excising the practical knowledge of the deuterium isotope effect from the toolkit of the POSA is counterfactual and incorrect.

10. Indeed, Dr. Prestwich acknowledges that the deuterium kinetic isotope effect was a recognized and versatile tool for studying chemical and biological processes, and particularly for elucidating biosynthetic pathways. EX2052, ¶¶129-138. Dr. Prestwich thus acknowledges that deuterated compounds had been "widely used" and that it was routine practice to use deuteration to demonstrate that a given step in a pathway affected the rate of its direct or downstream products (i.e., was rate-limiting). EX2052, ¶¶129-138, 187 & FN33-34, FN47.

11. Dr. Prestwich acknowledges that it was known by September 2007 that deuterium substitution was useful to stabilize existing drugs against undesirable enzymatic metabolism and to retain drug efficacy for the drug's known indication while reducing the level of toxic metabolites the drug produces, but he argues that deuterium substitution would not always be therapeutically useful to slow every undesirable reaction. EX2052, ¶¶139-157. Dr. Prestwich misapprehends my testimony, which was specific to the reaction at issue. Vitamin

A was already being used to treat macular degeneration patients, as evidenced by the prior art. Making a form of vitamin A that was stabilized against undesirable A2E formation is very analogous to the many successful uses of the kinetic isotope effect (KIE), as acknowledged by Dr. Prestwich. EX2052, ¶167. Employing deuteration in the relatively straightforward A2E/lipofuscin pathway is even more predictable than the deuterium-substitution approaches he embraces.

12. Dr. Prestwich argues that many deuterated drugs have not found application in drug therapy. EX2052, ¶¶155-156. However, the claims at issue are satisfied by administration to rodents and do not require administration to humans or FDA approval. EX1070, 59:22-66:6. Moreover, Dr. Prestwich ignores testimony that Patent Owner's counsel submitted in this case explaining that it has been understood for many decades to use targeted deuterium substitution to slow C-H bond breakage on biological or pharmaceutical compounds to improve safety and/or efficacy where the C-H bond breakage was at least partially rate-limiting. EX2008, 25-27. Patent Owner's counsel submitted testimony that deuterium substitution was expected to maintain a compound's selectivity and potency. EX2008, 31. In the scenario at issue here, that means that C₂₀-deuterated vitamin A was expected to favorably support the essential ocular functions of vitamin A (including the visual cycle) while decreasing the amount of undesirable A2E/lipofuscin formed. It was thus a predictable result to a POSA that C₂₀-

deuterated vitamin A substitution would reduce A2E/lipofuscin formation without interfering with the visual cycle.

13. In the testimony that Patent Owner's counsel submitted, I identified some companies interested in deuterated pharmaceuticals in the lead-up to the September 2007 critical date, including three companies whose business model was established based on synthesizing deuterated analogs of known pharmaceutical compounds. EX2008, 31 (citing Auspex (2001), Protia (2003), and Concert (2006)). Patent Owner's counsel also submitted my testimony that these companies reported successful deuteration results for a number of known pharmaceutical compounds prior to the September 2007 critical date. EX2008, 32-39. Though deuteration had been known to be useful for decades, a POSA would have been especially cognizant of deuteration as a well-embraced and readily available strategy leading up to the critical date in September 2007 (e.g., EX2019). Patent Owner submitted my testimony that this accelerated interest in deuterium substitution in the 2005-2007 time-frame resulted in an increase in patent publications and grants over the following couple of years and naturally reflected acceptance of deuteration as a standard strategic approach. EX2008, 39-41. I thus disagree with the Patent Owner's attempt to define the POSA in a manner that excises the deuterium-substitution knowledge from the POSA's tool-kit.

14. Dr. Prestwich does not explain or attempt to justify the decision to eliminate practical knowledge about deuterium isotope effect from the skill set of the POSA. Significantly, Dr. Prestwich does not assert that he had a practical knowledge about kinetic deuterium isotope effects before he began working on this case. Instead, he testified that he had not read the references relied upon in his declaration until he began work on this case (e.g., EX1070, 21:15-22), which references include discussions of kinetic deuterium isotope effects.

15. Regardless of whether the Patent Owner's definition is adopted, however, I have specialized knowledge with respect to the biosynthesis and structure of related natural products incorporated into the Patent Owner's definition, including naturally occurring terpenoids (including retinoids and steroids), as well as mechanisms of retinal degeneration. EX1003. Building on my pre-existing knowledge, education, and experience, my review of the prior art literature further supports my ability to testify regarding the perspective of a POSA at the relevant time regardless of which definition is applied.

III. MOTIVATION TO SUBSTITUTE C₂₀-DEUTERATED VITAMIN A TO SLOW A2E FORMATION WITH REASONABLE EXPECTATION OF SUCCESS

A. Patent Owner's Rate-Limiting Step Arguments Are Incorrect

i. Patent Owner Mischaracterizes My Testimony

16. I understand that Patent Owner argued that during my deposition that I "abandoned the key premise that a '1,5 shift' in Mata's" A2E biosynthetic

pathway “was ‘likely’ rate limiting, admitting [I] could not say this, that a POSA would not be looking for the rate-limiting step, and that other steps could be slower and rate-limiting.” E.g., POR at 2, 26-27 (citing, e.g., EX2103, 50:8-54:14, 55:3-13, 56:13-23, 64:15-65:14, 88:12-89:21; EX1002, ¶¶98, 178, 181, 184, 260, 353). This argument fundamentally mischaracterizes my testimony.

17. Patent Owner’s argument conflates the concept that the 1,5-sigmatropic rearrangement was likely a rate-limiting step in the formation of A2E (i.e., a step for which attenuation of the rate would be likely to slow production of A2E) with whether this step was “the” rate-limiting step (i.e., the only step the slowing of which would be likely to slow production of A2E). Patent Owner’s argument mischaracterizes my deposition as abandoning my testimony that a POSA would have recognized by September 2007 that slowing the 1,5-sigmatropic rearrangement likely would slow A2E production. Patent Owner is wrong. A POSA by September 2007 (before the filing date of the challenged patent) viewing the A2E biosynthetic pathway in Mata would have recognized that slowing the 1,5-sigmatropic rearrangement likely would slow A2E production, as I testified in my first declaration.

18. During my deposition, I again explained that a POSA would have recognized from viewing the biosynthetic pathways in Mata that the 1,5-sigmatropic rearrangement was likely “a” rate-limiting step in the overall process,

that requiring identification of “the” one and only rate-limiting step was unnecessary for this pathway, and that a POSA would have recognized that slowing the 1,5-sigmatropic rearrangement likely would slow the production of A2E regardless of whether any other steps identified by Mata also could be inhibited to slow A2E production. EX2103, 55:12-56:10 (“So you may have *more than one rate-limiting step* [i]n the process.”), 56:24-57:14 (“As I said, we tend not to use the concept of *the* overall rate-limiting step unless there’s particular evidence about rates of specific steps.”), 57:22-23 (“As I said, you can have *multiple slow steps*”), 64:1-14 (“This is not a cyclic process... This is a linear reaction...you will actually slow down the production of the final product”), 65:3-7 (“one should [be able to] slow down the overall production of the undesirable materials, that being the A2PE and the A2E”). What makes a step rate-limiting for A2E formation is that slowing that step slows the formation of A2E. A POSA looking at Mata’s disclosure would have recognized by September 2007 that the 1,5-sigmatropic rearrangement was a step that should be inhibited to slow A2E formation.

19. I testified during my deposition that the rate-limiting step that “first” would have jumped out to a POSA from the Mata biosynthetic A2E pathway was the 1,5-sigmatropic rearrangement. EX2103, 58:2-12 (“These are strictly chemical reactions, and in many ways, they’re actually simpler. So if you inhibit the first

step...after the condensation of the phosphatidyl [ethanolamine], *if you inhibit that step [the 1,5-sigmatropic rearrangement], you will block the accumulation of the APE intermediate*, and then *you'll actually have less material to go on to the subsequent products*, regardless of how slow or fast they are.”), 63:19-25 (“*it doesn't matter if the subsequent steps are slow* if you can actually inhibit the first one. Or I should say *attenuate the first one. Then you will actually lead to less of a final product.*”), 65:8-21 (“It turns out that the 1,5-sigmatropic rearrangement presents what...a POSA would consider *the easiest route to inhibition* because all one had to do was introduce the different [isotope] of hydrogen at a particular position, which was *already known and reported in the literature.*”); 89:13-21 (If you can slow down the “first step” after the initial condensation (i.e., the 1,5-sigmatropic rearrangement), “then *you can slow down the overall reaction*. That’s the whole point here.”); *see also* EX2103, 56:13-23 (“[T]he first step [a POSA would have understood was rate-limiting] is the 1,5-sigmatropic rearrangement [that] involves the breaking of [a] carbon-hydrogen bond,” which made it the most obvious and likely step to inhibit among the possibilities). Contrary to the Patent Owner’s argument, I did not abandon my opinion that a POSA would have recognized C-20 deuteration was likely to inhibit the 1,5-sigmatropic rearrangement and thereby favorably inhibit A2E formation, regardless of whether

inhibiting subsequent steps (e.g., the 3,3-sigmatropic rearrangement) also was likely to slow A2E formation to some extent.

20. I also understand the Patent Owner has argued that I testified during deposition that nothing in Mata or Fishkin suggested the 1,5-shift was rate-limiting. POR at 33-34 (citing EX2103, 121:6-124:4). That is not correct. Counsel for Patent Owner asked me whether the prior art expressly teaches that cleavage of the C-20 hydrogen bond “was recognized to be relatively slow under physiological conditions.” EX2103, 121:6-123:12. I explained that the conditions of the reaction (e.g., how long they took even under “forced” experimental conditions) indicated to a POSA the reaction was slow under physiological conditions. *Id.* I also testified that Mata and Fishkin attribute in vivo lipofuscin formation to reactions involving removal of the hydrogen from carbon-20 of vitamin A and its active analogues, though the challenged patent and the patent agency process with the patent owner did not really discuss the fact of this prior art disclosure. EX2103, 51:17-52:4, 52:25-53:6, 53:14-19.

ii. The [1,5]-Shift Need Not Be The Slowest Step to Reduce A2E/Lipofuscin Formation

21. Dr. Prestwich testifies that “[f]aster steps before or after the rate-limiting [step] in a multi-step chemical reaction do not significantly influence the overall reaction rate, as the system can only proceed as quickly as the slowest component allows.” EX2052, ¶51. This statement is not necessarily correct as Dr.

Prestwich presents it, and Dr. Prestwich (like the Patent Owner) incorrectly conflates the concept of “rate-limiting steps” with a concept of “the Rate-Limiting Step.” EX2052, ¶¶50-54 (Section V.A). Even Dr. Prestwich’s cited literature rebuts his assumption that there is necessarily a single “the rate-limiting” step that must be identified as a prerequisite for reasonably expecting that the pathway will be inhibited by inhibiting one of its steps. See, e.g., EX2052, ¶119 (inhibiting the visual cycle sufficiently to prevent formation of retinotoxic A2E lipofuscins “requires identification of rate-limiting *steps* in the operation of the visual cycle”) (quoting Maiti 2006, EX2066). He identifies multiple **steps** in the visual cycle as rate-limiting, and then proposes inhibiting still other steps to reduce A2E formation. EX2052, ¶¶76 (identifying reduction of all-*trans*-retinal to all-*trans*-retinol as a rate-limiting step), 84 (again), 85 (identifying RPE65 as located on the rate-limiting pathway), 116 (proposing to reduce A2E formation by inhibiting a third enzymatic step—11-*cis*-RDH—on the visual cycle using isotretinoin). In other words, it is not correct to insist that necessarily there is only one step (i.e., the slowest of all steps) in a pathway that must be inhibited to inhibit the pathway. Dr. Prestwich provides no good reason to assume there would be any such prerequisite in the A2E biosynthetic pathway. Slowing the A2E biosynthetic pathway was more straightforward than the enzymatic examples Dr. Prestwich discusses, in which one step was potentially much, much slower than others step in the enzymatic cycle.

22. Dr. Prestwich's assertion depends on a flawed assumption that the reaction rate of one step in a linear chain of reactions is unaffected by the rate of the steps that precede it. As Dr. Prestwich admits elsewhere, however, a reaction rate often increases as the concentration of the reactants increases. EX2052, ¶184 ("In the multistep reaction described by Mata 2000," calculating the magnitudes of the rate constants of the individual steps "necessarily requires at least an understanding of the rate constants and *concentration of the reactants* involved in each individual step"); see also EX2052, ¶¶104 & 198 (reaction rates vary based on the concentrations of the reactants), 110 ("the processes are intimately interconnected" and "Changes to any one process could, and likely would, have multiple effects elsewhere in the tightly interconnected system" as "concentrations of ATR transiently accumulate[e] in the OS" (outer segment of the photoreceptor cells)), 185 (rate constant varies with changes in "local concentration").

23. The reaction rate will similarly decrease as the concentration of the reactants decreases. This fact is evidenced by Dr. Prestwich's assertions that restricting ATR from the eye would reduce A2E concentration (multiple steps downstream from ATR in the biosynthesis pathway for the A2E byproduct). EX2052, ¶¶50, 56. This example also amply demonstrates the error of assuming a reaction must be "the Rate-Limiting Step" in a pathway to impact the concentration of the ultimate product. The creation of ATR in the visual cycle is a

very rapid step induced by exposure of 11-*cis*-retinal to light. EX2052, ¶56, Figure 2. This reaction takes place very rapidly (much faster than a [1,5]-sigmatropic rearrangement or even a base-catalyzed removal of a carbon atom), every time our brains receive a visual impulse. Formation of ATR is thus rate-limiting for A2E formation in the sense that eliminating or drastically reducing ATR concentrations from the photoreceptor outer segments can reduce or eliminate A2E formation. But that does not imply that conversion of 11-*cis*-retinal to ATR is the slowest reaction step in the A2E synthesis pathway. By September 2007, a POSA would have recognized that the opposite was true (i.e., ATR formation itself may likely have been the fastest step in the A2E pathway).

24. Accordingly, for the linear chemical reaction at issue in A2E formation, a POSA would have reasonably expected that slowing the rate of the [1,5]-hydrogen shift in NRPE would reduce the concentration of the products of that shift, and this slowed reaction step would reverberate down the linear path of products that follow. I explained this at length during my deposition. E.g., EX2103, 63:19-64:14 (“it doesn’t matter if the subsequent steps are slow if you can actually inhibit the first one. Or I should say attenuate the first one. Then you will actually lead to less of a final product.”), 89:17-21 (if you can slow down the first step after the initial (ATR-PE) condensation, then you can slow down the overall reactions). Being upstream of most of the pathway, inhibiting the [1,5]-shift

would impact all downstream products. The location of the [1,5]-sigmatropic rearrangement in the linear pathway thus provided strong reason to look specifically to the [1,5]-shift for inhibition of the undesirable A2E byproduct.

iii. **Calculating Rate Constants Was Not Necessary**

25. Dr. Prestwich argues that it would have been difficult to predict the absolute or relative rates of individual reaction steps in the formation of A2E sufficient to guarantee that the [1,5]-shift was “*the* rate-limiting step in Mata 2000’s proposed A2E pathway.” EX2052, ¶¶110-111, 158, 160, 179-195. As I explained above, however, there was no need to identify a sole and exclusive (“the”) rate-limiting step and no need to calculate the rates of all individual reaction steps *a priori*. The information presented by Mata was sufficient for a POSA to have a reasonable expectation that the [1,5]-shift was “a” rate-limiting step.

26. Dr. Prestwich’s arguments about calculating rate constants falsely assume a POSA would eschew the routine practice of using deuterium kinetic isotope studies to identify rate-limiting steps. Ultimately, even Dr. Prestwich admits that it was routine practice to confirm the identity of rate-limiting steps using kinetic isotope studies, as taught in the prior art, without having to calculate rate constants *a priori*. EX2052, ¶187 FN47. He concedes that, “In practice,” a chemist would measure the effect of the deuterium substitution using routine

kinetic isotope studies, as the inventors did in the '045 patent, rather than engaging in the cumbersome task of trying to calculate and measure rate constants and concentrations. EX2052, ¶¶184-186, 187 FN 47. I agree with Dr. Prestwich that a POSA would have been motivated by the critical date in September 2007 to measure the effects of the deuterium substitution using routine kinetic isotope studies, and that such studies would have been reasonably likely to succeed.

27. Dr. Prestwich argues that subsequent literature identified the '045 patent as identifying the [1,5]-shift as rate-limiting in A2E formation. EX2052, ¶¶228-230; EX2014, 13; EX2015, 8; EX2016, 23; EX2017, 2; EX2075, 12. This merely reflects that the authors were the individuals who reported the results of this routine experimentation.

B. Inhibiting the [1,5]-Shift Was Specifically Desirable

i. Specific Motivation to Inhibit the A2E Byproduct Pathway

28. Dr. Prestwich argues that prior experiments reduced A2E/lipofuscin accumulation by reducing the amount of excess ATR available to form lipofuscin pigments, by restricting supply of vitamin A to the eye or by inhibiting the visual cycle. EX2052, ¶¶112-128.

29. Dr. Prestwich concedes that there was “intense interest” in reducing lipofuscin formation to treat macular degeneration and Stargardt disease, but argues that references discussing “targeting” lipofuscin formation for

pharmacological inhibition were focused exclusively on inhibiting the visual cycle rather than directly inhibiting the A2E byproduct pathway. EX2052, ¶¶165-171, 219, 221-227, 300-306; but see EX1069 (Del Priore Transcript), 203:6-14 (POSA by September 2007 “would have been aware that recent efforts for treating AMD and Stargardt macular dystrophy have centered on targeting A2E formation in RPE cells as a therapeutic strategy for AMD and AMD-like retinal disorders”). Dr. Prestwich argues that the claims are thus only obvious in hindsight. I disagree.

30. The literature that used visual cycle inhibition (isotretinoin, RPE65 inhibitors, etc.) to inhibit A2E formation helped to validate the proposed A2E biosynthetic pathway (as a byproduct of the visual cycle that breaks off from the cycle after ATR is formed if the ATR is not first reduced to all-*trans*-retinol). EX1070, 118:5-19. The experiments thus validated the concept that attenuating or blocking this byproduct pathway would reduce A2E/lipofuscin formation. That conceptual validation strongly supported the suggestion in the prior art to directly inhibit the byproduct pathway rather than the visual cycle.

31. Building on the mechanistic studies using isotretinoin and RPE65 inhibitors, for example, the art expressly suggested directly inhibiting the byproduct pathway itself to reduce A2E/lipofuscin formation without the concomitant adverse effects that predictably followed from inhibiting the visual cycle (which requires ATR formation). In addition to the prior art suggestion to

inhibit the A2E byproduct pathway itself, which I discussed in my opening declaration (e.g., in Mata (EX1010)), Dr. Prestwich submitted additional literature corroborating that there arose in 2007 an express suggestion to specifically inhibit the A2E byproduct pathway itself (without inhibiting the visual cycle).

32. For example, Dr. Prestwich repeatedly relies as prior art on the September 4, 2007, publication by Kim et al. in Biochemistry (EX2019). E.g., EX2052, ¶¶79, 94. Identifying prior attempts to treat macular degeneration, Kim 2007 cites references discussing the use of RPE65 antagonists, 13-*cis*-retinoic acid/isotretinoin, and fenretinide/4-HPR (Maiti (EX2066), Sieving (EX1038), Radu 2003 (EX1035), and Radu 2005 (EX1030)) to reduce the formation of lipofuscin pigments. EX2019, 7. In contrast to these existing approaches, Kim 2007 expressly suggests employing “yet other novel approaches to therapy” based on an “[i]mproved understanding of the mode of genesis of A2E and other RPE lipofuscin compounds” (e.g., ATR-dimer). EX2019, 7. Kim 2007 described the biosynthesis pathway for A2E, explaining that they had previously corroborated the first step in the byproduct pathway (when A2E forms by conjugating ATR with phosphatidylethanolamine to form NRPE), and the subsequent formation of A2PE. EX2019, 6-7 & Fig. 1. Kim 2007’s experiments then corroborated that formation of dihydro-A2PE precedes the formation of A2PE. EX2019, 6-7. In other words, the “considerable interest in retarding A2E formation as a means to prevent vision

loss in Stargardt disease and, perhaps, age-related macular degeneration” (EX2052, ¶301; EX2058) climaxed before the critical date in September 2007 with a new focus on inhibiting the byproduct pathway itself rather than the visual cycle. Given Kim 2007’s corroboration of Mata’s biosynthetic pathway, a POSA readily would have appreciated that using C₂₀-deuteration to inhibit the formation of the phosphatidyl analogue of an enamine was most accessible and a promising approach for inhibiting the formation of undesirable A2E/lipofuscin.

33. By the critical date in September 2007, a POSA was well aware that impaired night vision, delayed dark adaptation, and photoreceptor cell death were all known consequences of inhibiting the visual cycle, including via vitamin A deficiency. EX1069 (Del Priore Transcript), 216:20-217:2 (A POSA by September 2007 “would have been aware that long-term slowing of the visual cycle leads to photoreceptor cell death and loss of vision”), 217:12-16 (“slowing down the visual cycle causes delayed dark adaptation and night blindness”); 135:8-136:16 (agreeing it was known to a POSA before 2007 that “Deficiency in vitamin A is well known to cause night blindness and eventual death of photoreceptors”), 29:18-32:16 (“long-term deprivation of vitamin A leads to [] photoreceptor cell death in the eye,” six months “would be plenty of time to cause damage,” and there is only a “short period of time during which you could deprive the [ocular] tissue

of vitamin A, but not have it be irreversible [damage]”), 57:1-9 (vitamin A is essential to vision).

34. The Patent Owner’s expert testified that these predictable effects of inhibiting the visual cycle were so undesirable that they rendered such approaches impractical as a therapy. EX1069, 215:17-216:11 (“fenretinide was known to cause delayed dark adaptation and other side effects”), 217:17-24 (isotretinoin and fenretinide can slow down the visual cycle, causing delayed dark adaptation and night blindness), 208:21-209:13 (isotretinoin predicted to cause adverse night blindness by inhibiting the visual cycle); 33:1-20 (night blindness impairs rod photoreceptors, macular degeneration patients already have impaired cone photoreceptors), 33:21-36:8 (delayed dark adaptation “will give you all sorts of problems,” including making it difficult to drive or even walk at night, and is associated with macular degenerations including Stargardt disease), 214:13-215:11 (isotretinoin was considered “too toxic for long-term administration in humans” and its side effects in humans, including birth defects, depression and suicide “would preclude long-term therapy with this drug”), 210:2-211:8 (isotretinoin doses necessary to reduce A2E in humans “would be toxic”), 203:15-204:21 (reducing dietary vitamin A was judged “impractical as a treatment or therapy” to inhibit A2E/lipofuscin accumulation), 45:17-25 (by inhibiting any enzyme of the visual cycle “you get disease”), 46:17-24 (“So you need the integrity of this visual

pathway in order for vision to function properly. If you interfere at any step...[t]here is a variety of things that can happen, none of which are good.”), 52:15-53:6 (inhibiting 11-*cis*-RDH predictably leads to vision loss), 54:6-22 (functionally inhibiting 11-*cis*-RDH “could have negative downstream consequences”), 55:2-14 (“for RPE 65, it was recognized that there would be negative consequences from that enzyme not working properly, and in fact there was a form of Leber’s congenital amaurosis that was targeted for gene therapy later on because of that reason”), 49:19-50:9 (Leber’s congenital amaurosis results in severe loss of vision because it inhibits the visual cycle); EX1002, ¶¶65, 67-68, 71, 76 (night blindness known to result from impairing visual cycle; POSA motivated to inhibit A2E/lipofuscin formation without inhibiting the visual cycle).

35. Because the [1,5]-shift was known to occur downstream of the formation of ATR in the visual cycle (and within the A2E byproduct pathway but not part of the visual cycle itself), a POSA would have recognized that inhibiting the [1,5]-shift would predictably avoid the night blindness, delayed dark adaptation, and eventual cell receptor death known to result from inhibiting the visual cycle. EX1002, ¶¶59-69; EX1069 (Del Priore Transcript), 181:9-182:16 (A2E is a minor and unavoidable byproduct of the visual cycle formed by non-enzymatic reactions in photoreceptor outer segments and RPE phagolysosomes), 183:14-20 (inhibiting the A2E byproduct pathway “should not impact the vision

cycle”), 192:20-25 (A2E is a side reaction; not a necessary component of the visual cycle). A POSA thus would have had good reason to inhibit the [1,5]-shift to reduce A2E/lipofuscin formation as opposed to using isotretinoin, fenretinide, RPE65 inhibitors, or vitamin A restriction to avoid their predictable side effects.

36. Dr. Prestwich points to the enzymes of the visual cycle, a chiral lipid membrane, and transport of NRPE and ATR within the outer segment as influencing the calculations of the rate constants. EX2052, ¶185. As I explained above, however, inhibiting the enzymes that drive the visual cycle was known to have predictable and undesirable detriments (night blindness, delayed dark adaptation, photoreceptor cell death, and ultimately blindness) and other toxicity issues that weighed strongly in favor of inhibiting the A2E byproduct pathway itself. Whether or not any of these factors influence the values of the rate constants, Dr. Prestwich identifies no reason that they would make C₂₀-deuteration less likely to inhibit A2E/lipofuscin formation.

37. Narrowly defining pharmacologic inhibition to require using small molecules to bind enzymes, receptors or other proteins wrongly ignores the teachings in the prior art to target the A2E biosynthetic pathway itself, which was said to be essentially non-enzymatic. See paragraph 63 below; EX2074, 4. When Mata discussed “pharmacological targets” for inhibition and “[p]armacologic inhibition of one or more steps in the A2E synthetic pathway,” these statements

were not directed to inhibiting proteins. EX1010, Abstract, 7159. Instead, the pharmacological targets were the “precursors of A2E identified in this study” (e.g., APE/NRPE conversion ultimately to A2PE-H₂), not enzymes. EX1010, Abstract. Classic antagonist inhibitors are very frequently molecules that are similar to an operative molecule but are not susceptible to, or are less susceptible to, the reaction at issue. Using C₂₀-deuterated vitamin A to feed the visual cycle but inhibit A2E formation via the [1,5]-shift falls squarely within the paradigm for pharmacological inhibition referenced by Mata.

ii. **Additional Disclosed Benefits of Inhibiting the [1,5]-Shift**

38. Dr. Prestwich argues that all steps on the lipofuscin chromophore biosynthesis pathways were upstream of A2E, downstream of ATR formation, and thus represented equally favorable candidates for inhibition to prevent A2E formation. E.g., EX2052, ¶¶158-178. This argument misapprehends my point, however. Mata provided good reason before the '045 patent was filed to inhibit the [1,5]-shift by first disclosing that the 1,5-sigmatropic rearrangement is just upstream of the intermediate that Fishkin teaches results in **both** A2E and ATR-dimer, but sufficiently downstream of ATR formation to inhibit undesirable lipofuscin formation without interfering with the visual cycle. EX1002 ¶¶84-85, 93-98, 184. I testified that the [1,5]-shift is “just upstream of the intermediate that **results in both A2E and ATR-dimer** but sufficiently downstream of ATR

formation, thus reducing the formation of undesirable lipofuscin without interfering with the visual cycle.” *Id.*, ¶184. My point is the prior art **before** the challenged patent disclosed the favorability of inhibiting **at this specific point** in the pathway. EX2103, 39:9-43:3 (“I’m not relying on [the patent]...[I’m] just say[ing] that it’s in the patent, but it is also in the open literature...that was published well before the patent was applied for....[T]he fact is that the patent was actually using the scheme, basic scheme, that was already published.”). It is simply not true that all intermediates in Mata 2000 are just upstream of both A2E and ATR-dimer. Dr. Prestwich is completely mistaken. The specific location of the [1,5]-shift in the linear biosynthetic pathways was clearly favorable because it was upstream of **both** the A2E and ATR-dimer pathways, as taught by Fishkin (EX1011), while also being downstream of the visual cycle. Dr. Prestwich ignores this feature.

39. Dr. Prestwich also ignores other important aspects of the A2E/lipofuscin biosynthetic pathway disclosed by Mata. Though Dr. Prestwich acknowledged during his deposition that Mata taught that the formation of dihydro-A2PE was essentially irreversible under physiological conditions (EX1070, 137:3-19), Dr. Prestwich ignores the importance of inhibiting the pathway before this point of no return. It would have been apparent to a POSA before September 2007 that the [1,5]-shift was the first truly favorable step from an

inhibition standpoint in the A2E biosynthesis pathway that would not interfere with the visual cycle and that would advantageously inhibit ATR-dimer formation as well.

40. A POSA before September 2007 also would have recognized that inhibiting the [1,5]-shift would not impair the body's natural mechanisms for removing ATR from the outer segment of the photoreceptor cells to avoid undesirable lipofuscin formation. The natural utility of conjugating ATR with PE to make NRPE is that this PE-conjugation allows flippase enzymes (e.g., RmP encoded by ABCR gene) to translocate the ATR out of the disc space of the photoreceptor outer segments so that the ATR can be converted to retinol. EX2074, 4; EX1035, 1; EX1070, 95:5-97:15; EX1069 (Del Priore Transcript), 44:16-45:9, 185:17-186:1, 187:7-21, 190:4-21. Conversion of all-*trans*-retinal to all-*trans*-retinol is critical to visual function in at least two respects: (1) it continues to feed the visual cycle; and (2) retinol will not directly feed A2E formation, as Dr. Prestwich acknowledged during his deposition. EX1070, 118:5-19. ATR-PE conjugation (forming NRPE) is thus an important step in the body's natural processes to fight against A2E formation. Formation of NRPE happens very quickly and reversibly, allowing the ATR to be released from the PE on the outer surface of the disc membrane. EX2103, 65:22-67:5. Though Stargardt 1 patients and other ABCR-negative patients are characterized by impaired RmP function,

age-related macular degeneration patients do not necessarily have impaired RmP function (as their lipofuscin has accumulated much more slowly over time).

Inhibiting NRPE formation would thus be counterproductive for AMD and many other non-ABCR-linked macular degeneration patients. A POSA before September 2007 thus would have recognized that the [1,5]-shift was the earliest and best location for inhibiting A2E formation in the pathway.

iii. Dr. Prestwich's Discussion of Other Steps in the Pathway Casts No Doubt on Motivation or Reasonable Expectation of Success Using the [1,5]-Shift.

41. Dr. Prestwich argues that other steps might have been slower than the [1,5]-shift. EX2052, ¶¶196-216. But Dr. Prestwich identifies no reason that C₂₀-deuteration would be unable to slow the pathway sufficiently to reduce A2E formation.

42. First, Dr. Prestwich argues that a POSA would have looked to inhibit the bimolecular condensation of NRPE with a second ATR molecule by limiting the ATR concentration in the outer segment. EX2052, ¶¶197-206. Dr. Prestwich reasons that the rate of the bimolecular reaction would be multiply-dependent on ATR concentration and would be unlikely to occur frequently in a complex, chiral protein-lipid membrane environment. But Dr. Prestwich's point that ATR concentrations in the disc space of the photoreceptor outer segment were elevated points in the opposite direction than what he says: it indicates that the phosphatidyl

analogue of enamine (via C₂₀-deuteration) is the limiting reactant. Reducing the concentration of the limiting reactant (in this case, inhibiting the [1,5]-shift) would predictably slow the biomolecular condensation and the downstream, irreversible, and undesirable formation of dihydro-A2PE more potently and easier than reducing ATR concentrations, and without the predictable and undesirable adverse effects on vision that resulted from reducing ATR formation.

43. Dr. Prestwich next points to acid hydrolysis of A2PE to A2E, noting that this step requires overnight incubation in acid when performed in vitro. EX2052, ¶¶207-211. But none of the literature Dr. Prestwich points to purports to describe A2PE conversion to A2E as being slower (certainly not much slower) than the [1,5]-shift. Instead, these references are commenting that this conversion occurs slowly in comparison to reactions known to be catalyzed under acidic environments. Dr. Prestwich does not assert that the [1,5]-shift qualifies as such. These references do not undermine the motivation to inhibit the [1,5]-shift by C₂₀-deuteration.

44. Instead, their analysis was directed to the suggestion that conversion of A2PE may be enzymatically catalyzed by phospholipase D in the photoreceptor outer segment. EX2052, ¶210 FN50. Dr. Prestwich notes that I testified that it was unlikely that an enzyme had developed specifically to perform the [1,5]-shift. Phospholipase D is not proposed to operate on the [1,5]-shift and is a non-specific

enzyme that is not proposed to be specifically directed to A2E formation. Whether or not A2PE conversion to A2E occurred via acid-catalyst in the RPE lysosomes or via phospholipase D in the photoreceptor outer segment, inhibiting the [1,5]-shift would reduce the amount of dihydro-A2PE and the resulting concentration of A2E.

45. Finally, Dr. Prestwich argues that phagocytosis was more likely to be rate-limiting than the [1,5]-shift and a step to which Dr. Prestwich analogizes waiting for a car ferry. EX2052, ¶¶212-216. Regardless of Dr. Prestwich's analogy, a POSA would have recognized that the key to inhibiting A2E/lipofuscin formation was slowing the [1,5]-shift. A build-up of higher concentrations of dihydro-A2PE in the outer segments was undesirable, even if Dr. Prestwich were correct that RPE phagocytosis of those outer segments was periodic like a car ferry.

iv. Dr. Prestwich Mischaracterizes My Prior Statements About C-H Bond Cleavage

46. Dr. Prestwich argues a POSA would not have recognized the [1,5]-shift was a slow reaction. EX2052, ¶¶217-230. His argument is premised on an incorrect and partial quote of a portion of EX2083 as if it contradicts my testimony that a POSA would have recognized the [1,5]-shift was likely to have a large KIE. EX2052, ¶218 FN 55. Citing my research published between 1988 and 2005, the 2005 publication Dr. Prestwich cited explains that any tendency to regard the breaking of the particular C-H bond at issue there (in a different reaction in a

different context than the [1,5]-shift at issue here) as generally being relatively rapid, already had been demonstrated to be false. EX2083, 1 (“Although many of the expressed kinetic isotope effects cited in the literature are low and there has been a tendency to regard C-H bond breaking as generally being relatively rapid, **our own work has shown relatively high expressed kinetic isotope effects for several reactions catalyzed by mammalian P450 enzymes.**”) (citing refs. 40-45); see also EX2009, 199:4-201:5 (discussing postulation before 2012 that other steps in “the P450 catalytic cycle” were also partially rate-limiting). Dr. Prestwich’s partial quotation of this reference is misleading and erroneous.

C. C₂₀-Deuteration of Vitamin A Is a Classic Application of Deuterium Improvement of a Known Active

47. Dr. Prestwich argues that the prior art did not teach that deuterium will slow all undesirable biological reactions, but instead was used to optimize (i.e., stabilize) known drugs being used for their intended purposes. EX2052, ¶¶231-237. In so doing, Dr. Prestwich concedes that using deuterium to slow the [1,5]-shift was within the “technical ability” of a POSA, but argues that applying this technical ability to vitamin A would require conceiving of a new conceptual framework. EX2052, ¶236. He further argues that using deuterium to slow the undesirable A2E byproduct pathways is not analogous to slowing the enzymatic metabolism of a desired drug or to altering the metabolism of a drug to reduce production of toxic metabolites. EX2052, ¶¶238-252. I disagree.

48. ATR is a compound that is vital to vision in the visual cycle. EX1069 (Del Priore Transcript), 37:4-45:25; EX1069, 57:1-9 (vitamin A is essential to visual cycle). Enzymes (e.g., atRDH) in the body are designed to preserve those vitamin A molecules for use in the visual cycle by recycling them (e.g., converting ATR to all-*trans*-retinol). EX2052, ¶84 (“Since the reduction of retinal to retinol is the rate-limiting step in the vitamin A cycle, the sequestration of all-*trans*-retinal as NRPE and access of the latter to all-*trans*-retinol dehydrogenase [atRHD], appears to be important in limiting the accumulation of all-*trans*-retinal in the outer segment.”); EX1036 (Fishkin 2003), 2. A POSA would have understood from Mata, Kim 2007, and other references that the [1,5]-shift unleashes the conversion of the essential vitamin A nutrient into a toxic and undesirable byproduct. A POSA would have reasonably expected C₂₀-deuteration to thus preserve the vitamin A nutrient (analogous to stabilizing the desired drug for a prolonged, desired effect) while also reducing production of the undesirable, toxic byproduct (analogous to metabolic switching). C₂₀-deuteration of vitamin A thus fits well within the established paradigm of improving existing compounds through targeted deuteration.

49. By inhibiting the [1,5]-shift, the NRPE would remain available for active transport in cells with functioning ABCR transporters (e.g., in AMD patients), for conversion back to retinol (and subsequent use in the visual cycle),

and for passive transport even in cells without functioning ABCR transporters. EX2052, ¶¶60-61, 185 & Figure 3 (discussing active and passive transport); EX2052, ¶84 (“Since the reduction of retinal to retinol is the rate-limiting step in the vitamin A cycle, the sequestration of all-*trans*-retinal as NRPE and access of the latter to all-*trans*-retinol dehydrogenase [atRHD], appears to be important in limiting the accumulation of all-*trans*-retinal in the outer segment.” (citing EX1036 (Fishkin 2003))), ¶89 (“removal [of ATR from the inner leaflet of the outer segment disc membrane] refers to its direct enzymatic reduction to all-*trans*-retinol, or formation of a reversible Schiff base linkage with phosphatidylethanolamine (PE) and *N*-retinylidene phosphatidylethanolamine (NRPE) and its transport across to the outer leaflet of OS disc membrane, where subsequent reduction to all-*trans*-retinol can occur”) (citing EX2062 (Rózanowska 2005), 4).

50. Dr. Prestwich argues that “metabolic switching” is inapplicable because he assumes that ATR is the “toxic metabolite” and that there is no non-toxic metabolite that vitamin A could switch to and produce instead of ATR. EX2052, ¶¶246-252. But Dr. Prestwich misapprehends the point. ATR is not the toxic metabolite. The products of the [1,5]-shift, and ultimately A2E, are the toxic metabolites. The point is to preserve vitamin A (ATR that can be reduced to all-*trans*-retinol and proceed through the visual cycle) and to avoid the undesirable byproduct pathway involving the [1,5]-shift and downstream lipofuscin pigment

products. Contrary to Dr. Prestwich's argument, there was no need for "metabolic switching" of enzymes involved in the visual cycle. Indeed, the point of C₂₀-deuteration is that it was not expected to impair the enzymatic action of the visual cycle but was expected to impair the undesirable A2E byproduct pathway.

D. Dr. Prestwich Fails to Properly Distinguish Roth & Itou

51. Dr. Prestwich argues that Roth and Itou would not have motivated a POSA to employ C₂₀-deuterated vitamin A in place of non-deuterated vitamin A. EX2052, ¶¶220, 253-256. Dr. Prestwich provides several reasons that he believes that the KIE reported in Roth and Itou would not be expected for the [1,5]-shift described in Mata. EX2052, ¶¶220, 257-299.

52. First, Dr. Prestwich argues that Roth and Itou do not identify the rate of the [1,5]-shift relative to the pathway shown in Mata 2000 for the formation of A2E and that Mata does not contain dedicated kinetic studies for the A2E biosynthetic pathway. EX2052, ¶¶259-267. Dr. Prestwich misunderstands my reliance on Roth and Itou as being "circular," arguing that I have argued one must conduct testing to recognize the significance of the [1,5]-shift. That is not correct. Roth and Itou provided strong prior art evidence that the C₂₀-deuteration would markedly slow the [1,5]-shift, which Mata informed was a prerequisite for A2E/lipofuscin formation (to which Fishkin added ATR-dimer formation). Doering, a 2006 publication that the Patent Owner submitted in this case,

corroborated the teachings of Roth and Itou that a large KIE was expected for the 1,5-sigmatropic rearrangement (disclosed in Mata). EX2025. Where Roth reported a KIE of 12.2, Doering, the reference Patent Owner submitted, taught that—at room temperature—the KIE would be even larger (16.6).

53. Like Roth, Doering could not observe the 1,5-sigmatropic rearrangement under physiological conditions because it was simply too slow of a reaction. Like Roth, Doering thus forced the reaction (339 days at elevated temperatures including 98.4 °C). EX2025, Abstract, 9084. Fishkin and Mata similarly had to force “a slow reaction” that was not very efficient under physiological conditions. EX2103, 120:6-19; EX2103, 123:2-6 (“they are not what I call physiological conditions. I think my opinion would be that these conditions were actually used to force the reaction to make these products”), 124:8-21 (Roth & Konig and subsequent material published since then, but before the patent—namely Doering (EX2025)— recognized that cleavage of the referenced carbon-hydrogen bond would have been slow under physiological conditions), 61:24-62:2 (“Itou and...D[oe]ring later on talked about...basically it’s an irreversible step”), 73:6-74:4 (“there’s another experimental study later by D[oe]ring as well”), 75:5-6 (“I think there were more than one in D[oe]ring, actually, as I recall”). Accordingly, both the nature of the reaction and its position in the pathway made it a prime and favorable location to inhibit lipofuscin formation, as I explained

repeatedly before. A priori calculations of the specific rate constants of the various steps in the pathway were not required to reasonably conclude that C₂₀-deuteration would reduce the concentration of activated ([1,5]-shifted) NRPE, the limiting reactant required for the bimolecular condensation reactions that resulted in undesirable lipofuscin pigments A2E and ATR-dimer.

54. Dr. Prestwich testifies about KIE masking (primarily in enzymatic cycles). E.g., EX2052, ¶¶136-138, 259-262. Because of the pathway at issue here (which is both linear and essentially non-enzymatic), the nature of the [1,5]-shift, and its significant susceptibility to a very strong KIE, masking would not undermine the reasonable expectation of success. Dr. Prestwich's masking argument is speculative, and at most goes to the degree of the KIE that would be observed when measuring A2E rather than whether a KIE likely would result. As I explained previously, and as admitted by the patent, the KIE measured in the challenged patent is the natural result of the C₂₀-deuteration, which was already disclosed in the prior art. A POSA thus would have had a reasonable expectation of success for reducing A2E/lipofuscin formation based on the information available before September 2007. The ease with which this reasonable expectation would have been easily confirmed using routine kinetic isotope studies, as even Dr. Prestwich agrees, demonstrates that it was a straightforward matter (i.e., there was

no technical barrier) and there was a low bar for a POSA to provide experimental data for the substitution.

55. Next, Dr. Prestwich argues that a POSA would not have reasonably expected the KIE in Roth to apply to NRPE. EX2052, ¶¶268-269. First, Dr. Prestwich argues that Mata's disclosure that A2E formed as a result of the same [1,5]-sigmatropic rearrangement discussed in Roth and Itou diverged from other lipofuscin literature that referred to a "[1,6]-proton tautomerization" or a "[1,6] H-shift,' not a sigmatropic rearrangement." EX2052, ¶¶270-273. Dr. Prestwich argues that a sigmatropic rearrangement is mechanistically different from a proton tautomerization, though yielding a "similar" net result. EX2052, ¶¶270-272. Dr. Prestwich proposes that the [1,5]-shift occurs via enzymatic catalysis, and created a graphic to illustrate his proposed mechanism. EX2052, ¶¶274 & Figure 12. Notably, however, Dr. Prestwich does not identify any prior art source for his schematic, and he also does not assert that his proposed reaction mechanism would lack a significant KIE. A significant KIE still would have been reasonably expected for Dr. Prestwich's proposed enzymatic deprotonation.

56. Dr. Prestwich argues that "the description of this reaction in Mata 2000 as a 'sigmatropic rearrangement' is a clear outlier from the rest of the prior art, which expressly describes the reaction as a 'tautomerization' or a 'proton tautomerization,'" and that a POSA would have imagined the same reaction

mechanism he created for his Figure 12. EX2052, ¶277 (citing EX1036, 2; EX1034, 1; EX1018, 1; EX2019, 10; EX2051, 1; EX1011, 5 & Fig. 10); EX1070, 132:20-133:12 (Prestwich Fig. 12 cites no evidentiary source and was drawn up by Dr. Prestwich), 136:2-11 (Dr. Prestwich omitted Mata's proposed biosynthetic pathway from his declaration). Though these references use the term tautomerization or tautomer, none of them provide the reaction scheme Dr. Prestwich created for Figure 12. Moreover, Dr. Prestwich does not dispute that Mata discloses the [1,5]-sigmatropic rearrangement in the prior art, and does not even assert that a POSA would expect C₂₀-deuteration to lack a significant KIE in his proposed reaction.

57. Dr. Prestwich opines that the large structure branching out from the 1,3-pentadiene in NRPE rendered Roth irrelevant. EX2052, ¶¶220, 274, 295-299. Dr. Prestwich opines that the "symmetrical structure" of (Z)-1,3-pentadiene "was expected to produce a significant KIE due to a highly symmetrical transition state," but that NRPE has "bulky and amphiphilic" arms and a nitrogen that he speculates might "stabilize the transition state differently" or "affect" the KIE. EX2052, ¶¶297-298. Dr. Prestwich's testimony gives the false impression that the transition state symmetry refers to the structural symmetry of the molecule. That is not correct. Dr. Prestwich provides no support for his arguments conflating structural symmetry with symmetrical transition states. Contrary to Dr. Prestwich's

unsupported speculation, a POSA would not assume that the transition state of the reaction was asymmetrical. Rather, based on Mata's identification of the NRPE reaction as a [1,5]-sigmatropic rearrangement, a POSA would have recognized that the transition state of the reaction was likely to be symmetrical and subject to a strong KIE as Roth and Itou taught. Dr. Prestwich never testifies that the nitrogen in NRPE would obliterate or diminish the strong KIE. It would not. In fact, analogous molecules were well known in the art to be prone to strong KIEs.

58. Dr. Prestwich argues that Roth measured the KIE in a gas phase but that NRPE's [1,5]-shift can occur via general acid-base chemistry under aqueous conditions, "as with in vivo systems." EX2052, ¶¶220, 278-281 (citing EX2077, 1; EX2078, 1, 3); see also EX2052, ¶¶289-294 (arguing "13-*cis*-retinylidene-*n*-butylamine easily isomerizes" when non-physiological bases are employed). But these references used non-endogenous, caustic (and even combustible) bases (e.g., sodium hydride) to force a specific base-catalysis reaction. Dr. Prestwich admitted that this does not reflect physiological conditions. EX1070, 159:16-161:13. Nor is it general acid-base catalysis. The fact that Mowery and Verdegem had to introduce non-physiological, strong bases into the system to force the reaction is not dissimilar to the high temperatures (resulting in gas phase reactions) required to drive the [1,5]-sigmatropic rearrangement in Roth and Itou. In each case, extreme conditions were applied because the reaction is so slow under

physiological conditions. Accordingly, a POSA would have reasonably expected a strong KIE even under Dr. Prestwich's proposed mechanism.

E. Dr. Prestwich's Proposed Base-Catalyzed [1,5]-Shift Does not Undermine Motivation or Reasonable Expectation of Success

59. Dr. Prestwich argues that ATR-dimer may form via "general acid-base catalysis by membrane-bound proteins in the outer segment," and that this reaction may have been very slow because of the complex and chiral nature of the protein environment. EX2052, ¶¶98-105, 282-283 (citing EX1011, 5). Dr. Prestwich thus argues that the [1,5]-shift in Roth and Itou is a different mechanism than the [1,5]-shift in Mata because the polarity of an aqueous environment made a general acid-base tautomerization more likely if basic amino acid side chains present on a lipid membrane were to remove "acidic hydrogen atoms," but that such general-acid base chemistry would be unlikely in the gas phase reactions measured in Roth. EX2052, ¶¶284-286. Dr. Prestwich also argues that Roth and Itou did not assert that "all types of hydrogen-transfer reactions" would have the same KIE as the [1,5]-sigmatropic rearrangement, and notes that some acid/base-catalyzed mechanisms may have an inverse isotope effect. EX2052, ¶¶287-288 & FN72. Notably, however, Dr. Prestwich does not assert that is the case for the type of acid-base catalysis he proposes for the [1,5]-shift. Indeed, Dr. Prestwich does not assert that chiral-protein-based catalysis weighs against a strong KIE from C₂₀-deuteration. Indeed, enzymes known to perform the type of general acid-base

catalysis invoked by Dr. Prestwich (EX2052, ¶¶95 (FN20)) were known to be prone to strong KIEs. To the extent Dr. Prestwich is correct that a chiral protein-based catalysis was involved in *ATR-dimer formation*, this does not argue against C₂₀-deuteration to reduce *A2E formation*. Instead, it provides good reason to expect C₂₀-deuteration to slow ATR-dimer formation as well.

60. Dr. Prestwich's testimony amounts to nothing more than saying there is no guarantee of success. For my testimony, I applied a standard of reasonable expectation of success rather than one of guaranteed success. In view of the literature, and having reviewed Dr. Prestwich's testimony, it remains my opinion that a POSA by September 2007 had a reasonable likelihood of success.

61. Dr. Prestwich speculates that "due to the involvement of imines and enamines in the reaction and the biphasic aqueous-lipid environment," there was likely to be a "relatively fast" tautomerization reaction "with relatively low activation energies" if the "basic conditions" used in Mowery and Verdegem were employed in the outer segments of the photoreceptor cells. EX2052, ¶¶289-294. However, the "basic conditions" under which Mowery and Verdegem experimented are not prevalent in outer segments of the photoreceptor cells, as Dr. Prestwich himself admits. EX2052, ¶¶94-96 (A2PE formation from ATR and PE is "optimal at neutral pH" and A2PE is formed in the photoreceptor outer segments, which are "characterized by a neutral pH"). Indeed, Dr. Prestwich testified that

sodium hydride is a combustible, insoluble base that does not appear endogenously. EX1070, 159:11-161:13. It can ignite in the presence of water or even air.

62. Moreover, I disagree with Dr. Prestwich's assumption that the description of the biosynthetic pathways as including a tautomer implies that the [1,5]-shift is a rapid reaction. Indeed, some tautomerization reactions are "very slow." EX2033, 10. In the case of an enamine-imine tautomerization proposed by Dr. Prestwich, an imine was generally known to be "more stable" and heavily favored kinetically as compared to an enamine. EX2033, 13 ("Enamines are normally stable only when there is no hydrogen on the nitrogen ($R_2C=CR-NR_2$). Otherwise, the imine form predominates."). Accordingly, the reaction Dr. Prestwich identifies as rapid is actually not the one needed to form dihydro-A2PE from NRPE. EX2018, 3-4 (an enamine tautomer "if" formed initially will "rapidly" return to the more stable imino form). Dr. Prestwich is not justified in his assumption that NRPE conversion to tautomer x is itself a "lower-energy and faster tautomerization." EX2052, ¶294. In contrast to the energetically disfavored conversion of NRPE to tautomer x, Fishkin illustrates the facile ability of "tautomer x" once formed to rotate around the C14-C15 single bond, permitting conjugation with a second molecule of ATR at either of two different locations.

Depending on the state of the tautomer at the time of conjugation, Fishkin teaches that the conjugation product can result in either A2E or ATR-dimer.

63. The slowness apparent to a chemist of ordinary skill before September 2007 of the [1,5]-shift under physiological conditions—regardless of whether the mechanism disclosed in Mata/Roth/Itou is believed or whether acid-base tautomerization is considered as proposed by Dr. Prestwich—explains Dr. Prestwich’s hypothesis that an enzyme might be responsible for the [1,5]-shift resulting in *ATR-dimer*. But Dr. Prestwich does not explain or justify his assumption that *A2E* might be formed via enzyme-mediated acid/base-catalysis of the [1,5]-shift. Fishkin 2005 teaches specifically that the A2-PE intermediate that results in A2E occurs “through a series of random/nonenzyme-mediated reactions.” EX1011, 7091.

64. Nor does Dr. Prestwich assert that C₂₀-deuteration would be expected to lack a significant KIE even under his enzyme-catalyst scenario. Though a POSA before 2007 would think it was unlikely an enzyme existed specifically to catalyze the [1,5]-shift, a POSA would expect that enzymes that non-specifically trigger the [1,5]-shift would be very susceptible to the KIE. Dr. Prestwich’s enzyme-catalyst-[1,5]-shift hypothesis does not undermine the motivation for C₂₀-deuteration or the reasonable expectation of success.

F. Dr. Prestwich's Complexity Arguments are Unavailing

65. Dr. Prestwich argues that a POSA would have been unable to inhibit the *A2E byproduct pathway* because various enzymes participate in the *visual cycle*. EX2052, ¶¶55-66. But there is no conflict. Dr. Prestwich's Figure 3 uses the same Figure from Kuska (EX1050) that I used in my opening declaration, which identifies the enzymes involved in the visual cycle and how the body converts ATR into retinol. EX2052, ¶60. Dr. Prestwich's Figure 2 illustrates that A2E and ATR-dimer are formed as non-essential byproducts of the visual cycle, and were not necessary to the functioning of the visual cycle itself. EX2052, ¶56; EX2058, 1. Rattner 2006, a reference on which Dr. Prestwich relies, expressly teaches that "A2E forms by non-enzymatic reactions in photoreceptor outer segments and RPE phagolysosomes, apparently as a minor and unavoidable by-product of the retinoid cycle." EX2074, 4; see also *id.*, 5-6; EX2052, ¶210 FN50; EX2052, ¶100 FN21 ("The formation of lipofuscin begins in the photoreceptor outer segments where [ATR] reacts spontaneously (i.e., non-enzymatically) with the membrane lipid [PE] to form [NRPE]"; EX1034, 1). Dr. Prestwich admits that ATR accumulation "in the disc interior rather than being translocated to the outer leaflet" of the photoreceptor outer segment where it could be readily converted to retinol was believed to be the cause of the "'excess' ATR believed to be the substrate for A2E formation in Mata's proposed pathway." EX2052, ¶¶89 & FN15; EX1070, 106:1-

107:20 (for excess ATR to accumulate in the outer segment, its rate of accumulation must exceed its rate of removal), 111:8-21 (location of “excess” ATR accumulation is the disc interior of the outer segment). Accordingly, a POSA would have recognized by September 2007 that inhibiting the undesirable A2E biosynthetic pathway did not require inhibiting the essential visual cycle. Dr. Prestwich’s concern about unanswered questions in the retinoid cycle were of no moment.

66. Dr. Prestwich argues that there was ongoing debate over certain aspects of the biosynthetic pathway for A2E/lipofuscin. EX2052, ¶¶67-80. Dr. Prestwich appears to agree that the process begins when excess ATR in the disc space of the outer segment of the photoreceptor cells because the ATR that was not converted to retinol in a timely manner reacted with phosphatidyl ethanolamine to form NRPE. EX2052, ¶¶68-71; EX2052, ¶100 FN21 (“The formation of lipofuscin begins in the photoreceptor outer segments, where [ATR] reacts spontaneously (i.e. non-enzymatically) with the membrane lipid [PE] to form [NRPE]”); EX1034, 1. Dr. Prestwich concedes that Mata 2000 identified the mechanism by which NRPE began the process of forming A2E as a “1,5 sigmatropic rearrangement.” EX2052, ¶74. Dr. Prestwich argues that the wavelengths Mata 2000 attributed to the dihydro-A2PE intermediate were better attributed to an alternative lipofuscin fluorophore (ATR-dimer) later illustrated by Fishkin, and that it was Kim 2007 that

ultimately validated the role of dihydro-A2PE as an intermediate in the formation of A2E. EX2052, ¶¶77-79, 95, 195; EX1070, 142:22-145:8. But the wavelengths used in Mata cast no doubt on the ability of C₂₀-deuteration to treat macular degenerations by slowing A2E/lipofuscin formation. To the contrary, the identification of ATR-dimer as an undesirable byproduct downstream of the [1,5]-shift provides additional reason to inhibit the [1,5]-shift, as I explained above.

67. Dr. Prestwich argues that the visual cycle involves enzymatic interactions and substrate transportation across membranes and between cellular compartments, and that these interactions *could* affect the concentration of ATR in the photoreceptor outer segments that was believed to be correlated with undesirable A2E formation. EX2052, ¶¶81-90. But none of Dr. Prestwich's discussion weighs against inhibiting the A2E byproduct pathway itself rather than the visual cycle. Yes, it was predictable that inhibiting the enzymes involved in the visual cycle (e.g., RPE65, 11cRDH, atRDH—Prestwich Figure 2) would lead to night blindness, delayed dark adaptation, and eventually cell death (and blindness), as I explained above. It also was predictable that inhibiting atRDH, which Dr. Prestwich repeatedly calls the “rate-limiting step,” would **increase** A2E formation by reducing conversion of ATR to retinol. Prestwich Figure 2. EX2052, ¶¶60, 69-70 (atRDH reduces ATR to retinol); EX2052, ¶¶76, 84 (reduction of ATR to retinol “is the rate-limiting step in the vitamin A cycle”). However, none of Dr.

Prestwich's questions about the visual cycle fairly call into question the wisdom of inhibiting the undesirable A2E byproduct pathway itself rather than the visual cycle.

68. Dr. Prestwich argues that it was unresolved whether an enzyme (phospholipase) was involved in converting A2PE to A2E. EX2052, ¶87. But he identifies no manner in which phospholipase activity at this late step in the process would call into question the ability of C₂₀-deuteration to inhibit A2E formation.

69. Dr. Prestwich appears to agree that NRPE formation and the condensation of NRPE with a second ATR molecule both occur in the neutral environment of the disc space of the photoreceptor outer segments, but questions whether the dihydro-A2PE and A2PE intermediates and the A2E product form primarily in this same neutral environment or only subsequent to RPE-phagocytosis of the photoreceptor cells. EX2052, ¶¶91-97, 100 (FN21), 103 (FN22), 105 (FN23), 110 (excess ATR “transiently accumulating in the OS”); EX2062, 9. Dr. Prestwich's recognition that the prior art teaches that the neutral environment in the disc space of the photoreceptor outer segment was where “excess” ATR accumulation resulted in the undesirable [1,5]-shift and subsequent NRPE condensation with a second molecule of ATR underscores that the POSA had a reasonable expectation that C₂₀-deuteration would inhibit this shift and thereby would inhibit A2E formation.

70. Dr. Prestwich acknowledges that Kim 2007 teaches that “[s]everal lines of investigation also demonstrated that A2PE forms within photoreceptor outer segments.” EX2052, ¶94 FN19. Indeed, Kim 2007 teaches specifically that A2PE was isolated from photoreceptor outer segment debris. EX2019, 6; EX1070 (Prestwich Deposition), 141:16-142:6, 152:21-153:9, 156:3-158:2. Dr. Prestwich’s argument that dihydro-A2PE would convert rapidly to A2PE and ultimately A2E in the RPE lysosomes (EX2052, ¶97) merely demonstrates that a POSA would have recognized the importance by September 2007 of inhibiting the pathway at the [1,5]-shift (i.e., early in the pathway) to minimize formation of all of these downstream products.

71. Dr. Prestwich argues that A2E will not be found in the RPE unless the RPE cells phagocytose the photoreceptor outer segments. EX2052, ¶¶106-109. This point has very little relevance. By the time phagocytosis comes into play, the conversion of NRPE and the bimolecular condensation have already placed the molecule of ATR irreversibly on the path to becoming A2E.

G. Dr. Prestwich Cites Literature Supporting Motivation and Reasonable Expectation of Success

72. Dr. Prestwich argues without citation to support that the body was unable to clear A2E by physical or enzymatic means. EX2052, ¶236 FN56. But literature Dr. Prestwich cites instead teaches in relation to “Extracellular deposits and AMD” that “[c]urrent evidence suggests that at least some sub-RPE deposits

have a dynamic natural history in which accumulation reflects a balance between deposition and clearance.” EX2074, 5-6; EX1069 (Del Priore Transcript), 193:7-197:4 (“They [drusen/lipofuscin fluorophore] really do come and go.”).

73. Dr. Prestwich argues without citation to any support that “marginally slowing A2E biosynthesis would not be expected to produce any benefit” because C₂₀-deuterated vitamin A “would still generate A2E” eventually. EX2052, ¶¶243-245. I disagree. Dr. Prestwich ignores that less A2E would be formed over a given time period. Given how long it takes A2E to accumulate “over a lifetime,” even small reductions in A2E formation were expected to provide “substantial” benefits. Rattner 2006, for example, teaches that macular degenerations should be viewed “as disorders of homeostasis,” providing “good reasons to be optimistic” that slowing disease progression by as little as 10-20% would delay the onset of vision loss by 5-10 years. EX2074, 11; EX2052, ¶306. Rattner 2006 further teaches that “individuals with Stargardt disease might simply manifest an accelerated version of the ‘normal’ accumulation of A2E.” EX2074, 5-6.

74. Dr. Prestwich next argues that dietary sources of vitamin A would continue to make A2E at the same rate as before while supplementation with C₂₀-deuterated vitamin A would further increase the rate of A2E formation. EX2052, ¶244 FN58. I disagree. Many macular degeneration patients already were taking vitamin A supplements in addition to any dietary sources of vitamin A, as reflected

in the prior art. E.g., EX1002, ¶¶146-147, 155-156. Dietary sources of vitamin A often were less readily available for absorption, and the body carefully regulates the plasma concentration of vitamin A. EX1002, ¶¶70-72, 74-75; EX1069 (Del Priore Transcript), 143:4-12 (“highly regulated step”), 144:18-22 (“Vitamin A toxicity from provitamin A sources is largely impossible.”). Dr. Prestwich provides no reason to assume that maintaining sufficient vitamin A plasma levels using C₂₀-deuterated vitamin A as a replacement for non-deuterated sources of vitamin A (EX1002, ¶260) would fail to reduce A2E formation as compared to the status quo.

75. The Patent Owner’s own expert witness testified that it was common practice for at least certain patients in need of treatment for AMD to receive vitamin A supplementation to prevent disease progression. See, e.g., EX1069 (Del Priore Transcript), 57:12-60:23 (30-50% of Dr. Del Priore’s patients take a multi-vitamin, including Centrum, he does not discourage it, and Centrum includes recommended daily allowance (RDA) of vitamin A); EX1069 (Del Priore Transcript), 57:22-60:23 (vitamin A recommended daily allowance), 115:5-116:20 (Ortho Pharma is prior art), 116:21-119:20 (Ortho Pharma administers ARED dose of β -carotene in combination with RDA of vitamin A); EX1069 (Del Priore Transcript), 68:8-70:17, 71:6-74:15 (two-thirds of AMD patients in AREDS study took Centrum multi-vitamin containing β -carotene and presumably containing vitamin A); EX1022, 7-8; EX1065 (centrum contains β -carotene and vitamin A);

EX1069 (Del Priore Transcript), 87:1-88:22 (it was common after the widely-publicized AREDS study reported a 30% risk reduction in high-risk AMD patients to recommend the AREDS combination, and Dr. Del Priore recommended the same for his patients), 104:13-105:2 (high risk AMD patients “benefit the most” from the AREDS supplement), 90:6-92:19 (large, randomized, placebo-controlled, peer-reviewed study subjected to an extra level of scrutiny by a reputable journal). The β -carotene in the AREDS trial is a pro-vitamin A carotenoid that, when deuterated at Carbon 20, falls within the scope of the claims. EX1069 (Del Priore Transcript), 62:1-63:6, 142:11-25, 144:11-17 (pro-vitamin A carotenoid β -carotene). Accordingly, there was good reason to replace existing vitamin A sources in macular degeneration treatment practices with C₂₀-deuterated vitamin A to reduce A2E/lipofuscin formation.

76. Dietary antioxidants (e.g., β -carotene) “had long been suggested as useful for preventing...the development and progression of AMD” and “[t]he common perception” was that they “protect against AMD,” but the AREDS study demonstrated prevention of progression in high-risk AMD patients and did not evaluate primary prevention (prophylaxis) of AMD in its entirety. EX1069 (Del Priore Transcript), 97:9-99:14, 106:10-109:19. Additionally, vitamin A had been administered orally to treat Stargardt disease patients, retinitis pigmentosa patients, and Sorsby’s fundus patients, including at doses many times the RDA (e.g., 15 mg)

with no toxic effects. EX1069 (Del Priore Transcript), 123:2-129:22, 131:10-132:6, 159:17-24; EX1069, 164:15-167:14 (Berson study was a “tour de force,” a “rigorous,” “meticulously designed and extraordinarily well performed” study that represents an important scientific contribution, and resulted in a national campaign to persuade most patients with retinitis pigmentosa to begin a lifelong regimen of vitamin A supplementation). Just as Ortho Pharma’s lower doses are consistent with the AREDS treatment for AMD, Ortho Pharma’s higher doses of vitamin A are consistent with doses used in the prior art for the treatment of other claimed disease states. EX1069 (Del Priore Transcript), 120:12-121:2, 137:7-139:4

77. From the AREDS study, thousands of non-smoker AMD patients who took 15 mg daily doses of β -carotene for 6.3 years on average, including the two-thirds of those patients also taking RDA doses of vitamin A in a multi-vitamin, had no elevated vitamin A serum levels and no serious adverse effects. EX1069 (Del Priore Transcript), 63:10-68:7, 88:23-90:5; EX1022, 7-8 & Table 9; EX1069 (Del Priore Transcript), 144:18-22, 146:8-16 (“Vitamin A toxicity from provitamin A sources is largely impossible.”). Doses of vitamin A as high as 90 mg were administered to skin cancer patients for one year without incident. EX1069 (Del Priore Transcript), 159:1-162:7 (50,000 IU of vitamin A—15 mg—or 75,000 IU for 12 months resulted in no significant toxicities; 300,000 IU for one year was well tolerated), 152:3-155:6 (200,000 IU—60 mg—or 300,000 IU—90 mg—or

400,000 IU—120 mg—administered post-partem). Cholesterol levels in patients administered vitamin A remained stable. EX1069 (Del Priore Transcript), 163:22-164:11. There was thus a long history of using the type of higher doses of vitamin A taught in Ortho Pharma. A POSA would have recognized that replacing existing vitamin A sources with C₂₀-deuterated vitamin A would be reasonably likely to advantageously reduce A2E/lipofuscin formation.

IV. PATENT OWNER’S ARGUMENTS

78. I understand the Patent Owner has argued that the claims of the challenged patent are non-obvious because a reviewer’s comments prior to publication of an article by Dr. Washington used the words “novel” and “innovative” when discussing the article in relation to publication. E.g., POR at 3-4, 54-55 (citing EX2056, 2; EX2057, 1-2). I disagree. The standards for publication are not the same as for patentability. Reviewers at The Journal of Biological Chemistry are not examiners at the USPTO and were not tasked with assessing patentability. They analyzed papers by applying standards for publication, which are different than a patentability analysis. In the course of this case, I have conducted an analysis using the standards of patentability in mind and based upon a review of the prior art, including the Olson 1988 reference, which demonstrates that the C₂₀-trideuterated retinol acetate claimed in the challenged patent was not a novel molecule in September 2007, and the Ortho Pharma patent

that demonstrates that patients in need of treatment for age-related macular degeneration were already being treated with vitamin A. This patentability analysis was not the type of analysis involved in the review of Dr. Washington's manuscript.

79. I also understand that the Patent Owner has argued that "adding additional vitamin A (per Ortho) is 'counter[]' and 'diametrically opposed' to this strategy of reducing ATR formation" by reducing serum retinol levels. E.g., POR, 16 (citing EX2103, 173:8-19, 176:16-177:10). However, Patent Owner again mischaracterizes my testimony. I testified that the approaches of giving vitamin A and lowering retinal levels "almost" look like they are countering each other, but that this is "an oversimplification" because, in reality, a POSA would have understood that the body enforces homeostatic control of serum levels of retinoids. EX2103, 173:8-177:20. Accordingly, administering C₂₀-deuterated vitamin A may not raise serum levels significantly. Instead, administering C₂₀-deuterated vitamin A would be expected to substitute the lipofuscin-resistant (C₂₀-deuterated vitamin A) in place of lipofuscin-contributory vitamin A. The prior art literature teaches that patients in need of treatment for macular degeneration, including age-related macular degeneration and Stargardt disease, were also in need of vitamin A to enable vision through the visual cycle. A POSA thus would have recognized by the critical date in September 2007 that stabilizing the vitamin A via C₂₀-deuteration so

that it would continue to fill its critical roles while reducing A2E/lipofuscin formation was desirable.

V. CONCLUDING STATEMENTS

80. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

81. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 20 December, 2024

By: 
F. Peter Guengerich, Ph.D.

VI. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. RE47,045 to Washington et al.
1003	<i>Curriculum Vitae</i> of Dr. F. Peter Guengerich.
1006	Robert Bergen, H., Furr, H. C., & Olson, J. A., Synthesis of Tri-, Tetra-, and Penta-deuterated Forms of Vitamin A, <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> , 25(1), 11-21 (1988) (“Olsen 1988”).
1008	DE202006014588U1 (English Translation) (“Ortho Pharma”)
1010	Mata, N. L. et al., Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration, <i>Proceedings of the National Academy of Sciences of the United States of America</i> , 97(13), 7154-7159 (2000) (“Mata”)
1011	Fishkin et al., Isolation and Characterization of a Retinal Pigment Epithelial Cell Fluorophore: An All-trans-retinal Dimer Conjugate, <i>Proceedings of the National Academy of Sciences of the United States of America</i> , 102(20), 7091-7096 (2005) (“Fishkin”)
1015	Roth and König, Kinetic Isotope Effect of the 1.5-Hydrogen Displacement in <i>cis</i> -Pentadiene-(1.3), <i>Justus Liebigs Annalen Der Chemie</i> (1966) (“Roth”).
1016	Itou et al., Quantum Treatment of Hydrogen Nuclei in Primary Kinetic Isotope Effects in a Thermal [1, 5]-Sigmatropic Hydrogen (or Deuterium) Shift from (Z)-1, 3-Pentadiene. <i>The Journal of Physical Chemistry A</i> , 111(2), 261-267 (2007) (“Itou”)
1022	Age-Related Eye Disease Study Research Group, A Randomized, Placebo-controlled, Clinical Trial of High-dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-related Macular Degeneration and Vision Loss:

	AREDS report no. 8. <i>Archives of Ophthalmology</i> , 119(10), 1417-1436 (2001) (“AREDS”)
1035	Radu, Roxana A. et al. “Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt’s Macular Degeneration.” <i>Proceedings of the National Academy of Sciences of the United States of America</i> 100:4742-4747 (2003) (“Radu”)
1050	Kuksa V, Imanishi Y, Batten M, Palczewski K, Moise AR. Retinoid Cycle in the Vertebrate Retina: Experimental Approaches and Mechanisms of Isomerization, <i>Vision Res.</i> 43(28):2959-81 (2003) (“Kuska”)
1065	Centrum Silver Adults Label (200 Tablets) Multivitamin
1069	Deposition Transcript of Lucian Del Priore (November 13, 2024)
1070	Deposition Transcript of Glenn D. Prestwich, Ph.D. (November 15, 2024)