

Patent Owner
Demonstratives

Gene Company PTY LTD
v.
The Trustees of Columbia
University in the City of New York

IPR2024-00313
Patent RE47,045

March 27, 2025

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Overview

Petitioner Failed To Establish
Obviousness of Using An Effective
Amount of Deuterated Vitamin A to
Reduce Lipofuscin Accumulation or
Treat Macular Degeneration

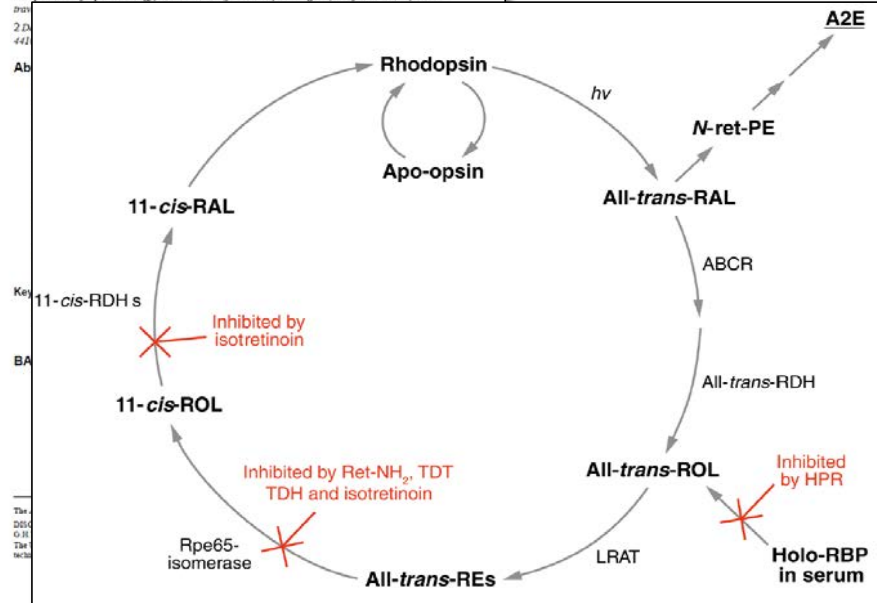
Vitamin A Visual Cycle and Hypothetical A2E Pathway

Travis 2007 (EX2003)

Several approaches have been tested or proposed to slow accumulation of A2E. All have an effect on visual-cycle retinoids and ultimately limit the formation of all-trans-RAL (Figure 5).

Gabriel H. Travis¹, Marcin Golczak², Alexander R. Moise², and Krzysztof Palczewski²
¹ Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California 90095; email: gtravis@ucla.edu

EX2003, 14



EX2003, 35

Mata (EX1010)

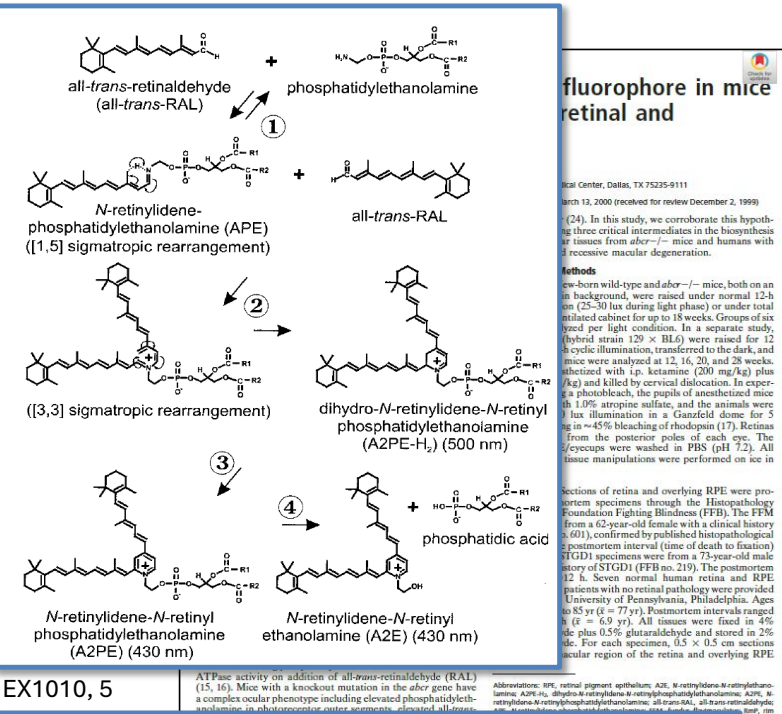
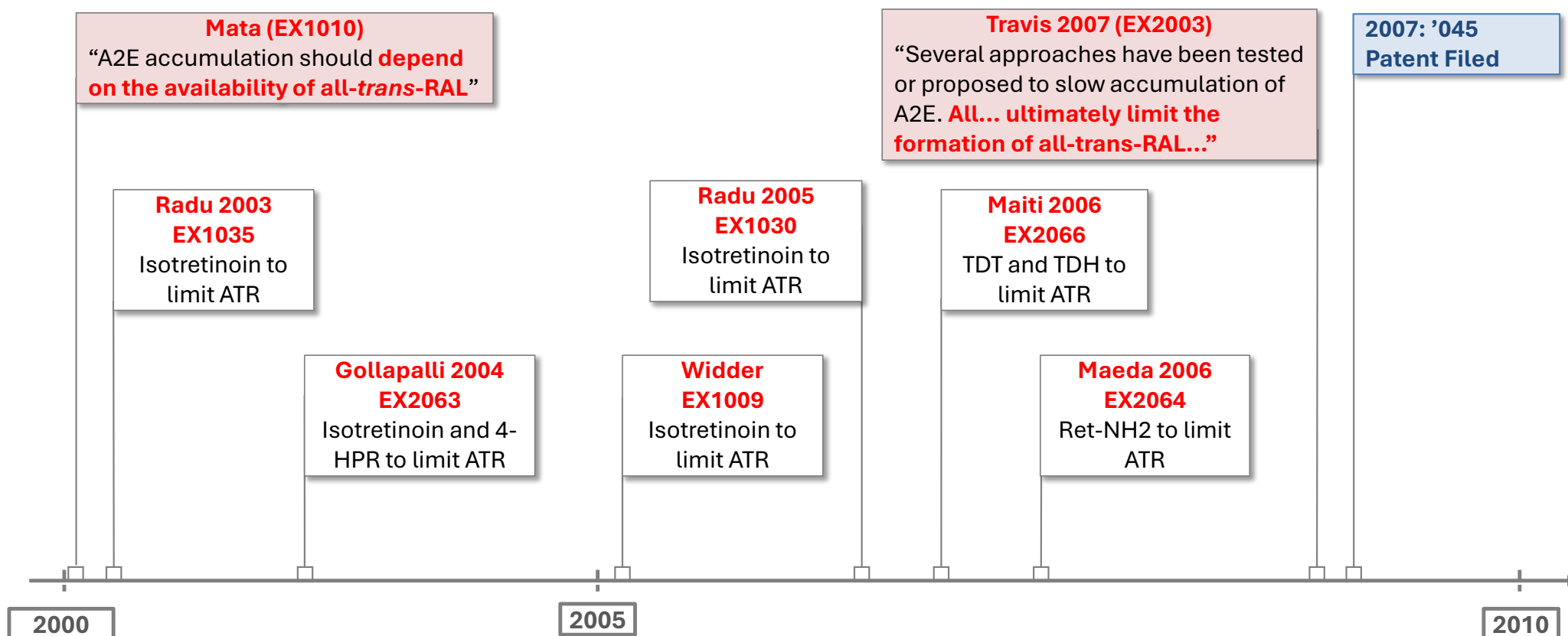


Fig. 5. Hypothetical biosynthetic pathway for A2E in mice and humans lacking the RmP transporter.

POR, 2, 36-37; Sur-Reply, 6, 10-11, 14-15; EX2052, ¶¶112-128, 161-171; EX2192, ¶¶70-83.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Prior Art Focused Exclusively on Reducing ATR

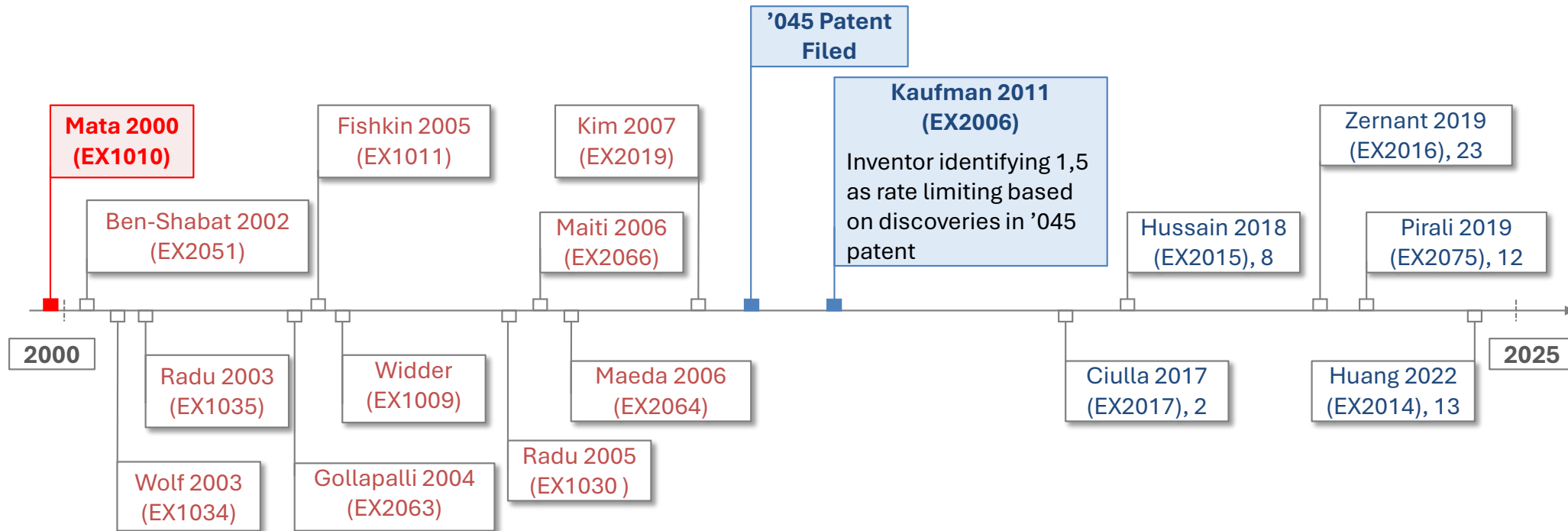


POR, 18-19, 32-33; Sur-Reply, 6, 14-16;
EX2052, ¶¶112-128, 221-230.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

5

No Prior Art Describes 1,5 as Rate Limiting



POR, 18-19, 32-33; Sur-Reply, 6, 14-16; EX2052, ¶¶112-129, 210, 221-230 (citing EX1009, EX1010, EX1011, EX1030, EX1034, EX1035, EX2011, EX2014, EX2015, EX2016, EX2017, EX2051, EX2063, EX2064, EX2066, EX2075).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

6

No Prior Art Describes 1,5 as Rate Limiting

Petition

As Dr. Guengerich explains, a POSA would have **understood from Mata's description** of the synthetic pathway that this C20-deprotonation was **likely a rate-limiting step**.

Pet., 67

Dr. Guengerich (EX1002)

This provides... very good reason to inhibit **the rate-limiting step** in **Mata's pathways...** the **[1,5]-sigmatropic rearrangement**

EX1002 ¶181

POR, 18-19, 24-28, 30-35; Sur-Reply, 2-3, 6, 14-16.

Dr. Guengerich Deposition (EX2103)

Q. Are you aware of anyone **prior to the '045 patent suggesting that deuteration of carbon-20** would **slow** the formation of **A2E**?

A. **No, I'm not.** I was just **looking at Fishkin, and I don't** specifically see **that mentioned** right here; although, obviously, the Columbia group actually was thinking about that shortly thereafter.

Q. Is there anything **specific in Mata** that you can point to teaching that cleavage of the carbon-hydrogen bond that you referenced was recognized to be relatively **slow under** physiological conditions?

A. **I don't see anything specifically in Mata**, since they were working primarily with extracts. I'm looking -- can we go on to Fishkin now?

Q. So is there something **specific in Fishkin** showing recognition that cleavage of the carbon-hydrogen bond you referred to in paragraph 98 was **recognized** as being **relatively slow** under physiological conditions?

A. **I don't see a specific, you know, reference in Fishkin to that.** Obviously, the authors were thinking about this because they came up with the patent the next year or two then, but I don't see a specific comment about this.

EX2103, 119:9-17, 121:6-16, 123:8-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

KIE Only Expected Where C-H Breaking is Rate Limiting

Journal of
Pharmaceutical
Sciences

Blake 1975

An observable isotope effect **will only be apparent**, of course, where the breaking of the **C–H or C–D bond is involved in the rate-determining step**.

EX1047, 3

THE JOURNAL OF THE PHARMACY SOCIETY OF GREAT BRITAIN
THE JOURNAL OF THE PHARMACY SOCIETY OF GREAT BRITAIN
J. A. WESTHEIMER
The Kinetic Isotope Effect in Organic Chemistry
London, 1960

Westheimer 1960

First of all, the **kinetic isotope effect obtains only** when a bond to the hydrogen atom is **broken (or formed) in the rate-controlling step**.

EX2084, 3

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD.

Patent

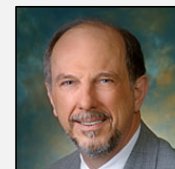
Dr. Prestwich

If the **C-H bond breaking step is fast relative to the other steps** and processes in the reaction, the[re] is **no basis to expect** that slowing the C-H bond breaking step ... will result in **an observed KIE for a multistep reaction** in a complex reaction environment.

EX2052 ¶138

Dr. Guengerich (EX2009)

If carbon-hydrogen bond breaking **isn't at least partial[ly] rate limiting**, there will be **no effect on the rate** of deuterium substitution.



EX2009, 188:1-189:10

Roth's Single-Step Sigmatropic Rearrangement Not Relevant

Petitioner KIE expectation relies on wrong reaction

Roth 1966 (EX1015)

EX1015, 3-4

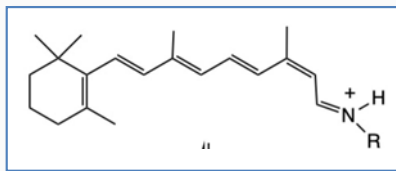


cis-pentadiene-(1,3)

Sigmatropic Rearrangement

Mowery 1979 (EX2077)

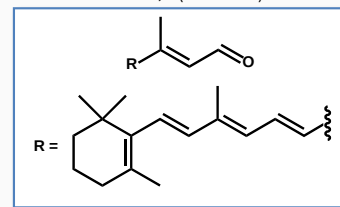
EX2052, ¶¶279-280, Fig. 13 (citing EX2077, 3, Fig. 5))



13-*cis*-retinylidene-*n*-butylamine

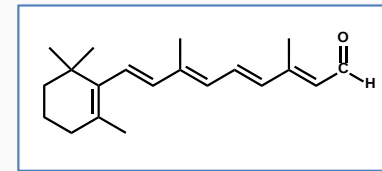
Verdegem 1997 (EX2078)

EX2078, 2 (Scheme 1)



all-*trans*-retinal

A2E Pathway

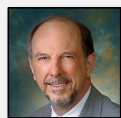


all-*trans*-retinal

General Base Tautomerization

Dr. Guengerich (EX2103)

Roth **intrinsic** single-step KIE does not inform **observed** KIE for multi-step A2E pathway



Q. So it's **necessarily the slowest step** because it's the **only step in Roth**, correct.

A. Well, I suppose one could say that, **yeah, it's the only step**. It's **a single reaction**, yes.

Q. Roth **doesn't tell** you whether sigmatropic shift in a different **multistep sequence** is going to be overall **rate limiting**, correct?

A. **It does not....**

EX2103, 62:3-23

“General Guidance” Insufficient for Motivation or REOS

No indication of **how** or **where** to inhibit; no REOS for any strategy

Mata 2000

Pharmacologic inhibition of **one or more steps** in the A2E synthetic pathway **may thus be an effective treatment strategy** for other macular degenerations associated with lipofuscin accumulation.

EX1010, 6

Kim 2007

Improved understanding of the mode of genesis of A2E and other RPE lipofuscin compounds **could** facilitate the introduction of yet other **novel approaches to therapy**.

EX2019, 7



“[P]atents are not barred just because it was obvious ‘to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.’”

Procter & Gamble Co. v. Teva Pharms. USA, Inc., 566 F.3d 989, 997 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988))

Petitioner does not cite a single example of creating a novel intervention with deuterium

Fisher 2006

[H]ypothesis of using deuteration... is **not expected** to be an **effective strategy** for CYPs **except in highly specific situations**.

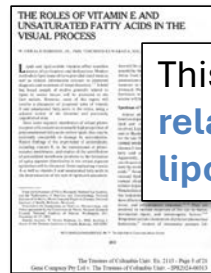
EX2076, 7

Miwa 1987

[C]onservative strategy... on **carbon atoms susceptible** to the cytochrome **P-450 oxidation**.

EX1051, 5

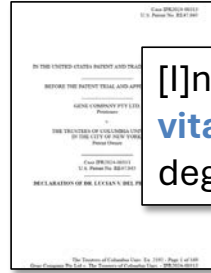
Art Taught Away from Vitamin A for Retarding Lipofuscin and Treating MD



Robinson 1982

This dose-related response suggests a **close relationship between dietary vitamin A and lipofuscin formation.**

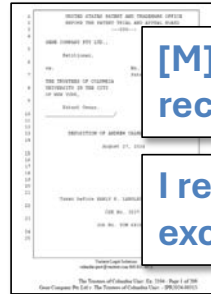
EX2113, 11



Dr. Del Priore

[I]n my own practice as of **2007**, I **did not** recommend **vitamin A supplementation** in patients with macular degeneration.

EX2192 ¶143



Dr. Calman

[M]ost clinicians, as far as I know today, do **not** recommend **vitamin A** supplementation for Stargardt's

I recommend that [Stargardt's patients] **not** consume **excessive vitamin A.**

EX2104, 17:2-24 (top) 12:22-13:14 (bottom)

Kennedy 1995 (EX2156)

LIPOFUSCIN OF THE RETINAL PIGMENT

Factors retarding lipofuscin formation

- Elimination of rod outer segments
- Vitamin A deficiency
- Ocular melanin
- Retinal antioxidants
 - Vitamin C
 - Vitamin E
 - Superoxide dismutase
 - Glutathione peroxidase
 - Peroxidase
 - Catalase
- Reduction in dietary calories or food intake

EX2156, 3, Table II

FLUORESCENT CHARACTERISTICS

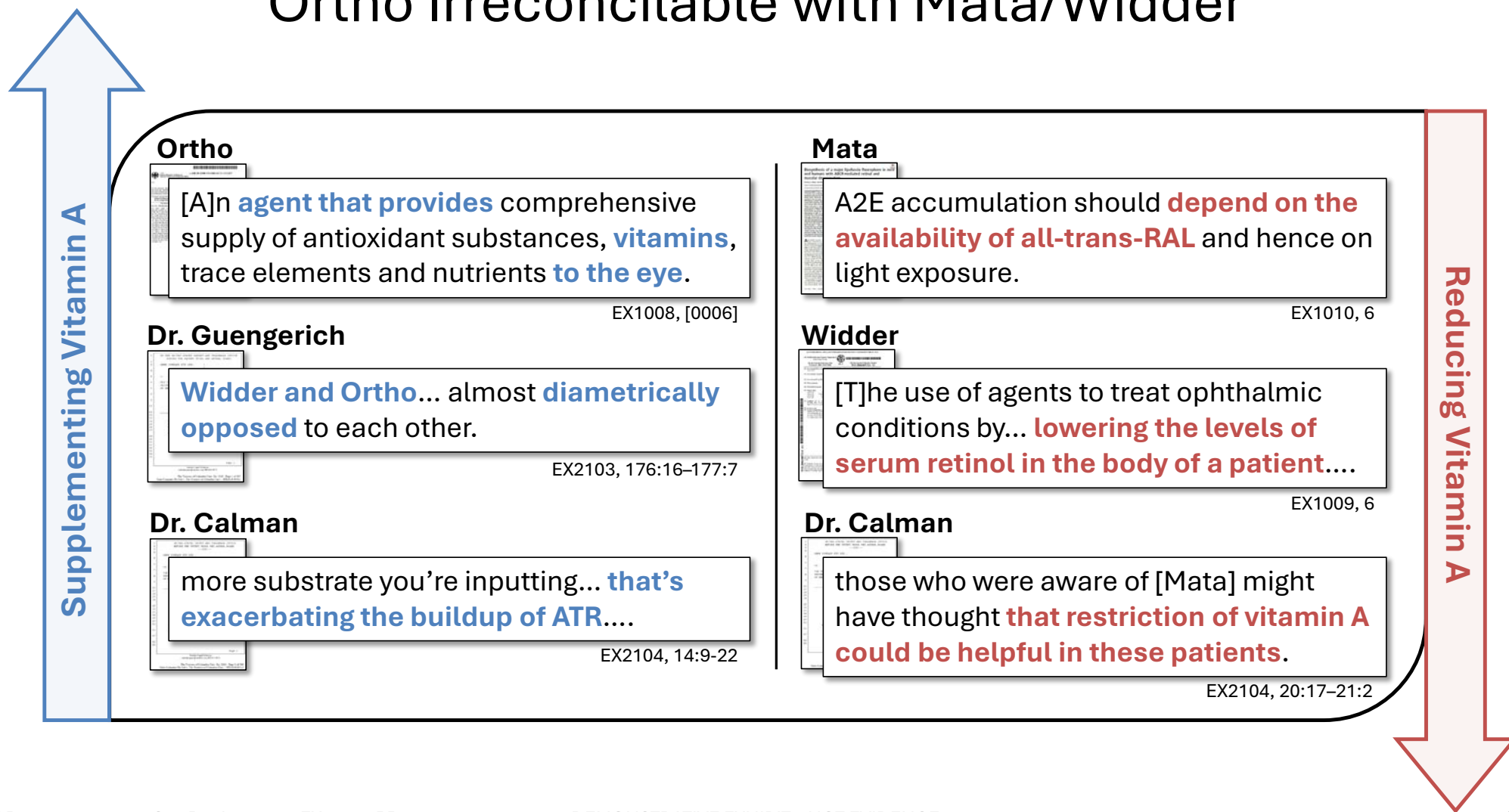
Lipofuscin is composed of a mixture of different fluorophores, reflecting the heterogeneous nature of this cellular pigment. Ten different fluorescent fractions have been identified within chloroform extractions of RPE cell lipofuscin.⁵ All these fluorophores have common absorption peaks in the

Eye (1995) 9, 763-771 © 1995 Royal College of Ophthalmologists

The Trustees of Columbia Univ. Ex. 2156 - Page 1 of 9

Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Ortho Irreconcilable with Mata/Widder



POR, 1-2, 16-21, 45; Sur-Reply, 10-11; EX2192, ¶¶180-192.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

12

Vitamin A Was **Never** the Standard of Care

Ortho:
Deficiency, **not** MD/ lipofuscin

Ortho (EX1008)

It is further known that the complaints can be aggravated, especially in old age, by an **incorrect diet or an inadequate supply of the necessary vitamins and nutrients**. In the state of the art, supportive care, especially for elderly patients, is known **to prevent deficiencies in the supply of vitamins and nutrients to the eye**.

EX1008, [0003]

AREDS:
 β -Carotene, **not** vitamin A

AREDS (EX1022)

[R]isks and benefits of **supplementing with either zinc, antioxidants (vitamins C and E and beta carotene)**, or the combination of both....

Vitamin A... showed no statistically significant difference[] in change from baseline....

EX1022 at 2, 7-8

Out-dated studies:
Do **not** reflect standard of care

Dr. Del Priore (EX1069)

People tried a variety of things, you know, for Stargardt's **before it was recognized** that it was actually a **problem with vitamin A....**

EX1069, 123:13-124:5

POR, 21-22; Sur-Reply, 13;
EX2192, ¶¶109-127, 149-153, 175-179, 210-222.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

13

No REOS for an “Effective Amount” of C₂₀-D₃ Vitamin A

Claims Require “Effective Amount” For:

- Reducing Lipofuscin Accumulation (claims 1-28)
- Treating MD (claims 4, 28-54)
- Treating AMD (claims 5-9, 32-37)
- Treating Stargardt’s (claims 11-14, 38-42)

✗ Ortho (EX1008)

- **No** therapeutic efficacy attributed to vitamin A
- **No** guidance on an “effective amount” of vitamin A for anything

✗ Olson (EX1006)

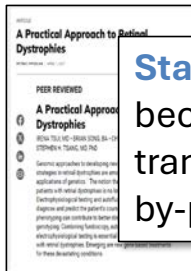
- **No** therapeutic purpose or effect of C20-deuterated vitamin A taught or suggested

✗ Widder (EX1009) Mata (EX1010)

- **Not** relied on by Petitioner to teach claimed effective amount
- Discloses opposite: **reducing** vitamin A to limit lipofuscin / treat AMD

Petitioner **does not address** evidence teaching away from vitamin A for Stargardt's Disease and *ABCA4*-Gene (Claims 11-15, 18, 38-42)

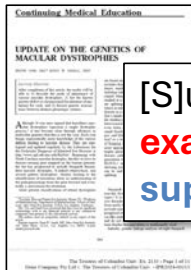
Tsui 2007



Stargardt patients should **avoid** a diet high in vitamin A because the defective gene (*ABCA4*) encodes for a transmembrane transporter of A2E intermediates, a toxic by-product of vitamin A.

EX2164, 12

Voo 2004



[S]uggested that **vitamin A supplements may actually exacerbate Stargardt disease**. Therefore, such vitamin supplements are not recommended.

EX2133, 2

Dr. Calman

I **recommend** that [Stargardt's patients] **not consume excessive vitamin A**.



[M]ost clinicians, as far as I know today, do **not recommend vitamin A** supplementation for Stargardt's.

EX2104, 17:2-24 (bottom), 12:22-13:14 (top)



"[A] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant"

Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1360-63 (Fed. Cir. 2017)

Objective Evidence Confirm Nonobviousness

Praise	• “Quite Novel” & “Innovative” (2010) • FDA - Breakthrough Therapy Designation (2021) • FDA - Patient Listening Session (2022) • Professor Gorin - “Groundbreaking” (2024)
Long-Felt Need + Failures of Others	• No Treatments By 2007 • Dry AMD Failed Clinical Attempts • Stargardt Disease Failed Clinical Attempts
Clinical Success: TEASE and SAGA	• TEASE + SAGA Practices Claims 1, 2, 4-15, 18, 19, 26, 28-30, 32-42, 45, 46, 53 • GA and Stargardt Disease Efficacy Reflect Overall MD Efficacy • Overcame Skepticism of Human Efficacy
Unexpected Results	• Lipofuscin Reduction without Visual Impairment • Rapid Replacement of Vitamin A

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

16

Praise: “Quite Novel” & “Innovative” (2010)

Dr. Guengerich:

Date: 9/21/10, 3:51 PM

Sincerely yours,

F. Guengerich
Associate Editor

One of the Reviewing Editors is of the opinion that there are important elements to the manuscript and that it addresses an important topic. The **novelty** of using a **deuterated** version of **vitamin A** is also **considered quite novel**.

EX2057, 1

Reviewer 2:

This manuscript describes the effect of feeding a deuterated version of vitamin A to mice... developing Stargardt's disease. There is **great interest in this disorder** and it is of **significant clinical importance**. The use of a **C20-D3-vitamin A** is quite novel and interesting.

EX2057, 2

Date: 9/24/10, 4:09 PM

Sincerely yours,

F. Guengerich
Associate Editor

Reviewer 3:

This is an **innovative paper** on the **use of deuterated vitamin A** to provide a **significant kinetic isotope effect** to slow down the rate of dimerization of retinaldehyde that can lead to the production of ATR dimers that precedes the **onset of macular degeneration**.

EX2056,1

'045 Patent Meets a Long-Felt Need

Guymer 2006 (EX2139)

As there is **no cure for AMD**, and **treatments** to stop its progression have met with **limited success....**

EX2139, 1

EX1001

One immediate **disadvantage** of slowing the **visual cycle** is that it leads to **delayed dark adaptation and poor vision in dim light or at night.**

EX1001, 3:32-40

Scholl 2022 (EX2088)

The growth rate of the square root of atrophic lesions in the **ALK-001 treated group was 21% slower** than in the untreated arm ($p < 0.001$). When using untransformed areas, the growth rate was **28% slower in the ALK-001 arm** than the untreated arm.

These data represent the **first time** that a therapeutic intervention **slows the progression of STGD1 in a clinically and statistically meaningful way.**

EX2088, 1-2

Scholl 2024 (EX2090)

ALK-001 was well-tolerated, with **no reports of night blindness or impaired dark adaptation....**

EX2090, 1-2

POR, 3-6, 49-51; Sur-Reply, 17-18, 22-23; EX2192, ¶¶55, 70, 74, 266-270, 284, 290-293, 309, 314.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

18

No Motivation or REOS for C₂₀-D₃- Vitamin A Slowing A2E

1,5 **Not** Reasonably Expected to be Rate
Limiting in A2E Formation

- KIE **Only** Expected Where C-H Breaking is Rate Limiting
- Petition Premised on 1,5 Being Rate Limiting in A2E Pathway
- Prior Art Does Not Suggest 1,5 Rate Limiting
- “Inhibition” Inconsistent with Adding More or Deuterium

Roth Irrelevant: Single-Step Intrinsic KIE,
Different Compound, Different Reaction

Petitioner’s Nonspecific Teachings and
Unsupported Assertions Fail

KIE Only Expected Where C-H Breaking is Rate Limiting

Journal of
Pharmaceutical
Sciences

Blake 1975

An observable isotope effect **will only be apparent**, of course, where the breaking of the **C–H or C–D bond is involved in the rate-determining step**.

EX1047, 3

THE BOARD OF THE PHARMACY SCHOOL GRADUATE BOARD
THE UNIVERSITY OF MICHIGAN
J. A. WESTHEIMER
Ph.D. Thesis (Chemistry, Physical Chemistry, Biochemistry)
Submitted August 1960

Westheimer 1960

First of all, the **kinetic isotope effect obtains only** when a bond to the hydrogen atom is **broken (or formed) in the rate-controlling step**.

EX2084, 3

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD
GENE COMPANY PTY LTD.
Petitioner

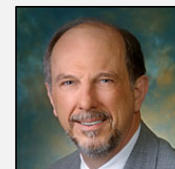
Dr. Prestwich

If the **C-H bond breaking step is fast relative to the other steps** and processes in the reaction, the[re] is **no basis to expect** that slowing the C-H bond breaking step ... will result in **an observed KIE for a multistep reaction** in a complex reaction environment.

EX2052 ¶138

Dr. Guengerich (EX2009)

If carbon-hydrogen bond breaking **isn't at least partial[ly] rate limiting**, there will be **no effect on the rate** of deuterium substitution.



EX2009, 188:1-189:10

Petition Premised on “Rate-Limiting” 1,5 Step

Petition

Filed on behalf of: Gene Company Pty Ltd
By: Jai A. Mills (jaimills@wsgr.com)
Michael T. Rosato (mrosato@wsgr.com)
Matthew Bresnahan (mbresnahan@wsgr.com)

[A] POSA would have been **well aware** that the **1,5-sigmatropic shift** disclosed in Mata was likely a **rate limiting step** in A2E-formation....

[A] POSA would have **understood from Mata’s description...** that this **C20-deprotonation** was likely a **rate-limiting step**.

Pet., 42, 76

Dr. Calman (EX1004)

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD
GENE COMPANY PTY LTD.

Dr. Guengerich explains that the deprotonation of **C-20** would have been **recognized as a rate-limiting step** in A2E formation.

EX1004 ¶¶68

Dr. Guengerich (EX1002)

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

It is **readily apparent** to a person of ordinary skill that the **(1,5)-sigmatropic** rearrangement is likely to be **the rate-limiting step....**

This provides... very good **reason** to **inhibit the rate-limiting step** in Mata’s pathways... the **[1,5]-sigmatropic rearrangement...**

EX1002 ¶¶178, 181

Institution Decision

Truho@uspto.gov Paper 13
571-272-7822 Entered: June 24, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

Dr. Guengerich testifies that ‘a person of ordinary skill in the art... **would have recognized that the [1,5]-sigmatropic shift was likely a rate-limiting step**’ described in **Mata’s A2E biosynthetic pathway....** Ex. 1002 ¶¶ 98, 178.

Paper 13, 47-48

Petitioner's Evolving "Any Step" Theory

Dr. Guengerich Petition:
"Readily apparent" 1,5 rate limiting

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

It is **readily apparent** to a person of ordinary skill that the **(1,5)-sigmatropic rearrangement** is likely to be the **rate-limiting step** in the pathway because ... the **(1,5)-sigmatropic rearrangement** would be **significantly slower than the (3,3)-sigmatropic rearrangement**.

EX1002 ¶178



Dr. Guengerich Deposition:
POSA not looking for rate limiting step

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

1 GENE COMPANY PTY LTD.)
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I don't think a POSA is looking for the rate-limiting step in a sequence like this.

Without further knowledge, **[the rate limiting step] could be the 3,3-sigmatropic rearrangement** or the dimerization process or perhaps even one of the other following the steps then.

EX2103, 56:13-23, 89:4-21



Dr. Guengerich Reply:
Multiple rate limiting; slowing any would slow A2E

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.

EX1080 ¶19

Mata Does **Not** Suggest 1,5 Is Rate Limiting

Petition

Filed on behalf of: Gene Company Pty Ltd
By: Jad A. Mills (jmills@wsgr.com)
Michael T. Rosato (mrosato@wsgr.com)
Nathan L. Mata (nmata@wsgr.com)

As Dr. Guengerich explains, a POSA would have **understood from Mata's description** of the synthetic pathway that this C20-deprotonation was **likely a rate-limiting step...**

Pet., 67

Dr. Guengerich (EX1002)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

REPLY D

This provides... very good reason to inhibit **the rate-limiting step** in **Mata's pathways...** the **[1,5]-sigmatropic rearrangement...**

EX1002 ¶181

Mata (EX1010)

Biosynthesis of A2E in mice and humans with macular degeneration

Nathan L. Mata, Jian Weng, and Charles A. Parish, Jr.
Center for Basic Neuroscience and Department of Chemistry
Communicated by David L. Garbert, University of California, San Diego

Increased accumulation of lipofuscin in the retinal pigment epithelium (RPE) is seen in several forms of age-related macular degeneration (AMD). Lipofuscin is the toxic bis-retinoid, N-retinylidene-N-retinylethanolamine (A2E). Previously, we generated a mouse model of AMD by targeting the RPE-specific ATP-binding cassette transporter 4 (ABCR4) gene. This gene encodes a transporter that is responsible for the export of A2E from the RPE. Here, we identify three tissues from *abcr4*^{-/-} mice and human AMD patients that express ABCR4. Our results support the hypothesis that ABCR4 is responsible for the export of A2E from the RPE. We propose that ABCR4 is a transporter for A2E. Our results support the hypothesis that ABCR4 is responsible for the export of A2E from the RPE. We propose that ABCR4 is a transporter for A2E.

Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly. The accumulation of fluorescent lipofuscin in the retinal pigment epithelium (RPE) is a hallmark of AMD. Lipofuscin is also associated with Stargardt disease (STGD), a recessive form of AMD caused by mutations in the *ABCR4* gene. The *ABCR4* gene encodes a transporter located in the RPE. The *ABCR4* gene may also predispose to AMD. Mice with a knockout mutation in the *ABCR4* gene exhibit a complex ocular phenotype including retinal degeneration and accumulation of A2E in the RPE. Observations, it has been suggested that A2E is the major component of lipofuscin in the RPE. Accumulation of A2E in the RPE (18, 19), is toxic to RPE cells (20–23) and A2E forms by condensation of

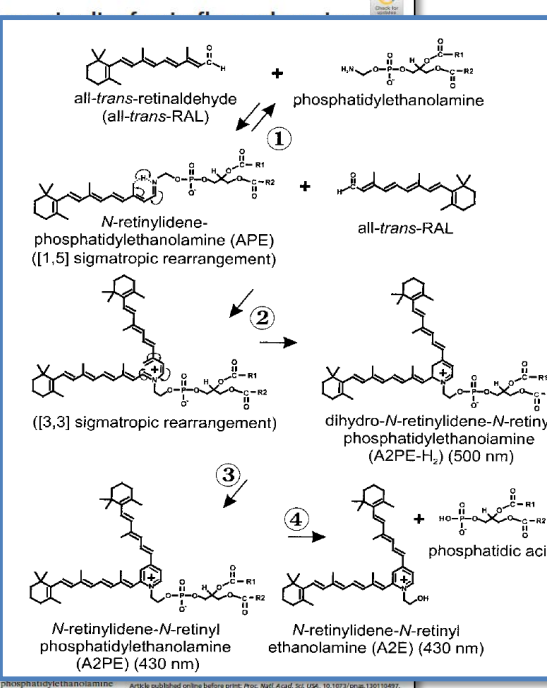


Fig. 5. Hypothetical biosynthetic pathway for A2E in mice and humans lacking the RmP transporter.

EX1010, 5

Mata Does **Not** Suggest 1,5 Is Rate Limiting

Petition

Filed on behalf of: Gene Company Pty Ltd
By: Jad A. Mills (jmills@wsgr.com)
Michael T. Rosato (mrosato@wsgr.com)
Matthew Rosenbaum (mrosenbaum@wsgr.com)

As Dr. Guengerich explains, a POSA would have **understood from Mata's description** of the synthetic pathway that this C20-deprotonation was **likely a rate-limiting step...**

Pet., 67

Dr. Guengerich (EX1002)

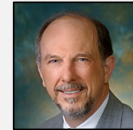
UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

REPLY D

This provides... very good reason to inhibit **the rate-limiting step in Mata's pathways...** the **[1,5]-sigmatropic rearrangement...**

EX1002 ¶181

Dr. Guengerich Deposition (EX2103)



Q. Is there anything specific in Mata that you can point to teaching that cleavage of the carbon-hydrogen bond that you referenced **was recognized to be relatively slow under physiological conditions?**

A. I don't see anything specifically in Mata, since they were working primarily with extracts. I'm looking -- can we go on to Fishkin now?

EX2103, 121:6-16

Mata Does **Not** Suggest 1,5 Is Rate Limiting

Petition

Filed on behalf of: Gene Company Pty Ltd
By: Jad A. Mills (jmills@wsgr.com)
Michael T. Rosato (mrosato@wsgr.com)
Matthew Rosenbaum (mrosenbaum@wsgr.com)

As Dr. Guengerich explains, a POSA would have **understood from Mata's description** of the synthetic pathway that this C20-deprotonation was **likely a rate-limiting step...**

Pet., 67

Dr. Guengerich (EX1002)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

REPLY D

This provides... very good reason to inhibit **the rate-limiting step in Mata's pathways...** the **[1,5]-sigmatropic rearrangement...**

EX1002 ¶181

Dr. Guengerich Deposition (EX2103)

Q. My question was: Would a person of ordinary skill in the art as of 2007 have been able to **evaluate the relative speed of each step in Figure 5 of Mata Exhibit 1010?**



A. **Of every step, my general answer would be no.** But as I said, I don't know that -- I don't think that that's actually an issue in this particular case, and a person of ordinary skill in the art would have been led to attack the -- the 1,5-sigmatropic rearrangement based on literature precedent about kinetic isotopic effects and the ease of preparing material with deuterium.

EX2103, 59:9-25

Mata Does **Not** Suggest 1,5 Is Rate Limiting

Petitioner relies solely on Dr. Guengerich's unsupported testimony

Petition

Filed
By:

As Dr. Guengerich explains, a POSA would have **understood from Mata's description** of the synthetic pathway that this **C20-deprotonation was** likely a **rate-limiting** step for which deuterium substitution would result in significantly slowing the formation of A2E. **EX1002 ¶¶141, 244, 260, 269, 298, 302.**

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

PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. RE47,045

Pet., 67

Dr. Guengerich (EX1002)

UNITED STATES
—
BEFORE THE
—
G

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN
—
DECLARATION

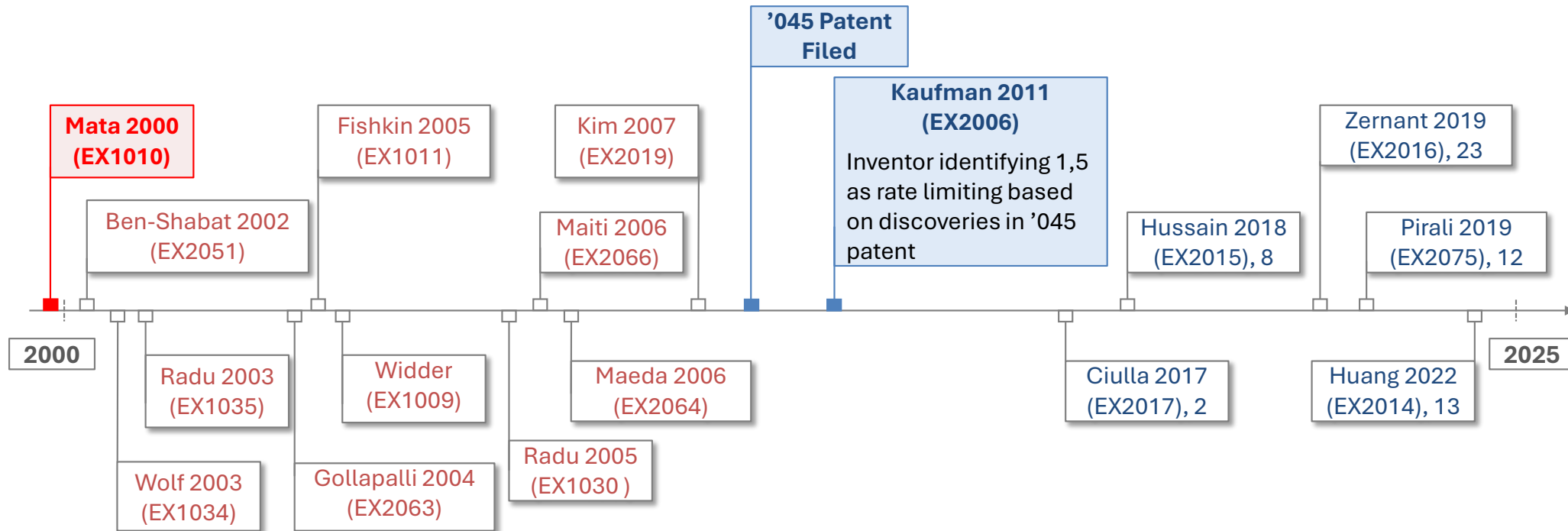
¶141: In light of Mata's disclosures, a person of ordinary skill in the art would thus have understood Olson 1988's C20D3-vitamin A compounds in a new light as a promising means to confirm Mata's synthesis pathway and to reduce lipofuscin formation.

¶¶244, 260, 269, 302: Mata suggests pharmacological inhibition of the A2E biosynthetic pathway that requires deprotonation of Carbon 20 through a 1,5-sigmatropic shift. **EX1010 (Mata), 7158-59 & FIG. 5.**

¶298: [A] person having ordinary skill in the art **would have expected C20-deuteration of vitamin A to retard formation of undesirable A2E/lipofuscin** and thereby treat or prevent diseases known to be associated with the accumulation of A2E/lipofuscin....

EX1002 ¶¶141, 244, 260, 269, 298, 302

No Prior Art Describes 1,5 as Rate Limiting



POR, 18-19, 32-33; Sur-Reply, 6, 14-16; EX2052, ¶¶112-129, 210, 221-230 (citing EX1009, EX1010, EX1011, EX1030, EX1034, EX1035, EX2011, EX2014, EX2015, EX2016, EX2017, EX2051, EX2063, EX2064, EX2066, EX2075).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

27

Prior Art Suggested Other Steps As Slow



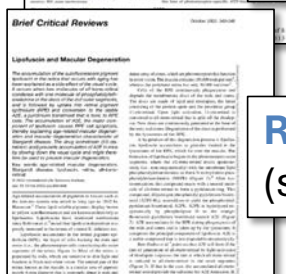
Ben-Shabat 2002 (EX2051)

Whereas the generation of **A2E from A2-PE by acid hydrolysis was found to occur very slowly....**

*A2E Is Generated by Acid Hydrolysis of A2-PE at a **Slow Rate**....*

A2E is generated from A2-PE at a **slow rate**.

EX2051, 1, 4, 7



Wolf 2003 (EX1034)

Rarely, a second molecule of atRAL will condense with NRPE to form A2P2-H₂ (step 2).

EX1034, 2



Sparrow 2003 (EX1033)

The reaction of NRPE with a second all-*trans*-retinal to form a molecule of A2-PE is likely to **occur very infrequently....**

EX1033, 2

“Inhibition” Does **Not** Mean Adding More

Mata Taught Reducing ATR

Mata (EX1010, 6)

One prediction of the pathway proposed in Fig. 5 is that A2E accumulation should **depend on the availability of all-trans-RAL** and hence on light exposure.

The observed inhibition of A2E accumulation in *abcr*^{-/-} mice raised under total darkness suggests that **limiting light exposure** may **reduce the rate of disease progression** in humans with recessive ABCR-mediated diseases.

Pharmacologic inhibition of one or more steps in the **A2E synthetic pathway** may thus be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.

EX1010, 6

Mata (EX1010, 5)

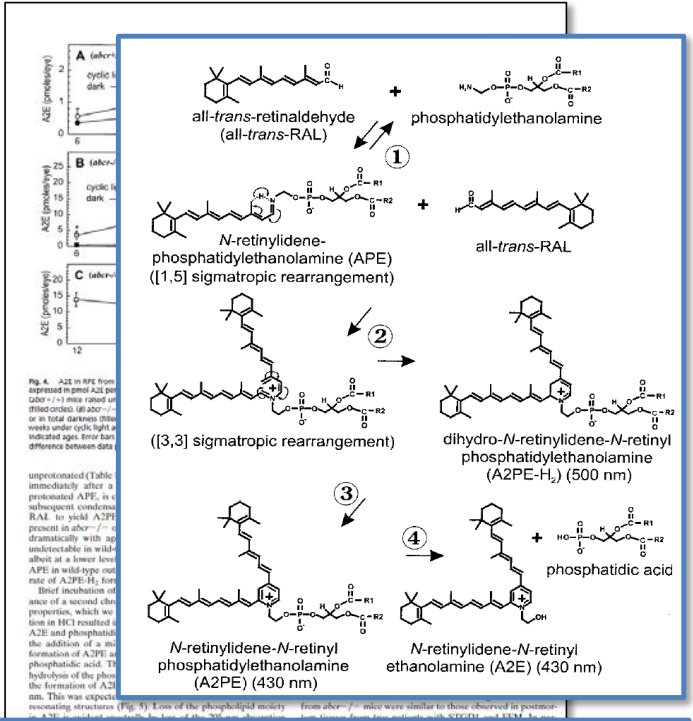


Fig. 5. Hypothetical biosynthetic pathway for A2E in mice and humans lacking the RmP transporter.

EX1010, 5

“Inhibition” Does **Not** Mean Adding More

Increased Substrate → Increased Product

Dr. Calman (EX2104)

Q. So to your understanding, **is Mata**, Exhibit 1010, the **origin for** the current practice of **recommending against vitamin A supplementation** for Stargardt's patients?

A. I think **that line of research is certainly one of the bases for that.**



Q. Can you explain what you meant when you said that more substrate inputted into the visual cycle potentially exacerbates the buildup of ATR?

A. Well, in chemical reactions generally, **if you increase the input of the initial reactant**, you are going to -- you are going to shift the equilibrium toward the end products; you are going to increase -- **potentially increase the buildup of the end product**, which in this case is ATR and its harmful lipofuscin products....

EX2104, 19:16-22 (top), 15:3-16:2 (bottom)

POR, 2, 16-21, 36-37; Sur-Reply, 10-11; EX2052, ¶¶161-171.

Dr. Del Priore (EX2192)

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

Ortho Pharma... product includes vitamin A 'to prevent deficiencies in the supply of' vitamin A.... This additional substrate for the visual cycle can lead to increased output of byproducts from the visual cycle.

Penmonet

v.

Mata, in contrast, contemplates **reducing precursors of A2E, including vitamin A** and byproducts from the visual cycle.

DECLARATION OF DR. LUCIAN V. DEL PRIORE, MD, PhD

Therefore, **Mata and Ortho Pharma** point the skilled artisan in **opposite directions.... Yet Dr. Calman fails to offer any reason to ignore this glaring incompatibility.**

The Trustees of Columbia Univ. Ex. 2192 - Page 1 of 169
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

EX2192 ¶¶181-183

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

30

C-20 Deuteration “**Not** An Inhibitor”

“Inhibition” understood as inhibiting druggable targets

Dr. Guengerich (EX2103)



[I]f we consider the subject matter of this whole discussion, which is **the 20 deuterated material**, that’s **actually not an inhibitor itself**; [it] is actually an alternate substream.

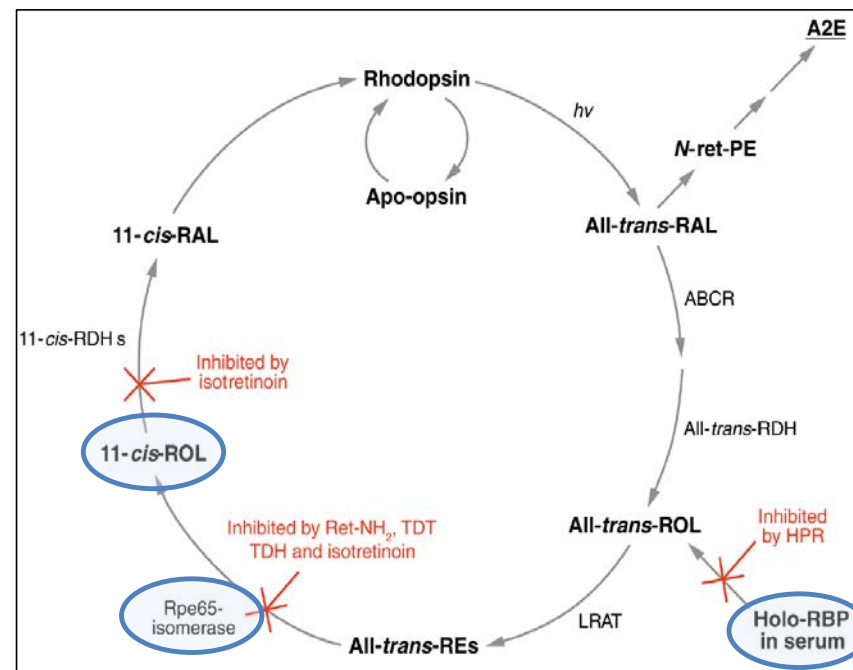
EX2103, 192:11-25

Dr. Prestwich (EX2052)

Specifically, in pharmaceutical research, ‘**pharmacologic inhibition**’ refers to the **use of drugs or compounds that interact with specific biological targets** to prevent or circumvent a particular process. This generally involves molecules binding to enzymes, receptors, or other proteins to interfere with their normal function. Such an enzyme, receptor, or other protein would be referred to as ‘**druggable**’ or as a ‘**drug target**.’

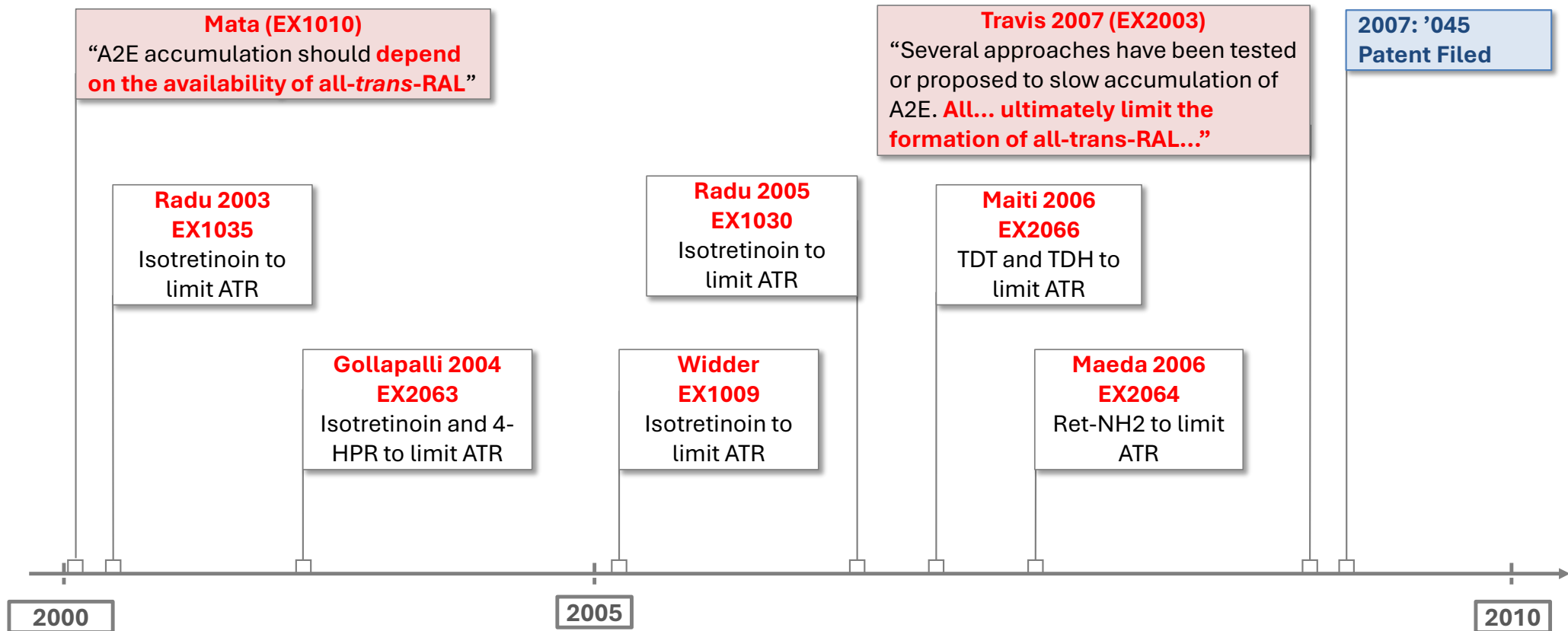
EX2052 ¶166

Inhibition referred to blocking **druggable targets**:
11-cis-rol, Rpe65-isomerase, Holo-RBP



Travis 2007 (EX2003, 35)

Prior Art Focused Exclusively on Reducing ATR



POR, 18-19, 32-33; Sur-Reply, 6, 14-16;
EX2052, ¶¶112-128, 221-230.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

32

Petitioner Cannot Shift the Burden

Petitioner's burden to show the 1,5 shift rate limiting, not PO's to disprove

Dr. Guengerich (EX1080)

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIEBUNAL
GENE COMPANY PTY LTD, v. THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Case No. IPR2024-00313
REPLY DECLARATION

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.

EX1080 ¶43

[I]t is not correct to insist that necessarily there is only one step... 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.

EX1080 ¶21

GENE COMPANY - EXHIBIT 1080
Gene Company PTY LTD, v.
The Trustees of Columbia University in the City of New York
IPR2024-00313



“[T]he burden of proving invalidity in an IPR remains on the petitioner throughout the proceeding.”

Fanduel, Inc. v. Interactive Games LLC, 966 F.3d 1334, 1341 (Fed. Cir. 2020)

**No Motivation
or REOS for
C₂₀-D₃-
Vitamin A
Slowing A2E**

1,5 Not Reasonably Expected to be Rate
Limiting in A2E Formation

Roth Irrelevant: Single-Step Intrinsic KIE,
Different Compound, Different Reaction

- A2E Pathway 1,5 Step Base Catalyzed Tautomerization, **Not** Sigmatropic Rearrangement
- Single-Step Intrinsic KIE Does **Not** Inform multi-step Observed KIE
- Roth Transition State Irrelevant to A2E Pathway

Petitioner's Nonspecific Teachings
and Unsupported Assertions Fail

Roth's Single-Step Sigmatropic Rearrangement Not Relevant

Petitioner KIE expectation relies on wrong reaction

Roth 1966 (EX1015)

EX1015, 3-4

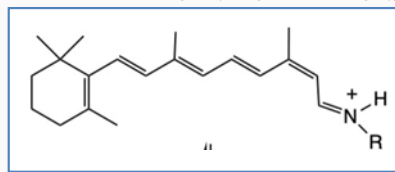


cis-pentadiene-(1,3)

Sigmatropic Rearrangement

Mowery 1979 (EX2077)

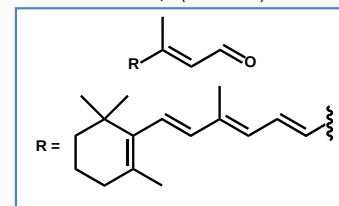
EX2052, ¶¶279-280, Fig. 13 (citing EX2077, 3, Fig. 5))



13-*cis*-retinylidene-*n*-butylamine

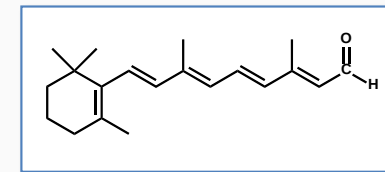
Verdegem 1997 (EX2078)

EX2078, 2 (Scheme 1)



all-*trans*-retinal

A2E Pathway

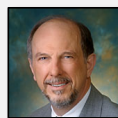


all-*trans*-retinal

General Base Tautomerization

Dr. Guengerich (EX2103)

Roth **intrinsic** single-step KIE does not inform **observed** KIE for multi-step A2E pathway



Q. So it's **necessarily the slowest step** because it's the **only step in Roth**, correct.

A. Well, I suppose one could say that, **yeah, it's the only step**. It's **a single reaction**, yes.

Q. Roth **doesn't tell** you whether sigmatropic shift in a different **multistep sequence** is going to be overall **rate limiting**, correct?

A. **It does not....**

EX2103, 62:3-23

KIE “Depends on the Mechanism”

Petitioner Relied on Sigmatropic Rearrangement Specifically

Petition

Filed on behalf of: Gene Company Pty Ltd
By: Jad A. Mills (j.mills@wsgr.com)
Michael T. Rosato (mrosato@wsgr.com)
Matthew Bresnahan (mbresnahan@wsgr.com)

As explained by Dr. Guengerich, prior art teachings about the deuterium isotope effect **specifically for a sigmatropic [1,5] shift** indicated that A2E formation would be reduced by as much as 12 times.

v.

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

Pet., 37

As Dr. Guengerich further explains, a POSA would have understood that deuterating C20 would slow A2E formation **because 1,5-sigmatropic shifts** were known to be **subject to strong primary deuterium KIEs**.

Pet., 42

Dr. Guengerich (EX2103)

Q. And in general, even if there are exceptions, is it correct that, in your opinion, for a nonenzymatic hydrogen subtraction reaction, that changing hydrogen to deuterium would slow the overall reaction?

A. Yeah. **That depends on the mechanism**, and **one can't say that that's always going to happen or not**. Yeah.



Q. In general, even if there are exceptions, is it correct that for linear nonenzymatic chemical reactions with a CH bond breaking, that it would be slowed by replacing hydrogen to deuterium?

A. My answer is the same. **It depends on the mechanism**. **Here we have [a]n 1,5-sigmatropic rearrangement, we have a concerted synchronous mechanism which is consistent with a high kinetic isotope effect....** EX2103, 130:19-131:12 (bottom), 131:14-24 (top)

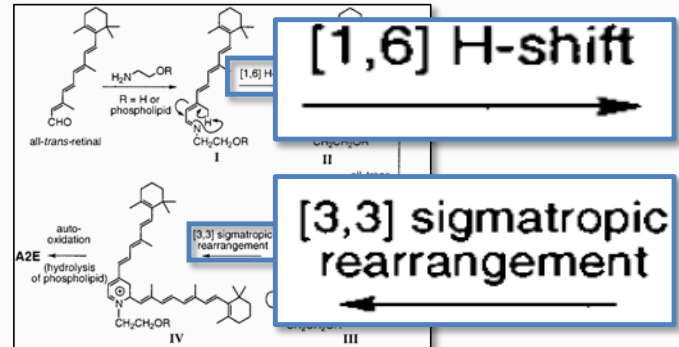
Mata's "Sigmatropic" is an Inconsistent Outlier

Majority of prior art describe 1,5 step as tautomerization

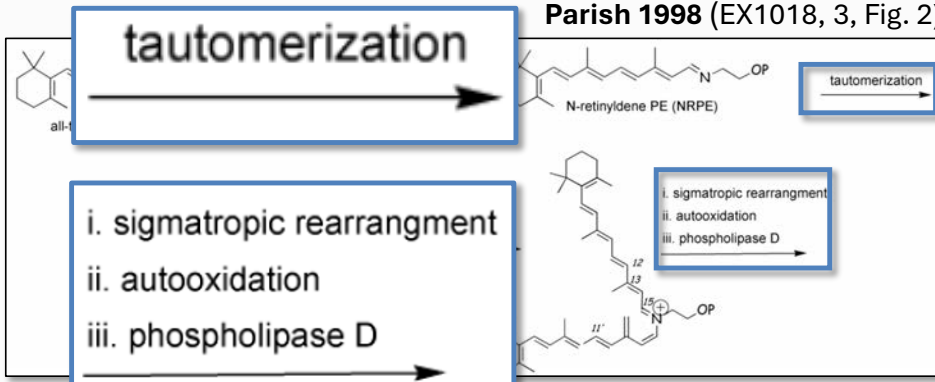
Fishkin 2003  [1,6]-proton tautomerization EX1036, 2	Kim 2007  [1,6]-proton tautomerization EX2019, 10
Wolf 2003  Tautomerization EX1034, 1	Ben-Shabbat 2002  [1,6]-proton tautomerization EX2051, 1
Parish 1998  [1,6]-proton tautomerization EX1018, 1	Fishkin 2005  Tautomer X EX1011, 5

Prior art distinguishes between 1,5 "tautomerization" or "shift" and subsequent 3,3 sigmatropic rearrangement

Fishkin 2003 (EX1036, 1, Fig. 1)



Parish 1998 (EX1018, 3, Fig. 2)



Unsupported “Prone” Reply Argument Irreconcilable with Petition

Petition argued sigmatropic “specifically”
and **no** other mechanisms

Petition

As explained by Dr. Guengerich, prior art teachings about the deuterium isotope effect **specifically for a sigmatropic [1,5] shift** indicated that A2E formation would be reduced by as much as 12 times.

Pet., 37



“[T]he Board did not misapply the law by **requiring [Petitioner] to prove the facts that it alleged.**”

Arctic Cat Inc. v. Polaris Industries, Inc.,
795 Fed. Appx. 827, 833

Single unsupported assertion for new
base-catalyzed “prone” to KIE argument

Pet. Reply

[M]echanism also was ‘**prone**’ to a strong KIE.
EX1080, ¶¶59-60, 63-64.

[T]his is true even if... the 1,5-shift was
unleashed endogenously via acid-base....
EX1080, ¶¶36, 58-64.

Pet. Reply, 12, 17



Dr. Guengerich

[G]eneral acid-base catalysis invoked by Dr.
Prestwich... **known to be prone to strong
KIEs.** ❌

EX1080 ¶59

Sur-Reply, 2-3, 9.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

38

Doering Adds Nothing Over Roth

Petitioner Reply: Doering (EX2025) “**corroborated** both the 1,5-sigmatropic rearrangement’s specific slowness and its large expected KIE.”

Same flaws as Roth

- ✗ Wrong reaction
- ✗ Single-step
- ✗ Simple model compound
- ✗ Gas phase

Doering does **not** “corroborate[]”

Doering 2006 (EX2025)

That the precision of these **data is insufficient to warrant extrapolation** to room temperature emerges starkly from calculation of the temperature dependence of k_H/k_D from the eight values in Table 3 (column 4). The resulting Arrhenius equation, $\ln(k_H/k_D) (-1.10 (0.62) + (1170 (280))/RT$ (standard errors at the 95% confidence level errors are (1.52 and (690 cal/mol, respectively), leads to **a value extrapolated** to room temperature of **16.8 (2-67!)**

Single-Step **Intrinsic** KIE Does **Not** Inform Multi-Step **Observed** KIE

Petitioner ignores “intrinsic” and “observed” KIE distinction

Dr. Prestwich (EX2052)

An **intrinsic isotope effect** (k_H/k_D) represents the ‘true’ difference in the rate of C-H bond breaking and the **rate** of a C-D bond-breaking in a reaction, **independent of other steps in the reaction....**

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IN THE CITY OF NEW YORK,
Patent Owner

Roth (EX1015) is an example of a study leveraging the **intrinsic isotope effect....** the authors obtained an **intrinsic KIE of 12.2.**

I declare that all statements made herein of my knowledge are true, that all

statements made

these statements

like so made

Title 18 of the

By:



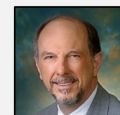
[A]n **observed isotope effect** (k_H/k_D)_{obs} is the ratio of reaction rates between **protium and deuterium** substrates for an **entire reaction process....** this measure depends on and reflects the **combined influence of all** the biological and physical processes....

Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

EX2052 ¶¶132-134

Dr. Guengerich (EX2103)

Q. There’s only **one step involved [in Roth]**-- the only step involved is the 1,5-sigmatropic shift, correct?

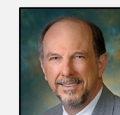


A. Yes.

Q. So it’s **necessarily the slowest step** because it’s the **only step in Roth**, correct.

A. Well, I suppose one could say that, **yeah, it’s the only step.** It’s a single reaction, yes.

EX2103, 61:18-21, 62:3-8



Q. Roth doesn’t tell you whether sigmatropic shift in a different **multistep sequence is** going to be overall **rate limiting**, correct?

A. It does not....

EX2103, 62:10-23

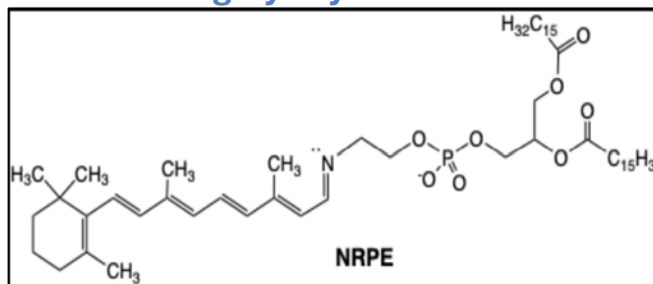
Roth Transition State Irrelevant to A2E Pathway

Roth 1966 (EX1015)

Extent [of KIE] is largely determined by the **symmetry** of the **transition state** and reaches a maximum value with a linear, symmetrical arrangement of the activated complex. **cis-pentadiene-(1,3) (1) therefore seemed particularly suitable** for investigating the isotope effect....

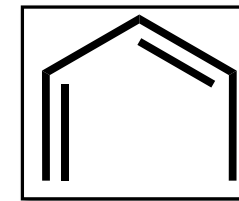
EX1015, 3-4

NRPE
"highly asymmetric"



EX2052 ¶¶132-133, 254, 274, 296-297

cis-pentadiene-(1,3)
"highly symmetric"



Dr. Guengerich (EX2209)



Q. Can you give me an example of one factor [that influences transition state]?

A. Well, I can. This is -- I don't know if it's really speculation but, basically, how much the product and substrate **differ in terms of their structures**. That's one of the things. There are many things. **It's not readily predictable.**

Q. Would **introducing an oxygen or a nitrogen** to [Roth's] compound potentially **affect the symmetry of the transition state**?

A. I don't know. **Possibly; possibly not. I didn't address that specifically in my declaration.**

EX2209, 14:5-22, 16:2-20

**No Motivation
or REOS for
C₂₀-D₃-
Vitamin A
Slowing A2E**

1,5 Not Reasonably Expected to be Rate
Limiting in A2E Formation

Roth Irrelevant: Single-Step Intrinsic KIE,
Different Compound, Different Reaction

**Petitioner's Nonspecific Teachings and
Unsupported Assertions Fail**

- General Guidance Does Not Provide Motivation or REOS
- Petitioner's Reply Arguments Fail

“General Guidance” Is Insufficient for Motivation or REOS

- ❌ No indication of **how** to inhibit -- not even general class of drugs
- ❌ No indication of **where** to inhibit – no druggable target
- ❌ No expectation of success for any strategy

Mata 2000

Pharmacologic inhibition of **one or more steps** in the A2E synthetic pathway **may thus be an effective treatment strategy** for other macular degenerations associated with lipofuscin accumulation.

EX1010, 6

Kim 2007

Improved understanding of the mode of genesis of A2E and other RPE lipofuscin compounds **could** facilitate the introduction of yet other **novel approaches to therapy**.

EX2019, 7



“[P]atents are not barred just because it was obvious “to explore a new technology or general approach that seemed to be a promising field of experimentation, where the **prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.”**

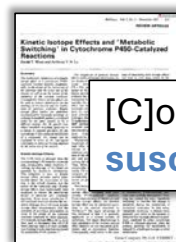
Procter & Gamble Co. v. Teva Pharms. USA, Inc., 566 F.3d 989, 997 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed.Cir.1988))

General KIE Background Insufficient for Motivation or REOS

✗ Petitioner does not cite a single example of creating a novel intervention / non-enzymatic improvement of drug

✗ General knowledge of phenomena does not motivate treating AMD or reducing lipofuscin with C₂₀-D₃-vitamin A

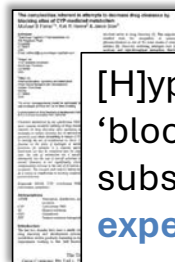
✗ Deuterium for enzymatic metabolism



Miwa 1987 (EX1051)

[C]onservative strategy... on **carbon atoms susceptible** to the cytochrome **P-450 oxidation**

EX1051, 5



Fisher 2006 (EX2076)

[H]ypothesis of using deuteration, or otherwise 'blocking' metabolism, to decrease overall substrate consumption via metabolism... is **not expected** to be an **effective strategy** for CYPs **except in highly specific situations**

EX2076, 7



General motivation “to make smaller, truncated proteins to solve the cloning difficulties... would not have supplied researchers with a reason to make the group of proteins claimed”

Genetics Inst., LLC v. Novartis Vaccines and Diagnostics, Inc., 655 F.3d 1291, 1306 (Fed. Cir. 2011)

Petitioner's "Forced Conditions" Does Not Suggest 1,5 Rate Limiting

Unidentified "slow" reaction **overall** says nothing of rate of 1,5 **specifically**

Q. Is there **anything specific in Fishkin** that you can point to teaching that cleavage of the carbon-hydrogen bond you referred to in paragraph 98 was recognized to be relatively slow under physiological conditions?



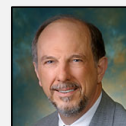
A. Well, I would say, looking at Fishkin, I think their conditions were fairly -- they started with all-trans-retinol -- retinal, and they **actually did some reactions here, and I think they were fairly long-term**, as, apparently, I'm looking here.

Q. But they didn't isolate the carbon-hydrogen bond cleavage measurements, correct?

A. **No. No, that's correct.**

EX2103, 121:18-122:11

Q. But to be clear, Doctor, **you can't conclude from babies not having high levels of lipofuscin deposits that the 1,5-sigmatropic rearrangement in Mata Figure 5 itself is slow**, correct?



A. **Well, no, I cannot do that.** I just mentioned that because you brought up the Mata just being spontaneous. I mentioned the model chemistry, which required very high temperatures, and I also just added this because, **as far as we understand, this is not a rapid process in humans at physiological temperatures.**

EX2103, 71:19-80:7

Prior Art Did **Not** Teach Targeting A2E Pathway “Specifically”

Art alleged to target A2E pathway is instead directed to reducing ATR

Dr. Guengerich Declaration (EX1080)

Dr. Prestwich... 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.... but see EX1069 (Del Priore Transcript), 203:6-14**

EX1080 ¶29

Dr. Del Priore deposition (EX1069) discussing Howes 2006 (EX2111)

EX1069, 197:12-204:21

Howes 2006 (EX2111) discussing visual cycle Inhibitors

EX2111, 2-4

Sur-Reply, 14-17, 27-28;
Pet. Reply, 5 (citing EX1069), 13, 22 (citing EX1080).

Dr. Guengerich (EX2209)

Q. So when [EX2111] says it’s -- **is discussing targeting lipofuscin** for an A2E formation, it’s discussing the **same visual cycle** we looked at in the **Radu paper, right?**

A. I think **that’s a reasonable statement.** The **HPR**, the **fenretinide**, it’s actually not specifically targeting the visual cycle, but **it’s inhibiting the retinol supply to the eye.** So it’s -- yeah, indirectly, **that’s correct.**



Q. And **neither** of those inhibitors **target** the **A2E pathway specifically?**

A. **I would agree with that.**

Q. So page 3 of **Exhibit 2111** when the authors say, ‘Recent efforts have centered on targeting A2E formation,’ they’re **referring to reducing the availability of ATR** with HPR or Accutane? Right?

A. **Well, right** -- well, in addition, it’s also **talking about reducing** dietary levels of **Vitamin A....**

EX2209, 63:3-65:2

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

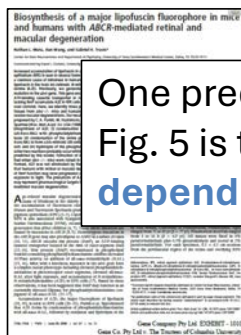
46

1,5 **Not** “First and Best” For Intervention

Petitioner Reply: “The 1,5-shift is thus the **first and best** point for intervention in the byproduct pathway and was expected to provide recognized benefits.”

Pet. Reply, 10

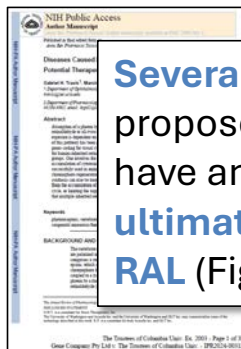
Mata 2000



One prediction of the pathway proposed in Fig. 5 is that **A2E** accumulation should **depend on the availability of all-trans-RAL**

EX1010, 6

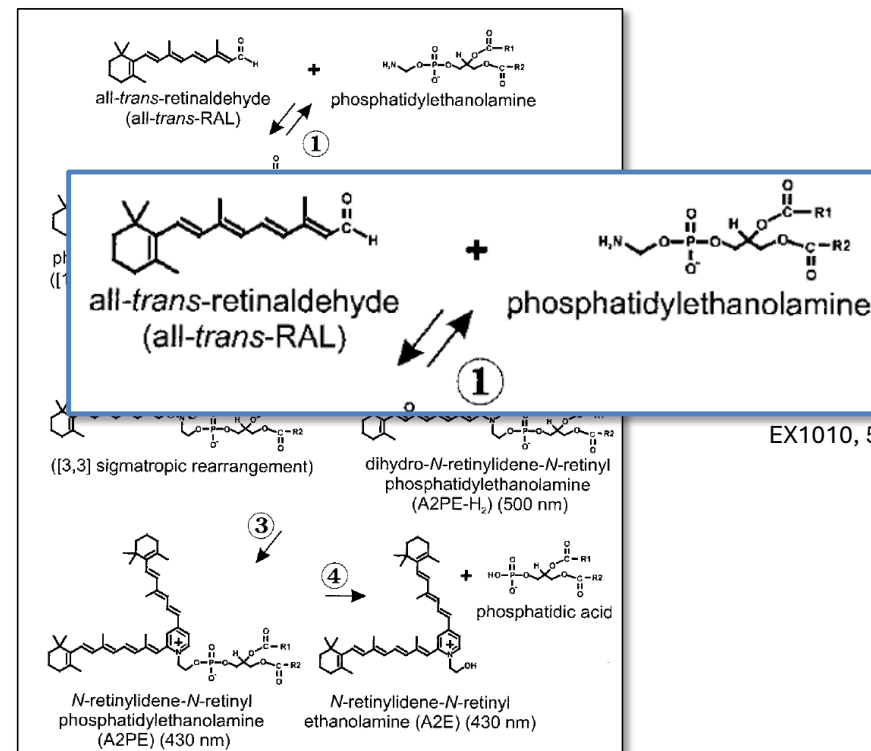
Travis 2007



Several approaches have been tested or proposed **to slow** accumulation of **A2E**. **All** have an effect on visual-cycle retinoids and **ultimately limit the formation of all-trans-RAL** (Figure 5).

EX2003, 14

Mata 2000



EX1010, 5

Multiple Rate-Limiting Steps in **Visual Cycle**

Does **Not** Show Multiple Rate Limiting Steps in **A2E Reaction**

Dr. Guengerich Declaration

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..... **He identifies multiple steps in the visual cycle as rate-limiting....** EX1080 ¶21

Dr. Guengerich Deposition



Q. So saying there's **a slow step** in the **visual cycle** is **different** than saying there's a **slow step** in the **A2E pathway**?

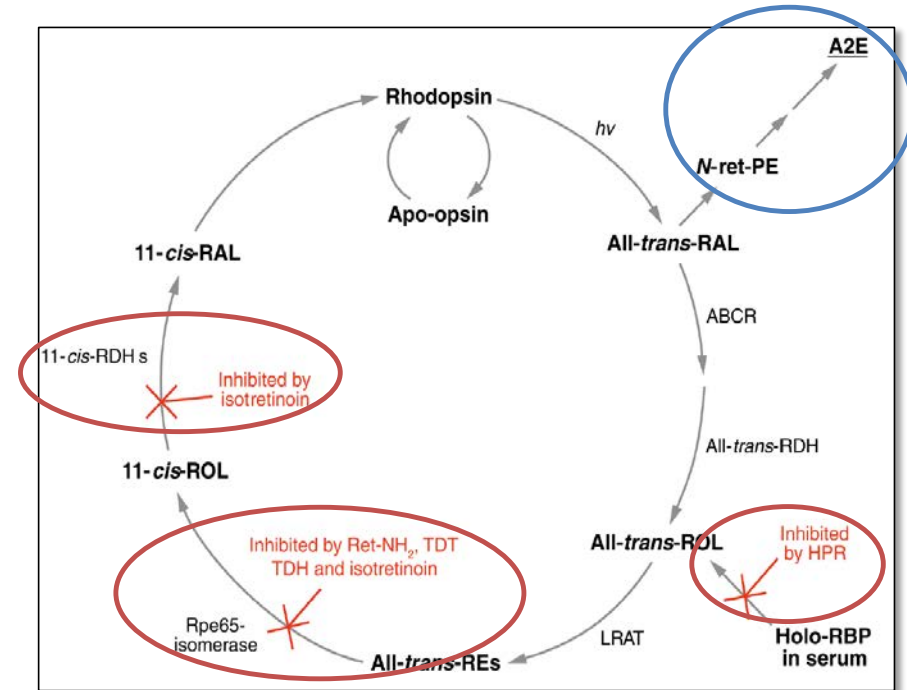
A. **Yes. That's certainly my opinion.**

Q. Those are **two different things**?

A. That is **correct.**

EX2209, 54:4-9

Multiple **reactions** in visual cycle vs. **A2E reaction**



EX2003, 35

Claimed Methods Were **Not** In The Prior Art

Hospira, Inc. v. Fresenius

- ✗ Composition claim, “was not a method claim”
- ✗ Involved a claimed property (shelf life) that “was necessarily present in the prior art”

Dr. Guengerich (EX2103)

Q. Are you aware of anyone prior to the '045 patent suggesting that deuteration of carbon-20 would slow the formation of A2E?



A. No, I'm not. I was just looking at Fishkin, and I don't specifically see that mentioned right here; although, **obviously, the Columbia group actually was thinking about that shortly thereafter.**

EX2103, 119:9-17



“The Board committed legal error by improperly relying on inherency to find obviousness and in its analysis of motivation to combine the references”

Honeywell Intl. Inc. v. Mexichem Amanco Holding S.A. DE C.V., 865 F.3d 1348, 1354 (Fed. Cir. 2017)

No Motivation or REOS For Vitamin A

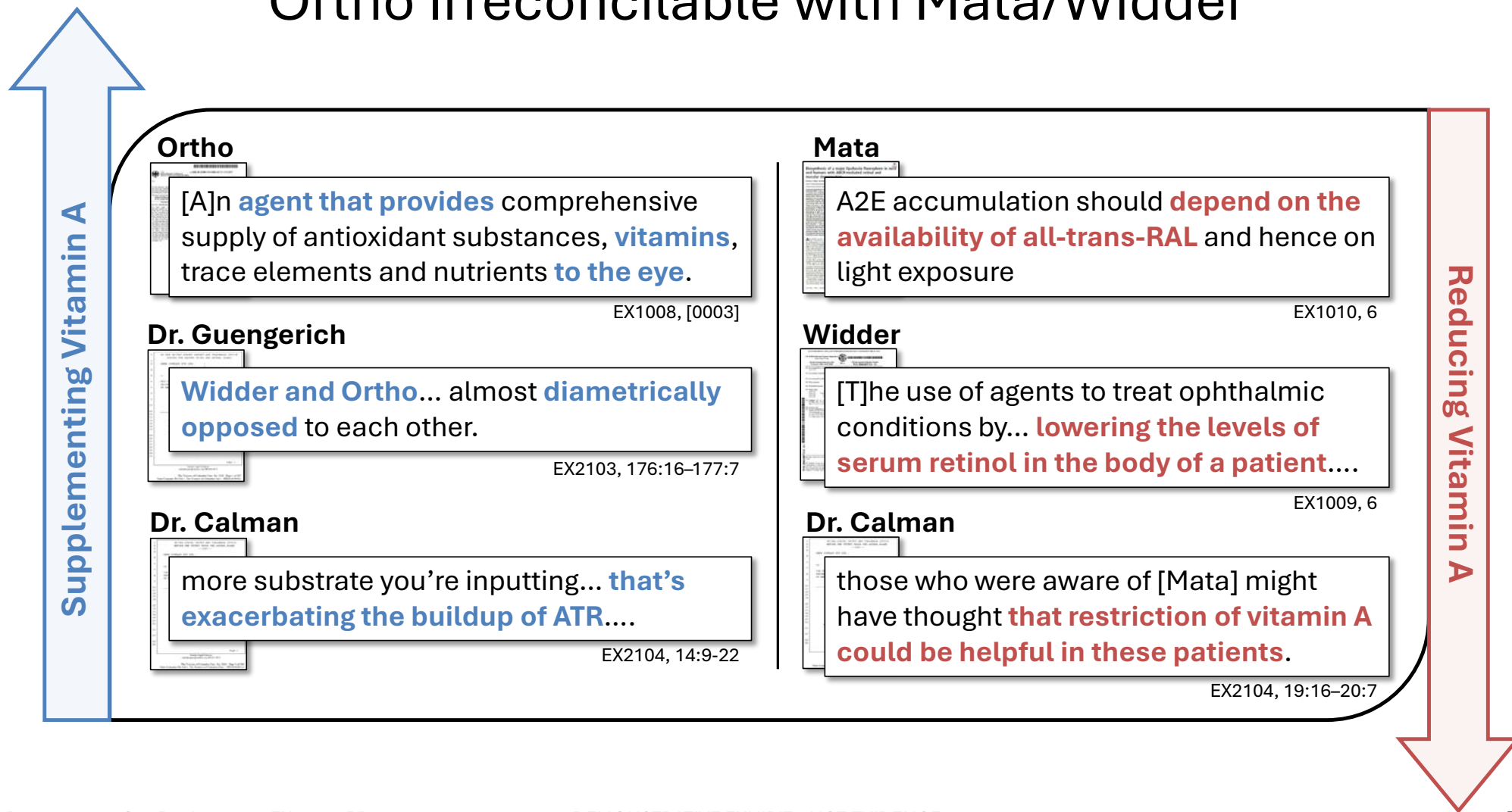
Ortho Irreconcilable with Mata/Widder

- Mata Taught Reducing ATR and Vitamin A
- Widder “Almost Diametrically Opposed to Ortho

Prior Art Taught Away from Vitamin A for
Macular Degeneration / Lipofuscin

Vitamin A Was Never the Standard of
Care

Ortho Irreconcilable with Mata/Widder



POR, 1-2, 16-21; Sur-Reply, 10-11; EX2192, ¶¶180-192.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

51

Ortho Irreconcilable with Mata/Widder

Dr. Calman (EX2104)

Q. Can you connect the dots for me **why the instructions are not to consume excess vitamin A for patients with this genetic disorder?**



A. Because of the **potential for exacerbating the buildup of all-trans-retinal**, r-e-t-i-n-a-l, which is the **precursor to lipofuscin** in the retina.

Q. And how would excess vitamin A build up ATR?

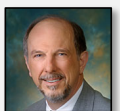
A. Well, potentially, the—you know, basically, **the more substrate you're inputting** into the visual cycle, potentially **that's exacerbating the buildup of ATR, which is the lipofuscin precursor**.

EX2103, 14:9-22

Dr. Guengerich (EX2103)

Q. And why did it make sense to reduce serum retinol levels to reduce formation of the lipofuscin pigments?

A. Yeah, it's hypothetical, and actually, if you look at some of the approaches that's historically used, some of those were actually almost **countering each other in terms of giving vitamin A and also lowering retinal levels then**.



Q. What would a person of ordinary skill in the art understand from Exhibit 1009 as **the benefit of reducing serum retinol levels?**

A. Well, my understanding was that if **you reduce the amount of retinols** and, you know, therefore retinal, you'll have **less material to go on and form these lipofuscin products**.

EX2103, 176:16-177:20

Ortho Teaches Supplement for Vitamin Deficiencies

Ortho (EX1008)



It is further known that the complaints can be aggravated, especially in old age, by an **incorrect diet or an inadequate supply of the necessary vitamins and nutrients**. In the state of the art, supportive care, especially for elderly patients, is known **to prevent deficiencies in the supply of vitamins and nutrients to the eye**.

EX1008, ¶13

Dr. Calman (EX2104)



Q. And leaving aside whatever **Ortho** teaches for carotinoids, it **doesn't provide any other or additional function for vitamin A**; correct?

A. It's a long document, so give me a moment.

Q. Take your time, Doctor.

A. I don't see a specific function listed for vitamin A in this document.

EX2104, 89:2-11

Dr. Guengerich (EX2103)



Q. And do you understand whether **Ortho is teaching use of vitamin A to address vitamin A deficiencies**?

A. That is -- that's a general statement, but, **yes, I would agree that basically you're -- it's a vitamin supplementation with a bunch of other stuff added too**. Yeah.

EX2103, 135:8-16

Mata Taught Reducing ATR and Vitamin A

Mata (EX1010)

Biosynthesis of a major lipofuscin fluorophore in mice and human macula

Nathan L. Mata
Center for Basic Research in Macular Degeneration
Communicated by
Increased accumulation of lipofuscin in the retinal pigment epithelium (RPE) is a common cause of age-related macular degeneration (AMD). The major fluorophore of lipofuscin is the bis-retinoid A2E. A mutation in the ATP-binding site of the RPE-specific phosphatidylethanolamine transferase (ABCR) gene, which is lacking in RPE of AMD patients, is associated with increased accumulation of A2E. We have investigated the biosynthesis of A2E. (i) condensation of all-trans-retinaldehyde (all-trans-RAL) with phosphatidylethanolamine to form a Schiff base; (ii) condensation of the Schiff base with a second all-trans-RAL to form a bis-retinoid; (iii) oxidation to yield a pyridinium salt; and (iv) hydrolysis of the phosphate ester to yield A2E. The latter two reactions were predicted by in vitro studies and were confirmed by mass spectrometry. The observed inhibition of A2E accumulation in *abcr* ^{-/-} mice raised under total darkness suggests that limiting light exposure may reduce the rate of disease progression in humans with recessive *ABCR*-mediated diseases.

Age-related macular degeneration (AMD) is a leading cause of blindness in the United States. The retinal pigment epithelium (RPE) is also a site of accumulation of lipofuscin, a mixture of fluorescent bis-retinoid fluorophores. The major fluorophore of lipofuscin is the bis-retinoid A2E. Accumulation of A2E in the RPE is associated with AMD. A mutation in the *ABCR* gene, which is associated with AMD, is associated with increased accumulation of A2E. We have investigated the biosynthesis of A2E. (i) condensation of all-trans-retinaldehyde (all-trans-RAL) with phosphatidylethanolamine to form a Schiff base; (ii) condensation of the Schiff base with a second all-trans-RAL to form a bis-retinoid; (iii) oxidation to yield a pyridinium salt; and (iv) hydrolysis of the phosphate ester to yield A2E. The latter two reactions were predicted by in vitro studies and were confirmed by mass spectrometry. The observed inhibition of A2E accumulation in *abcr* ^{-/-} mice raised under total darkness suggests that limiting light exposure may reduce the rate of disease progression in humans with recessive *ABCR*-mediated diseases.

Gene Company Pty Ltd. EXHIBIT - 1010
Gene Co. Pty Ltd v. The Trustees of Columbia University

EX1010, 6

EX1010, 6

Dr. Calman (EX2104)

Q. So to your understanding, is **Mata**, Exhibit 1010, the origin for the current practice of recommending against vitamin A supplementation for Stargardt's patients?

A. I think that line of research is certainly one of the bases for that.

Q. The question I asked before you had turned to **Mata** was: Was it also the practice in the 2007-2008 period to recommend against vitamin A supplementation for Stargardt's patients?

A. Yeah, I don't think there—I think I sort of answered that already. I don't believe there were any formal recommendations, and I think that those who were aware of some of this experimental literature might have thought that restriction of vitamin A could be helpful in these patients.



EX2104, 19:16–21:7

Widder “Almost Diametrically Opposed” to Ortho

Widder (EX1009)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

(51) Int. Cl.⁷
A61K 31/561
(21) Int. No.
(22) Int. No.
(25) Pub.
(26) Pub.
(30) Int. No.
601
601
601
(71) Applicant
SV
SAR
(72) Inventor
(73) Inventor
US
(11) Serial No.
92

[M]ethods and formulations comprise the use of agents to treat ophthalmic conditions by (a) lowering the levels of serum retinol in the body of a patient, (b) modulating the activity of enzymes or proteins in the eye of a patient wherein such enzymes or proteins are involved in the visual cycle....

(54) Title: METHODS AND COMPOSITIONS FOR TREATING OPHTHALMIC CONDITIONS WITH RETINYL DERIVATIVES

(57) Abstract: Compounds that cause reversible night blindness may be used to treat ophthalmic conditions associated with the overproduction of waste products that accumulate during the course of the visual cycle. We describe methods and compositions using such compounds and their derivatives to treat, for example, the macular degenerations and dysplasias or to alleviate symptoms associated with such ophthalmic conditions. Such compounds and their derivatives may be used as single agent therapy or in combination with other agents or therapies.

Gene Company Pty Ltd EXHIBIT - 1009
Gene Co. Pty Ltd v. The Trustees of Columbia University

EX1009.3

Dr. Guengerich (EX2103)



Q. And I'm asking now about the opposite of Widder, increasing serum retinol levels. What would a person of ordinary skill in the art in 2007 have known as to whether increasing serum retinol levels could increase lipofuscin formation?

A. That is a bit hypothetical because you said ‘could.’ Now, that's different than saying it would. In fact, Ortho -- assuming Ortho had some POSAs working for them, they were actually taking that approach, adding more, giving more vitamin A. So the -- I guess the overall point I'm making when you actually consider Widder and Ortho is that there were a mixture of approaches, and some of them seem almost diametrically opposed to each other.

Q. Decreasing serum retinol levels for Widder is the opposite of Ortho increasing serum retinol levels?

A. That's a -- that may be a gross overgeneralization, but there's **some merit to it.**

EX2103, 176:16-177:7-20

POR, 1-2, 17-21, 61-62; Sur-Reply, 10-11, 26; EX2192. ¶¶184-192.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

55

No Motivation or REOS For Vitamin A

Ortho Irreconcilable with Mata/Widder

Prior Art Taught Away from Vitamin A for
Macular Degeneration / Lipofuscin

- Vitamin A Increases Lipofuscin; Contraindicated
- Prior Art Universally Taught Reducing ATR to Treat Macular Degeneration; No Focus on A2E Pathway
- “Highly Regulated” Conflates β -carotene and Vitamin A

Vitamin A Was Never the Standard of Care

Vitamin A Increases Lipofuscin

Petitioner: “**PO provides no evidence** these **vitamin A serum levels** were associated with **increased lipofuscin** formation.”

Pet. Reply, 3

Robinson 1982 (EX2113)

THE ROLES OF VITAMIN E AND UNSATURATED FATTY ACIDS IN THE VISUAL PROCESS

W. GERALD ROBINSON, JR.

Lipids and lipid-soluble vitamins aspects of eye function and methods in lipid research have been well as clinical information, diagnosis and treatment of visual but broad sample of studies lipids in ocular tissues will fast action. However, most involve a discussion of proposed roles of Vitamin E and unsaturated fatty acids in the retina, using a selected review of the literature and previously unpublished data.

Since outer segment membranes of retinal photoreceptor cells contain an unusually high proportion of polyunsaturated fatty acids in their phospholipids, they are extremely susceptible to damage. Recent findings of the importance of Vitamin E, in the photoreceptor membranes, and studies of peroxidized membrane products of aging pigment (lipofuscin) in retinal diseases will be discussed. Data as well as Vitamin E and unsaturated fatty acids and the determination of the rate of

This dose-related response suggests a close relationship between dietary vitamin A and lipofuscin formation.

[V]itamin A deficiency and lowered vitamin A levels decreased the fluorescence in a dose-related manner. The high vitamin A retinas 23 mg/kg diet) showed more than normal lipofuscin autofluorescence.

From the Laboratory of Vision Research and the "Laboratory of Nutrition and Institute of Arthritis, Metabolism and Endocrinology, National Institutes of Health, Bethesda, Maryland. Presented at the Symposium on Nutrition sponsored by the Committee on Nutrition, National Academy of Sciences, November 16-17, 1981. Reprint requests: W. Gerald Robinson, M.D., National Institutes of Health, Bethesda, MD 20892.

263

EX2113, 11

The Trustees of Columbia Univ. Ex. 2113 - Page 3 of 21
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Dr. Calman (EX2104)

Q. Can you explain what you meant when you said that more substrate inputted into the visual cycle potentially exacerbates the buildup of ATR?



A. Well, in chemical reactions generally, if you **increase the input of the initial reactant**, you are going to -- you are going to shift the equilibrium toward the end products; **you are going to increase -- potentially increase the buildup of the end product, which in this case is ATR and its harmful lipofuscin products.**

EX2104, 15:3-16:2

Clinical Consensus Against Vitamin A

Petitioner addresses neither express teaching away nor Dr. Calman's admissions

Kennedy 1995

Factors **retarding lipofuscin** formation
.... **Vitamin A deficiency**....

EX2156, 3, Table II

Tsui 2007

Stargardt patients should **avoid** a diet high in vitamin A because the defective gene (*ABCA4*) encodes for a transmembrane transporter of A2E intermediates, a toxic by-product of vitamin A.

EX2164, 12

Hamel 2006

Vitamin A should **not be given** to RP patients with mutations in *ABCA4*.

EX2158, 8

Voo 2004

Because **ABCA4** gene mutations seem to impair the processing of vitamin A, it has been suggested that **vitamin A supplements may actually exacerbate Stargardt disease**. Therefore, such **vitamin supplements are not recommended**.

EX2133, 2

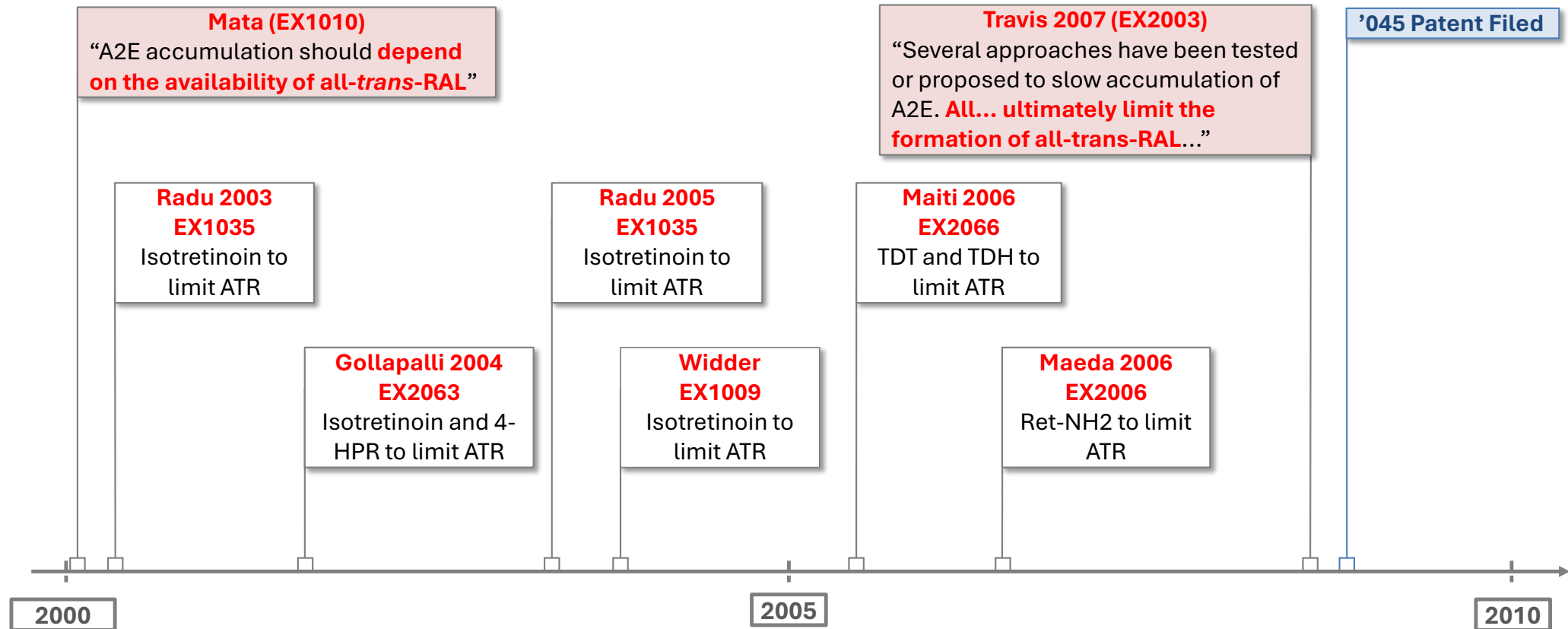
Dr. Calman



[T]he **more substrate** you're **inputting** into the visual cycle, potentially that's **exacerbating the buildup of ATR**, which is the lipofuscin precursor

EX2104, 14:8-22

Prior Art Focused On Reducing ATR -- **Not** Targeting A2E Pathway



POR, 18-19, 32-33; Sur-Reply, 6, 14-16;
EX2052, ¶¶112-128, 221-230.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

59

Prior Art Focused On Reducing ATR -- **Not** Targeting A2E Pathway

Dr. Guengerich (EX2103)

Q. Following Mata, is it correct that researchers in the field continued to look for ways to **either inhibit the visual cycle itself or reduce the serum concentration of vitamin A species?**



A. I would agree that those were two of the major approaches with the experimental drugs that were in use. The Ortho approach was to actually put in more vitamin A, so I think **those are major approaches that were used until the deuterated -- C20 deuterated material approach was tried.**

Q. And until the C20 deuterated approach was tried, no one had attempted to slow the reaction steps in Mata Figure 5, correct, to your knowledge?

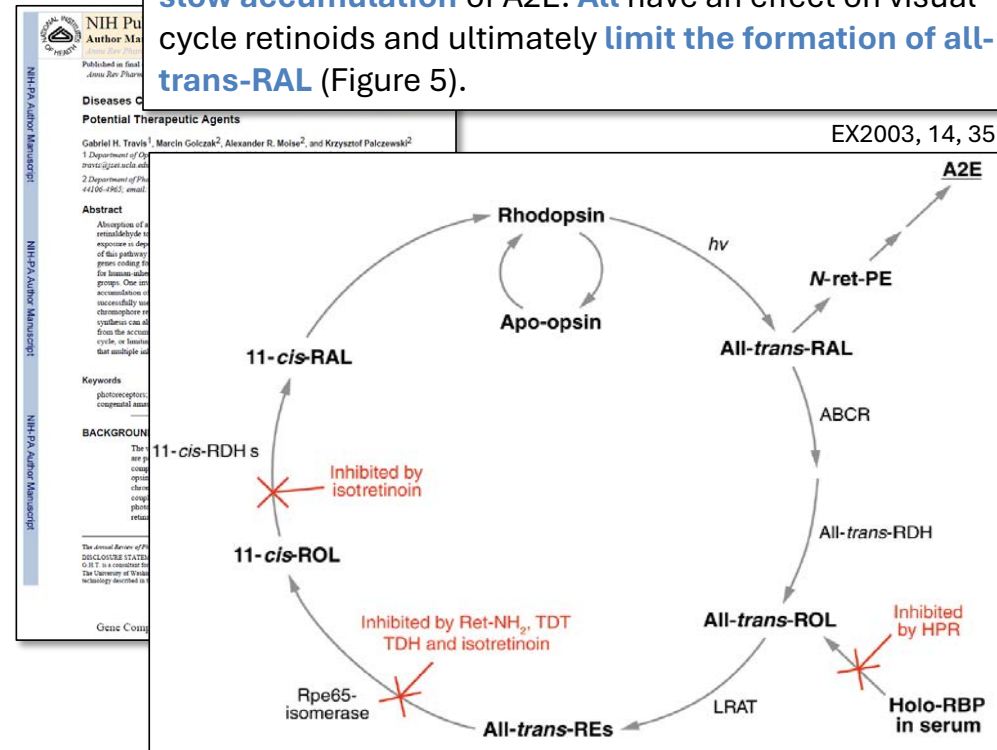
A. I'm not aware of any in that time period.

EX2103, 155:2-25

Travis 2007 (EX2003)

Several approaches have been tested or proposed **to slow accumulation** of A2E. **All** have an effect on visual-cycle retinoids and ultimately **limit the formation of all-trans-RAL** (Figure 5).

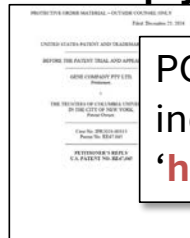
EX2003, 14, 35



Petitioner's "Highly Regulated" Conflates β -carotene and Vitamin A

β -carotene is highly regulated, **not vitamin A**

Pet. Reply



PO argues administering vitamin A would increase lipofuscin formation by increasing serum concentrations. But serum **vitamin A** concentrations were '**highly regulated**.' EX1069, 143:4-12

Pet. Reply, 3

EX1069 at 143:4-12 (Dr. Del Priore)



Q. -- on **this page of Exhibit 2150**, it says, 'The cleavage of **provitamin A carotenoids** to retinal is a **highly regulated** step.' Do you see that?

A. I do see that, yes.

EX1069, 143:4-12

EX2150 (Penniston 2006)



The cleavage of **provitamin A carotenoids** to retinal is a **highly regulated** step, and vitamin A toxicity from provitamin A sources is largely impossible. **In contrast, absorption and hepatic storage of preformed vitamin A occur very efficiently until a pathologic condition develops.**

EX2150, 1

Petitioner's "Highly Regulated" Conflates β -carotene and Vitamin A

AREDS administered **β -carotene**; administering **vitamin A** increased serum levels

Pet. Reply

PO argues administering vitamin A would increase lipofuscin formation by increasing serum concentrations. But **serum vitamin A** concentrations were 'highly regulated.' **AREDS** (EX1022, 7-8) **reported no significant vitamin A** serum-concentration increases after years of treatment.

Pet. Reply, 3
(citations omitted)

AREDS (EX1022)

[R]isks and benefits of **supplementing with** either zinc, antioxidants (vitamins C and E and **beta carotene**), or the combination of both....

Berson 1993 (EX1040)

Percentage **changes in serum retinol** concentrations for all randomized patients by treatment group from baseline to the mean of all follow-up visits were: **group A, +8.8%**; trace group, +0.3%; group A+E, +5.3%; and group E, -1.0%. Serum retinol values were **significantly elevated** ($P < .001$) **for those receiving vitamin A, 15000**

EX1040, 6

Glenn 1994 (EX2151)

After long-term ingestion of excessive vitamin A, a **constant elevation of the serum level occurs....**

EX2151, 4

No Motivation or REOS For Vitamin A

Ortho Irreconcilable with Mata/Widder

Prior Art Taught Away from Vitamin A for
Macular Degeneration / Lipofuscin

Vitamin A Was **Never** the Standard of Care

- Old Studies Do **Not** Teach Vitamin A Treatment
- Ortho Does **Not** Teach Vitamin A Treatment
- AREDS Does **Not** Teach Vitamin A Treatment
- No REOS for an “Effective Amount” of C₂₀-D₃ Vitamin A

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

63

Vitamin A was **Never** the Standard of Care for MD



No treatments, much less administration of vitamin A



Ortho vitamin A only for vitamin deficiency



AREDS administered β -carotene



Out-dated studies do not reflect the state of the art or “standard of care”

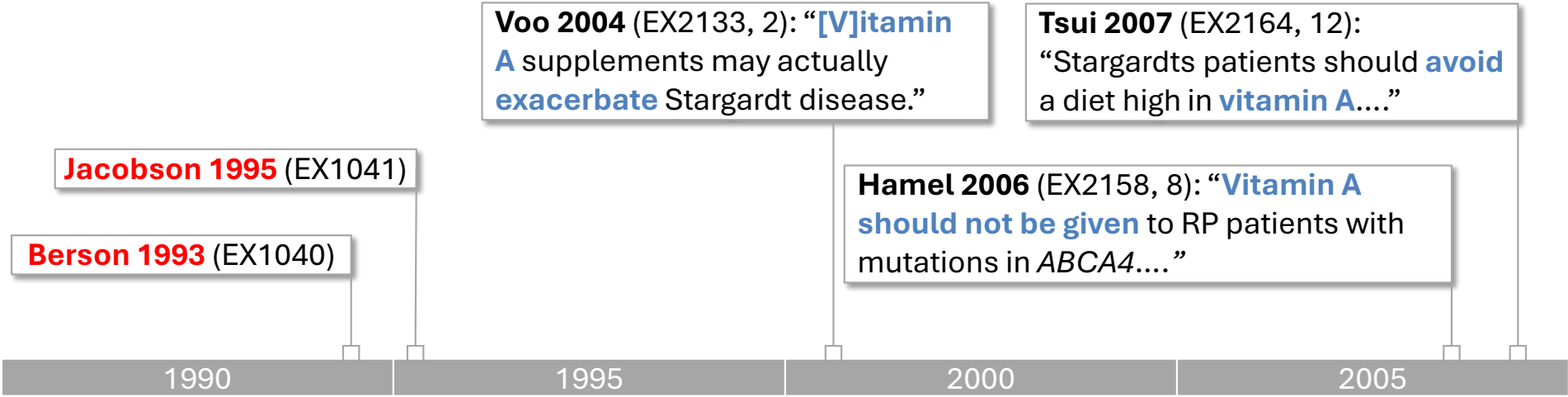
Old Studies Do **Not** Teach Vitamin A Treatment

Dr. Del Priore (EX1069)



People tried a variety of things, you know, for Stargardt’s before it was recognized that it was actually a problem with vitamin A....

EX1069, 123:13-124:5



MD Standard of Care in 2007: **No** Treatments, **Not** Vitamin A

Dr. Del Priore

In my own practice as of **2007**, I **did not recommend vitamin A supplementation** in patients with macular degeneration.

EX2192 ¶¶113, 143

Guymer 2006

Identifying modifiable risk factors **for AMD.... the only agreed upon modifiable risk factor is smoking.**

EX2139, 3

Dr. Calman



[M]ost clinicians, as far as I know today, do **not recommend vitamin A** supplementation for Stargardt's.

I recommend that [Stargardt's patients] **not consume excessive vitamin A.**

EX2104, 17:2-24 (top) 12:22-13:14 (bottom)

Kennedy 1995 (EX2156)

LIPOFUSCIN OF THE RETINAL PIGMENT

Factors retarding lipofuscin formation

- Elimination of rod outer segments
- Vitamin A deficiency**
- Ocular melanin
- Retinal antioxidants
 - Vitamin C
 - Vitamin E
 - Superoxide dismutase
 - Glutathione peroxidase
 - Peroxidase
 - Catalase
- Reduction in dietary calories or food intake**

FLUORESCENT CHARACTERISTICS

Lipofuscin is composed of a mixture of different fluorophores, reflecting the heterogeneous nature of this cellular pigment. Ten different fluorescent fractions have been identified within chloroform extractions of RPE cell lipofuscin. All these fluorophores have common absorption peaks in the

Eye (1995) 9, 763-771 © 1995 Royal College of Ophthalmologists
The Trustees of Columbia Univ. Ex. 2156 - Page 1 of 9
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

EX2156, 4-5, Table II

POR, 17-21, 23-24; Sur-Reply, 10-14, 26; EX2192, ¶¶ 59-83, 95-99, 109-127, 135-143, 210-222.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

66

Ortho Does **Not** Teach Vitamin A to Treat MD

Ortho (EX1008)



It is further known that the complaints can be aggravated, especially in old age, by an **incorrect diet or an inadequate supply of the necessary vitamins and nutrients**. In the state of the art, supportive care, especially for elderly patients, is known **to prevent deficiencies in the supply of vitamins and nutrients to the eye**.

EX1008, ¶13

Dr. Calman (EX2104)



Q. And leaving aside whatever **Ortho** teaches for carotinoids, it **doesn't provide any other or additional function for vitamin A**; correct?

A. It's a long document, so give me a moment.

Q. Take your time, Doctor.

A. **I don't see a specific function listed for vitamin A in this document.**

EX2104, 89:2-11

Dr. Guengerich (EX2103)



Q. And do you understand whether **Ortho is teaching use of vitamin A to address vitamin A deficiencies?**

A. That is -- that's a general statement, but, **yes, I would agree that basically you're -- it's a vitamin supplementation with a bunch of other stuff added too.** Yeah.

EX2103, 135:8-16



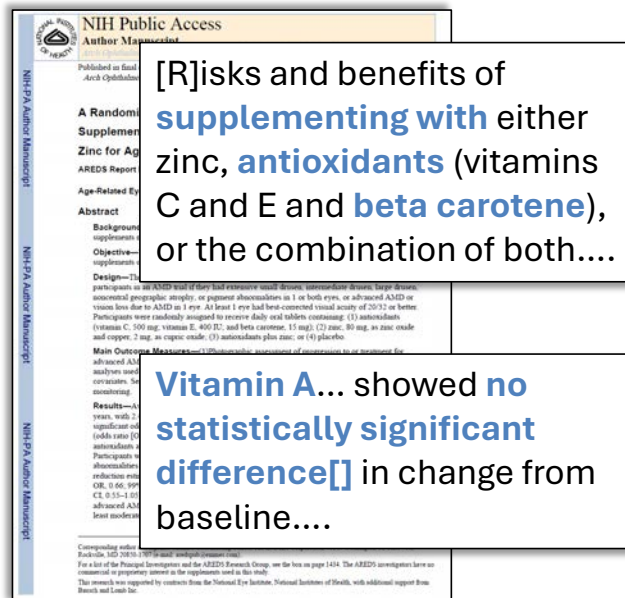
“[I]t is not enough for [the patent challenger] to merely demonstrate that elements of the claimed invention were independently known in the prior art.”

Metalcraft of Mayville, Inc. v. The Toro Co., 848 F.3d 1358, 1367 (Fed. Cir. 2017)

AREDS Does **Not** Teach Vitamin A Treatment

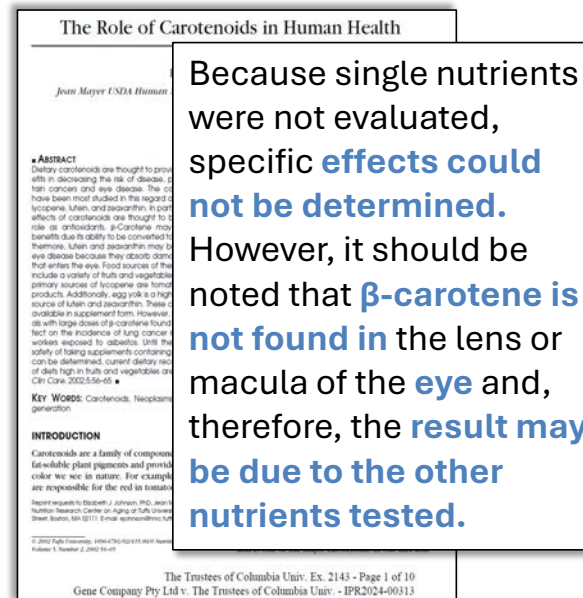
Petitioner Conflates β -carotene and vitamin A

Used β -carotene, **not** vitamin A



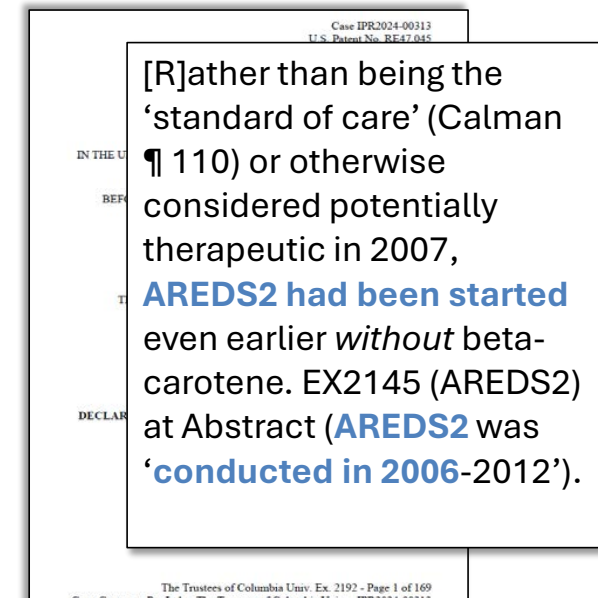
EX1022 at 2, 7-8

No effect attributed to β -carotene



EX2143, 4

2006 AREDS2 removed β -carotene



EX2192 ¶121

No REOS for an “Effective Amount” of C₂₀-D₃ Vitamin A

Claims Require “Effective Amount” For:

- Reducing Lipofuscin Accumulation (claims 1-28)
- Treating MD (claims 4, 28-54)
- Treating AMD (claims 5-9, 32-37)
- Treating Stargardt’s (claims 11-14, 38-42)

✗ Ortho (EX1008)

- **No** therapeutic efficacy attributed to vitamin A
- **No** guidance on an “effective amount” of vitamin A for anything

✗ Olson (EX1006)

- **No** therapeutic purpose or effect of C₂₀-deuterated vitamin A taught or suggested

✗ Widder (EX1009) ✗ Mata (EX1010)

- **Not** relied on by Petitioner to teach claimed effective amount
- Discloses opposite: **reducing** vitamin A to limit lipofuscin / treat AMD



“[W]here the prior art evidences only failures to achieve that at which the inventors succeeded, no reasonable fact finder could find an expectation of success based on the teachings of that same prior art.”

U. of Strathclyde v. Clear-Vu Lighting LLC, 17 F.4th 155, 165 (Fed. Cir. 2021)

Objective Evidence Confirms Nonobviousness

Praise

- “Quite Novel” & “Innovative” (2010)
- FDA - Breakthrough Therapy Designation (2021)
- FDA - Patient Listening Session (2022)
- Professor Gorin - “Groundbreaking” (2024)

Long-Felt Need + Failure of Others

Clinical Success: TEASE and SAGA

Unexpected Results

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

70

Praise: “Quite Novel” & “Innovative” (2010)

Dr. Guengerich:

Date: 9/21/10, 3:51 PM

Sincerely yours,

F. Guengerich
Associate Editor

One of the Reviewing Editors is of the opinion that there are important elements to the manuscript and that it addresses an important topic. The **novelty** of using a **deuterated** version of **vitamin A** is also **considered quite novel**.

EX2057, 1

Reviewer 2:

This manuscript describes the effect of feeding a deuterated version of vitamin A to mice... developing Stargardt's disease. There is **great interest in this disorder** and it is of **significant clinical importance**. The use of a **C20-D3-vitamin A** is quite novel and interesting.

EX2057, 2

Date: 9/24/10, 4:09 PM

Sincerely yours,

F. Guengerich
Associate Editor

Reviewer 3:

This is an **innovative paper** on the **use of deuterated vitamin A** to provide a **significant kinetic isotope effect** to slow down the rate of dimerization of retinaldehyde that can lead to the production of ATR dimers that precedes the **onset of macular degeneration**.

EX2056,1

Praise: FDA - Breakthrough Therapy Designation (2021)



Source: Alkeus Pharmaceuticals

July 14, 2021 07:00 ET

FDA Grants Alkeus Pharmaceuticals Breakthrough Therapy Designation for ALK-001 (C20-D3-vitamin A) for the Treatment of Stargardt Disease

- Only drug to receive Breakthrough Therapy Designation for Stargardt Disease
- Alkeus Pharmaceuticals to discuss next steps toward filing an NDA with the FDA
- Ongoing clinical trial of ALK-001 in dry age-related macular degeneration

Breakthrough Therapy

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

EX2107 (FDA Website), 1

EX2096, 1

POR, 51, 53-54; Sur-Reply, 24; Pet. Reply, 24; EX2191, ¶¶50-51; EX2192, ¶54; EX2194, ¶¶32-33.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Praise: FDA - Patient Listening Session (2022)

Stargardt Disease (STGD1)

FDA Patient-led Meeting

Minutes of the June 30, 2022 Meeting

Background
Stargardt disease is a rare, genetic condition that affects the back of the eye. Stargardt disease leads to irreversible challenges in the performance of activities of daily living, including recognizing faces. Although rare, Stargardt disease causes significant vision loss. No treatment currently exists to stop blindness in almost all patients.

Overview
On June 30, 2022, six patients and four caregivers along with one retina specialist addressed the FDA Patient Listening Session and provided first-hand accounts of what it is like living and caring for someone with this devastating condition. Numerous members from the FDA attended the meeting, representing 16 offices/divisions.

This document contains a summary of the topics covered, and of the patient and caregiver testimonies.

Key Points presented by speakers:

1. Stargardt Disease is a rare, genetic disease caused by mutations on the ABCA4 gene.
2. Stargardt causes progressive and irreversible vision loss which has a severe and devastating impact on patients' lives.
3. Most patients experience onset of symptoms in childhood.
4. The patient journey to proper diagnosis can be long and challenging.
5. Patients rapidly lose the ability to read, drive, work, social situations, and loss of independence.
6. No FDA-approved treatment exists. Potential therapies, have been explored for over 20 years.
7. As of June 2022, one potential treatment, ALK-001, is in clinical development.
8. Patients have challenges identifying clinical trials take many years to conduct due to the long treatment periods, as well as the small patient population and even smaller number of correctly diagnosed patients. Recently completed trials have taken over five years.

The Trustees of Columbia Univ. Ex. 2149 - Page 6 of 25
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Evie has gained some hope and happiness as she participates in a clinical trial for an investigational medical product (ALK-001) for Stargardt Disease. **She describes her experience with the investigational medical product as giving her the ability to enjoy her passions again, hope for her disease to stop progressing, and hope for future restoration of her vision.**

Every doctor responded that in their opinion, should the patient be their child, that **they would choose the oral investigational drug ALK-001 for their family.**

EX2149, 14-15, 19

Praise: Dr. Gorin, MD, PhD - “Groundbreaking” (2024)

TEASE-3 study: Positive interim data reported for Stargardt drug

March 17, 2024

By Lynda Charters

Publication Article

Modern Retina Digital Edition

Modern Retina Spring 2024

Volume 4 Issue 1

Reviewed by Michael B. Gorin, MD, PhD

Alkeus Pharmaceuticals Inc recently announced the interim results of TEASE-3, an open-label study designed to assess gildeuretinol (ALK-001) in early-stage Stargardt patients. It showed that treatment halted progression of early-stage Stargardt disease for up to 6 years.

This is a groundbreaking event in that Stargardt disease, which generally begins to cause visual symptoms during childhood, but in some cases, can begin occurring in adults, is an inherited genetic mutation that until now would progress unrelentingly to vision loss and blindness because of buildup of material in the retina, according to Michael B. Gorin, MD, PhD, who said he is encouraged by the results of the different TEASE trials.

(Image by Chrissy Bolton / MJH Life Sciences using AI)

EX2182, 1

POR, 53-54.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

74

Petitioner’s Attorney Arguments Contradict Precedent

Petitioner argues:	FDA Awards and Industry Recognition Evidence Nonobviousness
[B]reakthrough and orphan designations reflect a desire for successful results rather than a conclusion they were already obtained. Pet. Reply, 24. Dr. Guengerich explains the reviewer comments only reflect that the reviewers never performed a patentability analysis. Pet. Reply, 25.	 “<i>Supporting evidence demonstrated that there was a long-felt and unmet need for a treatment for menorrhagia that avoided adverse events, as the FDA recognized in granting ‘fast track’ status.</i>” <i>Ferring B.V. v. Watson Lab’ys, Inc.-Fla.</i>, 764 F.3d 1401, 1407 (Fed. Cir. 2014)  “the Board found that the <i>two industry awards weighed in favor of patentability</i>, as did, to a lesser extent, <i>the customer award</i>” <i>Henny Penny Corp. v. Frymaster LLC</i>, 938 F.3d 1324, 1330-33 (Fed. Cir. 2019)

**Objective
Evidence
Confirms
Nonobviousness**

Praise

Long-Felt Need + Failure of Others

- No Treatments By 2007
- Dry AMD Failed Clinical Attempts
- Stargardt Disease Failed Clinical Attempts

Clinical Success: TEASE and SAGA

Unexpected Results

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

76

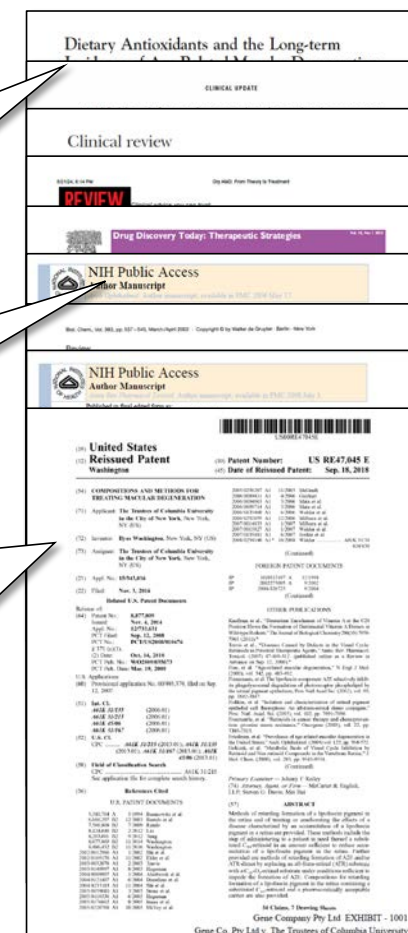
Long-Felt Need: No Treatments By 2007

Long-felt need
for retarding the
accumulation of
lipofuscin and
treating MD
without
worsening night
blindness and
dark adaptation

As there is no cure for AMD, and treatments to stop its progression have met with limited success....
EX2139, 1 (Guymer 2006).

Macular degeneration falls into a class of diseases that are generally considered difficult therapeutic targets.... EX2074, 11 (Rattner 2006).

Thus, recently proposed therapeutic approaches to limit lipofuscin formation are based upon slowing the visual cycle.... One immediate disadvantage of slowing the visual cycle is that it leads to delayed dark adaptation and poor vision in dim light or at night. EX1001, 3:32-40.



EX2141, 1;
EX2139, 1;
EX1039, 4;
EX2111, 1;
EX2161, 1;
EX1022, 2;
EX1020, 4;
EX2074, 11;
EX1001,
2:8-3:40

POR, 3-6, 49-50; Sur-Reply, 22-23; EX2192 ¶¶55, 70, 74, 284, 290-291, 309, 314.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

77

Long-Felt Need: Confirmed by Petitioner's Evidence and RPI

Shaban (EX1020)

[illegible]

[N]o treatments or preventive measures are currently available for patients with dry AMD

EX1020, 4

Petitioner Reply

PROTECTIVE ORDER MATERIAL – OUTSIDE COUNSEL ONLY

Filed December 28, 2024

Calling vi
inducing

FILED IN RE: [REDACTED]

PETITIONER'S REPLY
U.S. PATENT NO. RE: 73407

Calling visual cycle inhibitors “**blindness-inducing medications**”

Pet. Reply, 4

AREDS (EX1022)



NPH Public Access
Author Manuscript
 Published in *Stroke* ahead of the peer review process
 DOI: 10.1161/STROKEAHA.116.045028

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

At present,

treatment

the development

Abstract

Background: Age-related macular degeneration (AMD) is a leading cause of blindness in the United States. The National Eye Institute-funded Age-Related Eye Disease Study 2 (AREDS2) was designed to evaluate the efficacy of a new formulation of vitamins C, E, beta carotene, and zinc in preventing AMD progression. The study was conducted in a randomized, placebo-controlled, clinical trial. The primary outcome was the proportion of participants who developed AMD or vision loss over a 6-year period. The secondary outcome was the proportion of participants who developed AMD or vision loss over a 6-year period. The study was conducted in a randomized, placebo-controlled, clinical trial. The primary outcome was the proportion of participants who developed AMD or vision loss over a 6-year period. The secondary outcome was the proportion of participants who developed AMD or vision loss over a 6-year period.

Conclusions: The results of the AREDS2 trial suggest that high-dose supplementation with vitamins C, E, beta carotene, and zinc may be beneficial in preventing AMD progression. The study was conducted in a randomized, placebo-controlled, clinical trial. The primary outcome was the proportion of participants who developed AMD or vision loss over a 6-year period. The secondary outcome was the proportion of participants who developed AMD or vision loss over a 6-year period.

Keywords: Age-related macular degeneration, vision loss, vitamins C, E, beta carotene, zinc, AREDS2, clinical trial, randomized, placebo-controlled.

At present, there is **no proven treatment** that slows or prevents the development of advanced AMD.

EX1022, 2

Belite Bio Presentation (EX2190)

Early Intervention with

Unmet Market Opportunity

- **No** FDA approved **treatments**
- **No** FDA approved oral **treatments** for **GA**

Unmet Market Opportunity:

- **No** FDA approved **treatments** for **STGD1**
- **No** FDA approved orally administered **treatments** for **GA**

EX2190, 4

Failures: Dry AMD Failed Clinical Attempts

Case IPR2024-00313 U.S. Patent No. RE47,045 IN THE 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 IPR2024-00313 U.S. Patent No. RE47,045 DECLARATION OF DR. LUCIAN V. DEL PRIORE, MD, PhD The Trustees of Columbia Univ. Ex. 2192 - Page 1 of 169 Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313	Treatment	Status
	Posterior juxtasceral injection of Anecortave Acetate (15 or 30 mg) every 6 months	Alcon did “not continue development of Anecortave acetate for dry AMD because clinical trial results showed no reduction in the progression from dry to wet AMD and no change in the time it took for the development of sight threatening CNV.” EX2187 (Stokkermans 2009) at 5; <i>see also</i> EX2168 (NCT00307398).
	Oral Fenretinide (100 or 300 mg) once daily for 24 months	Fenretinide did not achieve statistically significant reductions in GA growth rate. EX2185 (Mata 2013) at 8; <i>see also</i> EX2169 (NCT00429936). Use of fenretinide was associated with impaired dark adaptation and dyschromatopsia. EX2185 (Mata 2013) at 2, 3-4, 8.
	OT-551 ophthalmic solution (0.3% or 0.45%) 2 drops 4 times daily for up to two years	“OT-551 does not appear to reduce the progression of the area of GA in subjects with AMD.” EX2186 (Stenberg 2010) at 2; <i>see also</i> EX2170 (NCT00485394) at 5.

EX2192, ¶¶276

POR, 50; EX2192, ¶¶ 276-277.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

79

Failures: Stargardt Disease Failed Clinical Attempts

Case IPR2024-00313 U.S. Patent No. RE47,045 IN THE 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 IPR2024-00313 U.S. Patent No. RE47,045 DECLARATION OF DR. LUCIAN V. DEL PRIORE, MD, PhD The Trustees of Columbia Univ. Ex. 2192 - Page 1 of 169 Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313	Treatment	Status
	Supplementation with oral vitamin A (50,000 IU daily) for 2 weeks	"[A] high dose of oral vitamin A taken for a 14-day period did not provide any subjective or objective improvement in dark-adaptive function in five [Stargardt's] patients." EX2151 (Glenn 1994) at 4; <i>see also</i> EX2173 (Anderson 1995) at 2 ("No therapy alters the progression of this condition (Glenn et al. 1994).").
	Supplementation with oral lutein (20 mg daily) for 6 months	"Central vision was unchanged after the period of supplementation." EX2184 (Aleman 2007) at 1; <i>see also id.</i> at 8.
	Intravenous infusions of 4-methylpyrazole (4-MP; fomepizole; Antizol) (15 mg/kg weekly) for 3 weeks	"4-MP is not likely to be a successful intervention against Stargardt disease at currently approved dosages. Dose escalation could be considered as rats tolerate acute dosages up to 30 times higher, but we are concerned that some of our subjects were already experiencing mild but potentially significant side effects such as dizziness and a metallic aftertaste." EX2174 (Jurgensmeier 2007) at 4-5; <i>See also</i> EX2175 (NCT00346853).
	Intravitreal ranibizumab injections following a pro re nata regimen for 24 months	"[V]isual function does not benefit from ranibizumab treatment over a 24-month follow-up." EX2176 (Parodi 2015) at 2-3.
	Supplementation with oral docosahexaenoic acid (DHA) (1000 mg twice daily)	"We did not find evidence to support the premise that DHA improved visual function in this [autosomal recessive Stargardt disease] cohort." EX2177 (Caruso 2008) at 1; <i>see also</i> EX2178 (NCT0060749) (study sponsored by the National Eye Institute).

EX2192, ¶1278

POR, 50; EX2192, ¶¶283-288; Sur-Reply, 22-23.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

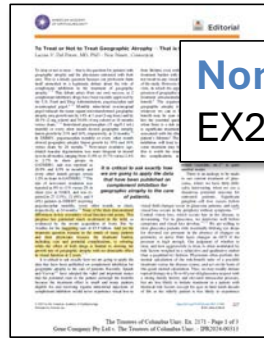
80

Long-Felt Need: Not Met By 2023 GA Products



Assessed “by filing date of the challenged invention”

Procter & Gamble Co. v. Teva Pharms. USA, Inc., 566 F.3d 989, 998 (Fed. Cir. 2009)



None of the trials demonstrated differences in key secondary visual function end points.
EX2171, 1 (Del Priore 2023 Article).

EX2104 (Calman Depo) 25:11-26:16

Q. You use both of those drugs?

A. I have used them. I have – I have stopped using them.

Q. And what do you use in their place? Anything?

A. Well, we don't really have anything.

Q. And why did you stop using it?

A. Because a percentage of patient will develop a catastrophic vascular event resulting in sudden and severe vision loss.



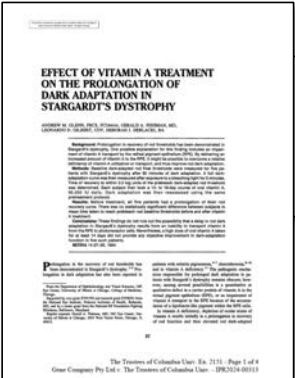
Petitioner’s No “Technical Obstacle” Exposes Its Hindsight



“Indeed this **considerable time lapse** suggests instead that the Board **only traverses the obstacles to this inventive enterprise with a resort to hindsight**. It took over a decade.... And, until the advancement made by the inventors of the '013 patent, no one had proposed a new formulation that would be storage stable.”

Leo Pharm. Prods., Ltd. v. Rea, 726 F.3d 1346, 1356 (Fed. Cir. 2013)

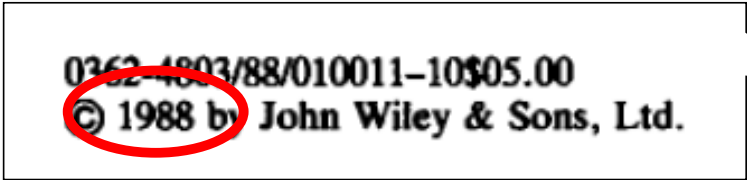
Vitamin A Not Effective in Stargardt Disease (1994)



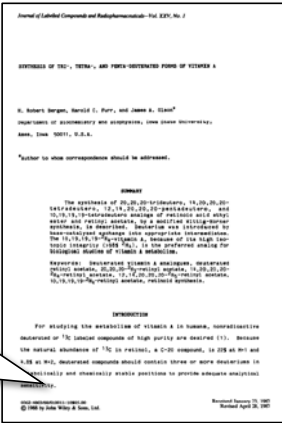
EX2151, 1

[A] high dose of oral vitamin A taken for at least 14 days did not provide any objective improvement in dark-adaptation function. EX2151, 1

Deuterated Vitamin A Known (1988)



Olson 1988



EX1006, 1

**Objective
Evidence
Confirms
Nonobviousness**

Praise

Long-Felt Need + Failure of Others

Clinical Success: TEASE and SAGA

- TEASE + SAGA Practices Claims 1, 2, 4-15, 18, 19, 26, 28-30, 32-42, 45, 46, 53
- GA and Stargardt Disease Efficacy Reflect Overall MD Efficacy
- Overcame Skepticism of Human Efficacy

Unexpected Results

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

83

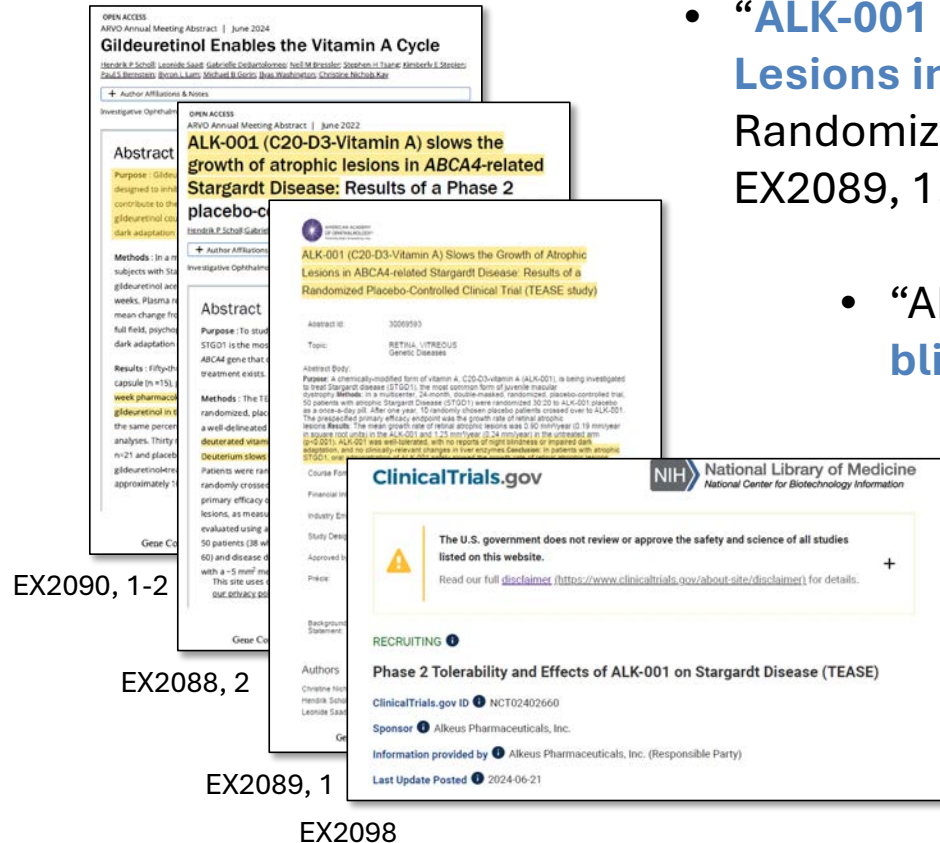
TEASE Practices:

Claims 1, 2, 4, 11-15, 18, 19, 26, 28-30, 38-42, 45, 46, 53

- “**ALK-001 (C20-D3-Vitamin A) Slows the Growth of Atrophic Lesions in ABCA4-related Stargardt Disease: Results of a Randomized Placebo-Controlled Clinical Trial (TEASE study).**” EX2089, 1.

- “ALK-001 was well-tolerated, with **no reports of night blindness or impaired dark adaptation....**” EX2089, 1.

- “**Gildeuretinol** (formally ALK-001 and C20D₃-Vitamin A) is a vitamin A substitute, **designed to inhibit the pathological dimerization of vitamin A**, a process thought to contribute to the development of **Stargardt disease....**” EX2090, 1.



POR, 51; Sur-Reply, 17-18; Pet. Reply, 18-19;
EX2192, ¶¶266-270, 292-293.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

84

SAGA Practices:

Claims 1, 2, 4-10, 19, 26, 28-30, 32-37, 46, 53

TITLE: Gildeuretinol in Geographic Atrophy: Results from SAGA, a 2-year, Randomized, Double-masked, Placebo-controlled Study

AUTHORS: Boyer DS¹, Saad L², Washington IF, Melamud A³, Graham KB⁴, O'Malley AE⁵, DeBartolomeo GM⁶, Jiang HF, Harris LD⁶, Kay CN⁷, Ferrone PJ⁶, Khan S⁷, on behalf of the SAGA Study Team

AFFILIATIONS:

1. Retina Vitreous Associates Medical Group, Los Angeles, California, USA
2. Alkermes Pharmaceuticals, Inc., Cambridge, Massachusetts, USA
3. Retina Group of Washington, Fairfax, Virginia, USA
4. Vitreoretinal Consultants of New York, Great Neck, New York, USA
5. Pacific Northwest Retina, Silverdale, Washington, USA
6. Houston Eye Associates, Houston, Texas, USA
7. Vitreo Retinal Associates, Gainesville, Florida, USA

ABSTRACT BODY (1000 characters max without spaces)

Purpose: Gildeuretinol acetate, a novel deuterated vitamin A, is an investigational treatment for age-related macular degeneration.

Methods: SAGA (NCT03845582) was a 2-year, randomized, double-masked, placebo-controlled study. Participants with geographic atrophy (GA) were randomized to receive either oral placebo or oral gildeuretinol 14 mg daily for 24 months. First interim analysis was conducted at 12 months.

Results: Baseline mean GA lesion area was 0.25 mm². At 24 months, the mean difference of 0.29 mm² (p=0.075). Sensitivity analysis showed that GA lesions were mild or moderate at baseline.

Conclusion: Oral gildeuretinol 14 mg daily was associated with a slower growth of GA lesions and improved visual acuity.

EX2094, 1

- “**ALK-001**, the study drug, is a modified form of vitamin A. When taken once a day as a capsule, it **replaces natural vitamin A in the body with one that forms vitamin A dimers more slowly**. This study will measure the extent to which treatment with ALK-001 slows the progression of Geographic Atrophy.” EX2099, 2.

ClinicalTrials.gov  **National Library of Medicine**
National Center for Biotechnology Information

 **The U.S. government does not review or approve the safety and science of all studies listed on this website.**

Read our full [disclaimer](https://www.clinicaltrials.gov/about-site/disclaimer) (<https://www.clinicaltrials.gov/about-site/disclaimer>) for details.

ACTIVE, NOT RECRUITING ⓘ

Phase 3 Study of ALK-001 in Geographic Atrophy (SAGA)

ClinicalTrials.gov ID ⓘ NCT03845582

Sponsor ⓘ Alkermes Pharmaceuticals, Inc.

EX2099, 1-2

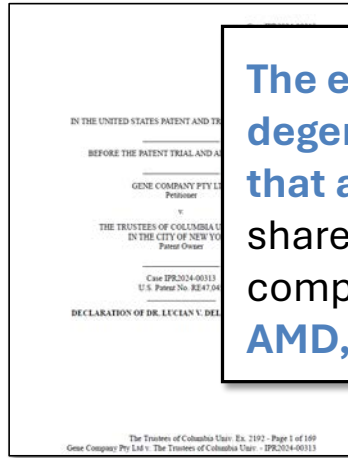
- “Oral gildeuretinol was associated with **slower growth of GA lesions and improved visual acuity.**” EX2094, 1.

POR, 51-52; Sur-Reply, 17-18; Pet. Reply, 18-19; EX2192, ¶¶274-280.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

85

GA and Stargardt Disease Efficacy Reflect Overall MD Efficacy



EX2192



The efficacy of ALK-001 in this particularly accelerated and aggressive form of macular degeneration [Stargardt disease], therefore, reflects an ability of ALK-001 to treat diseases that are related to ABCA4 and potentially a broad range of macular degenerations as they share the common feature of toxic lipofuscin accumulation at a generally slower rate as compared to Stargardt's disease. This is further confirmed by the efficacy of ALK-001 in dry AMD, as demonstrated in the SAGA trial discussed above. EX2192, ¶294.

“[W]hether a solvent is deoxygenated before or after the active ingredient has been dissolved is an insubstantial difference. Thus, **there is no reason to believe that any secondary considerations attendant** to Ofirmev®, in which the solvent is deoxygenated prior to the addition of the active ingredient, **would not also be present in formulations literally covered by the claims**, i.e., where the solvent is deoxygenated after the addition of active ingredient.”

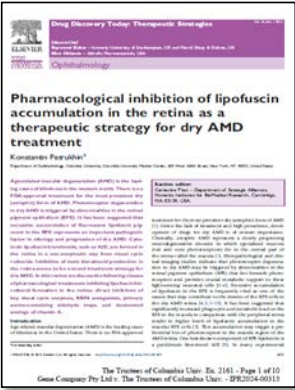
Cadence Pharms. Inc. v. Exela PharmSci Inc., 780 F.3d 1364, 1376 (Fed. Cir. 2015)

POR, 51-52; Sur-Reply, 19; EX2192, ¶¶103, 274-275, 278-280, 294.

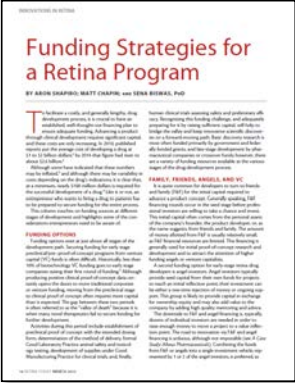
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

86

Skepticism: Clinical Efficacy Doubted



EX2161, 7



EX2179, 3

It should be kept in mind that preclinical efficacy for C20 –D₃ retinoids was demonstrated **only in the context of a complete replacement of natural vitamin A with its deuterated analogs. It remains to be proven whether pre-clinical efficacy demonstrated in animal models in the context of complete vitamin A replacement with the C20–D₃ analogs can be translated into clinical efficacy in humans** maintained on a standard vitamin A and b-carotene sufficient diet.

As CTV and Dr. Washington were trying to market his discovery to big pharmaceutical companies, biotech companies, VC groups, or angel investors, the answer was always the same: ‘Too early, **too risky**, come back with human data.’

Nexus: Presumed for Product of Claimed Invention



“[A] presumption of nexus applies in this case because Teleflex's ‘asserted objective evidence is tied to a specific product [i.e., the GuideLiner] and that product is the invention disclosed and claimed’ by the patents-in-suit.”

Medtronic, Inc. v. Teleflex Innovations S.a.r.l., 70 F.4th 1331, 1337 (Fed. Cir. 2023)



“Concluding otherwise would mean that nexus could never exist where the claimed invention is a unique combination of known elements from the prior art.”

Volvo Penta of the Americas, LLC v. Brunswick Corp., 81 F.4th 1202, 1211-12 (Fed. Cir. 2023)

Commensurate in Scope: Efficacy Across Formulations

EX2006

EX2181

EX2090

EX2097

EX1001



Efficacy across multiple formulations

- ALK-001 oral pill [EX2090, 1; EX2097, 2]
- Intraperitoneal Injection [EX2006, 2-3; EX1001, 19:40-21:22]
- Dietary Administration [EX2006, 2-3; EX1001, 19:40-21:22]
- Oil formulation [EX2181, 1-2]



“**[A] nexus** may still exist as long as it can be shown that such praise or success is also **due in part** to the claimed invention.”

Ex Parte Whirlpool Corp., Appeal 2013-008232, 15-16 (PTAB Oct. 30, 2013) (informative)



“As the party seeking additional discovery, Arctic Cat had the burden of proving that additional discovery was ‘in the interests of justice.’”

Arctic Cat Inc. v. Polaris Industries, Inc., 795 Fed. Appx. 827, 831-32 (Fed. Cir. 2019)

POR, 51-52, 55-57; Sur-Reply, 17-20; Pet. Reply, 18, 23; EX2192, ¶¶103, 274-275, 278-280, 294.

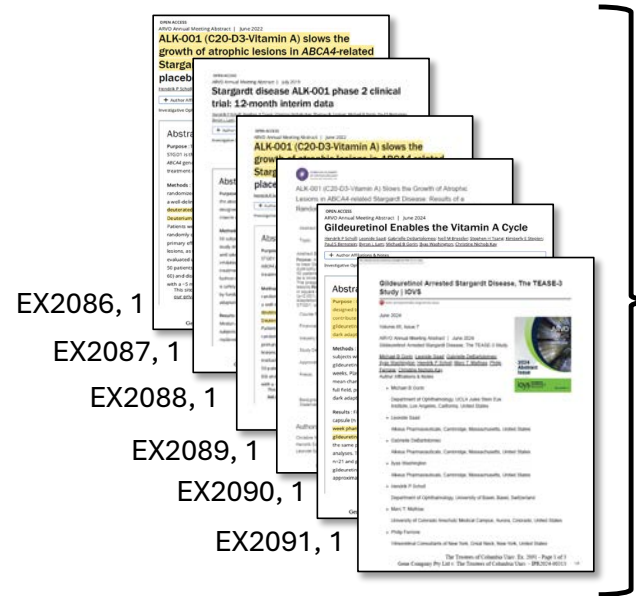
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

89

Clinical Trial Results Independently Confirmed and Peer Reviewed

- TEASE readers were qualified and blinded
- TEASE abstracts were peer-reviewed
- TEASE results independently confirmed

EX1079, 89:9-13, 91:18-21, 215:14-25, 216:1-218:9 (confidential)



Co-authored by
Dr. Scholl, CMO
of Petitioner's RPI

EX1079 (Saad Depo) 211:3-11

Q. Okay. To your understanding, are the IOVS abstracts peer-reviewed?

A. The – when submitting an abstract, IOVS, I believe that these abstracts are indeed peer-reviewed by the IOVS specialists.

**Objective
Evidence
Confirms
Nonobviousness**

Praise

Long-Felt Need + Failure of Others

Clinical Success: TEASE and SAGA

Unexpected Results

- Lipofuscin Reduction without Visual Impairment
- Rapid Replacement of Vitamin A

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

91

Unexpected Results:

Lipofuscin Reduction Without Visual Impairment

Reviewed by
Dr. Guengerich

EX2006



Results showed that dimerization of deuterium-enriched vitamin A was considerably slower than that of vitamin A at natural abundance as measured in vitro. **Administration of C20-D3-vitamin A to wild-type rodents with no obvious genetic defects in vitamin A processing, slowed A2E biosynthesis.** EX2006, 1.

EX1001



One immediate disadvantage of slowing the visual cycle is that it leads to delayed dark adaptation and poor vision in dim light or at night. EX1001, 3:38-40.

In the present invention,.... **many of the disadvantages**, such as, delayed dark adaptation, unformed visual pigment, which can lead[] to vision impairment and loss, high drug doses, and the potentially adverse side effects **of prior methods are avoided.** EX1001, 7:28-36.

EX2090



We found **no difference in dark adaptation parameters between gildeuretinol-treated and placebo cohorts** (Table 1), despite plasma retinal being approximately 10% that of normal levels in the gildeuretinol cohort, normally defined as severe vitamin A deficiency. EX2090, 1-2.

POR, 55-57; Sur-Reply, 20;
EX2192, ¶¶70, 74, 304-317.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Unexpected Results:



EX2094, 1

EX2090, 1-2

EX2089, 1

- DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Unexpected Results: Rapid Replacement of Vitamin A



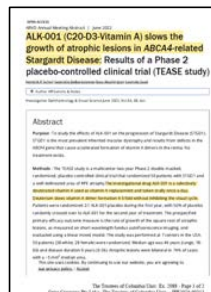
[A]n intervention based on controlling the concentration of retinal vitamin A has been questioned because 1) **the retina is notoriously hard to deplete of vitamin A....** EX2181, 1.

EX2181



At the **8-week pharmacokinetic analysis, 87% and 92% of plasma vitamin A was in the form of [C20D3-vitamin A] in the 14 and 24 mg cohorts, respectively.** EX2090, 1.

EX2090



On average, **~90% of vitamin A was replaced with deuterated vitamin A, which was maintained over time.** EX2088, 2.

EX2088

Petitioner's Unsupported Arguments



Objective evidence cannot be rebutted “with argument alone—it must present evidence.”

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1329 (Fed. Cir. 2016)

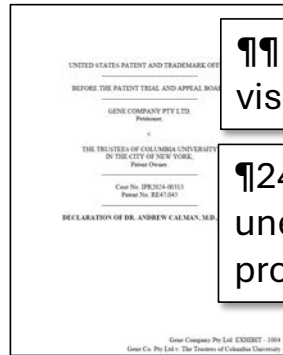


“[T]he cited declaration testimony is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight.”

Xerox Corp. v. Bytemark, Inc., IPR2022-00624, Paper 9, 15 (PTAB Aug. 24, 2022) (presidential)

Unsupported Arguments: Petitioner Fails to Rebut Unexpected Results

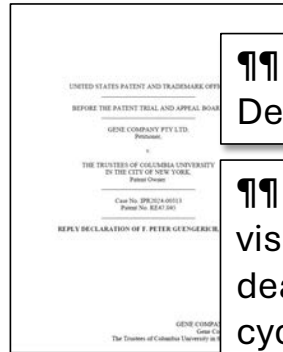
Dr. Calman (EX1004)



¶¶ 76-79. Law, Radu, and Sieving all teach: “inhibiting the visual cycle can lead to **deleterious visual effects**.”

¶243. “It is my opinion that in view of the prior art there were no unexpected results presented in the ’045 patent or during the prosecution of the ’045 patent.”

Dr. Guengerich (EX1080)



¶¶ 28-32, 35. Summarizing his own, Dr. Prestwich’s, and Dr. Del Priore’s previous statements

¶¶ 33-34, 36. “[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...”

No prior art
basis to expect
efficacy without
known
“deleterious
visual effects”

Ground and Claim- Specific Deficiencies

Additional Deficiencies of Ground 1 (Ortho and Olson 1988): Claims 1-9, 19-23, 25-26, 28-36, 46-50, and 52-53

- No Motivation to Combine Ortho and Olson with REOS
- Retarding the Accumulation of a Lipofuscin Pigment (claims 1 and 2-9, 19-23, 25-26)
- MD (claims 4, 28, 29-31, 46-50, 52-53) and AMD (5-9, 32-36)
- Forms A2E in vitro About 7 Times Slower (claim 9, 36, 53)

Additional Deficiencies of Ground 2 (Ground 1 in Further View of Mata): Ground 1 + Claims 10-15, 18, 37-42, and 45

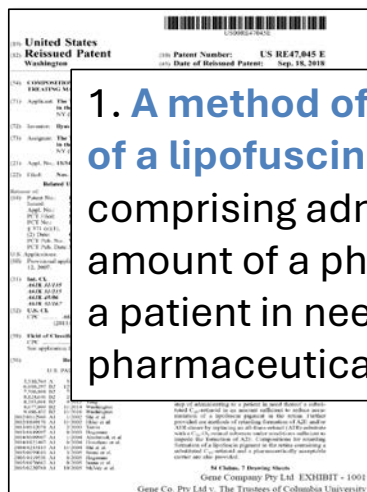
Additional Deficiencies of Ground 3 (Ground 1 and 2 in view of Widder): Claims 16-17, 24, 27, 43-44, 51, and 54

Petitioner Fails to Address Claimed Lipofuscin Limitation

Claims 1, 2-9, 19-23, 25-26

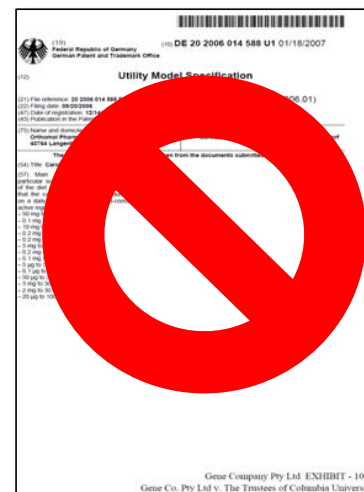
Not taught or suggested in ground references

'045 Patent (EX1001)

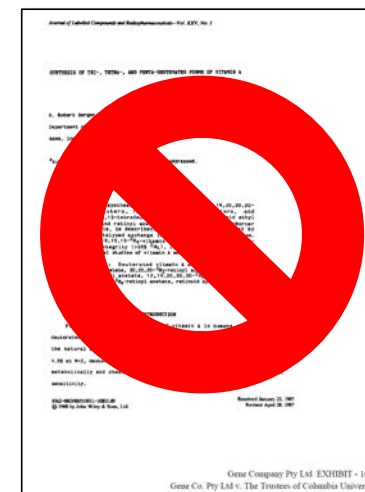


1. A method of retarding the accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises....

Ortho (EX1008)



Olson (EX1006)



Rejecting “unsupported and inferential theories” as substitute for missing claim limitation

Harmonic Inc. v. Avid Tech., Inc., 815 F.3d 1356, 1363 (Fed. Cir. 2016)

Ground and Claim-Specific Deficiencies

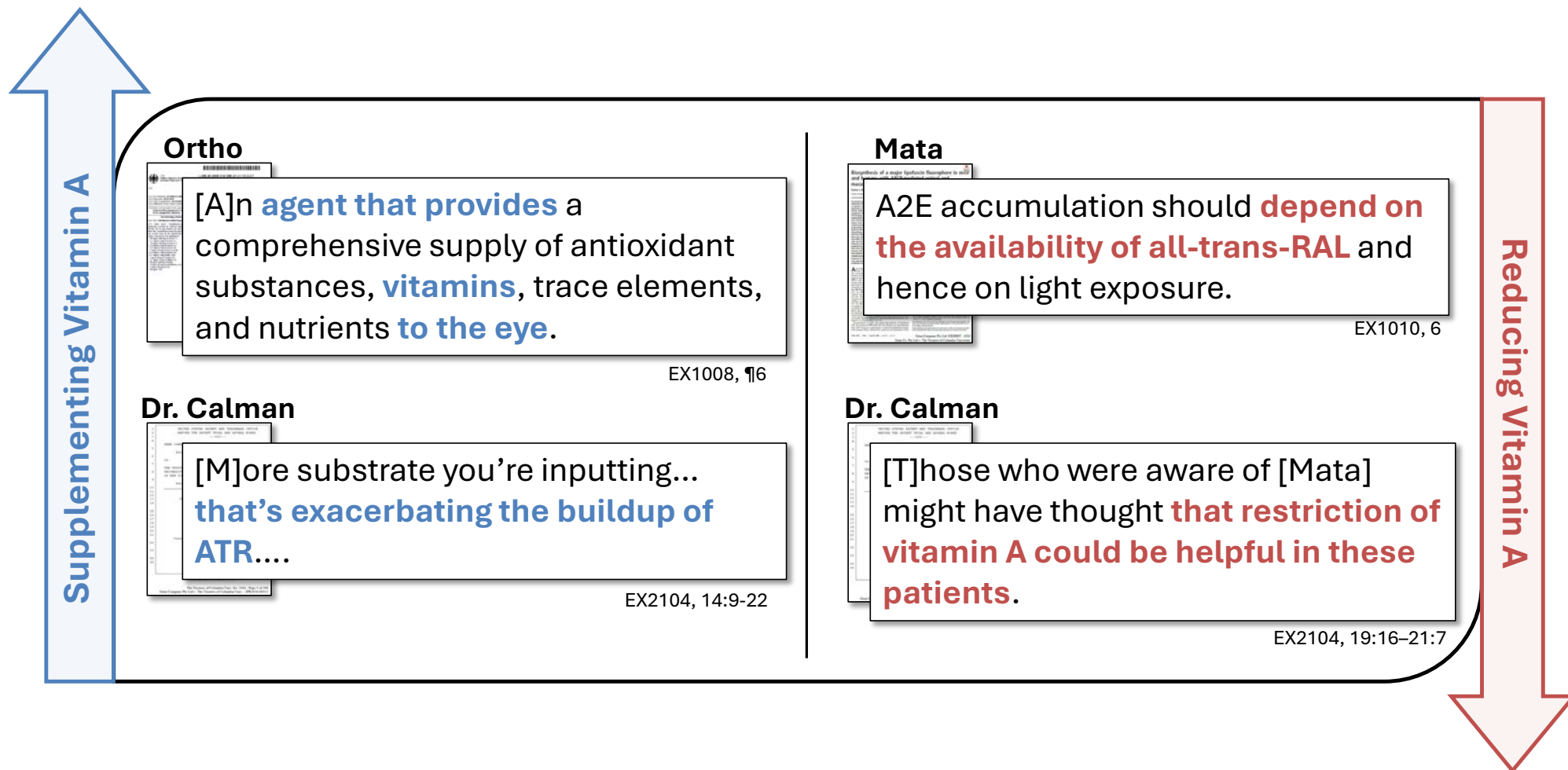
Additional Deficiencies of Ground 1 (Ortho and Olson 1988): Claims 1-9, 19-23, 25-26, 28-36, 46-50, and 52-53

Additional Deficiencies of Ground 2 (Ground 1 in Further View of Mata): Ground 1 + Claims 10-15, 18, 37-42, and 45

- No Motivation to Combine Ortho, Olson, and Mata with REOS:
- Dry (non-neovascular) AMD (claim 10, 37)
- Stargardt's Disease (claim 11-15, 38-42) and MD + ABCA4 Gene Mutation (claim 18, 45):
- Forms A2E in vitro About 7 Times Slower (claim 15, 42)

Additional Deficiencies of Ground 3 (Ground 1 and 2 in view of Widder): Claims 16-17, 24, 27, 43-44, 51, and 54

Ground 2 Fails: Ortho Irreconcilable with Mata



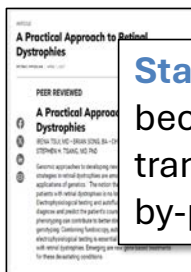
POR, 1-2, 16-22, 36-37, 45; Sur-Reply, 10-11;
EX2192, ¶¶180-183.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

100

Petitioner **does not** address evidence teaching away from vitamin A for Stargardt's Disease and *ABCA4*-Gene (Claims 11-15, 18, 38-42)

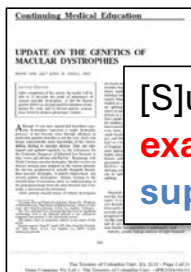
Tsui 2007



Stargardt patients should **avoid** a diet high in vitamin A because the defective gene (*ABCA4*) encodes for a transmembrane transporter of A2E intermediates, a toxic by-product of vitamin A.

EX2164, 12

Voo 2004



[S]uggested that **vitamin A supplements may actually exacerbate Stargardt disease**. Therefore, such vitamin supplements are not recommended.

EX2133, 2

Dr. Calman



I **recommend** that [Stargardt's patients] **not consume excessive vitamin A**.

[M]ost clinicians, as far as I know today, do **not recommend vitamin A** supplementation for Stargardt's

EX2104, 13:3-11, 15:8-18:15



"[A] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant"

Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1360-63 (Fed. Cir. 2017)

Ground and Claim- Specific Deficiencies

Additional Deficiencies of Ground 1 (Ortho and Olson 1988): Claims 1-9, 19-23, 25-26, 28-36, 46-50, and 52-53

Additional Deficiencies of Ground 2 (Ground 1 in Further View of Mata): Ground 1 + Claims 10-15, 18, 37-42, and 45

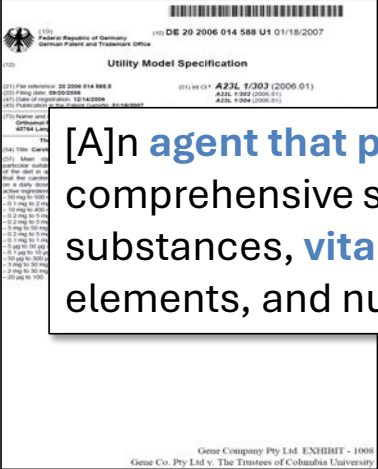
Additional Deficiencies of Ground 3 (Ground 1 and 2 in view of Widder): Claims 16-17, 24, 27, 43-44, 51, and 54

- No Motivation to Combine Ortho, Olson, Mata, and Widder with REOS
- Vitelliform or Best Disease, Sorsby's Fundus Dystrophy, Retinitis Pigmentosa, and Malattia Leventinese (claim 16 (+17), 43 (+44))
- Phosphatidylglycerol (Claims 24, 51)
- Directly to the Eye (Claims 27, 54)

Ground 3 Fails: Ortho Incompatible with Widder

Supplementing Vitamin A

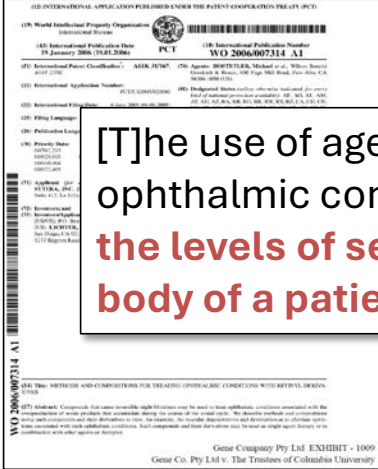
Ortho (EX1008)



[A]n agent that provides a comprehensive supply of antioxidant substances, **vitamins**, trace elements, and nutrients **to the eye**.

EX1008, ¶13

Widder (EX1009)



[T]he use of agents to treat ophthalmic conditions by... **lowering the levels of serum retinol in the body of a patient....**

EX1009, 3

Reducing Vitamin A



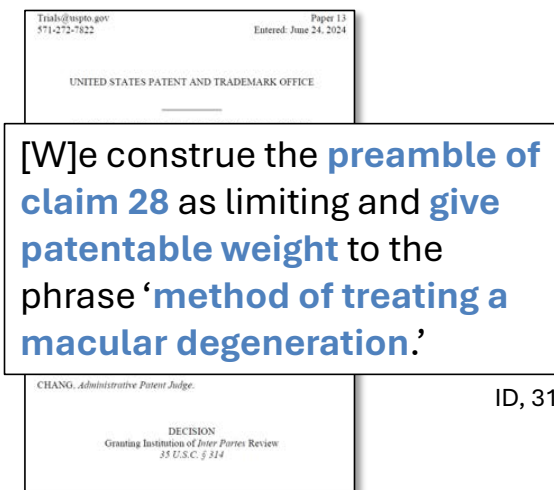
“[A] reference will teach away if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant”

Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1360-63 (Fed. Cir. 2017)
(quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994))

Claim Construction

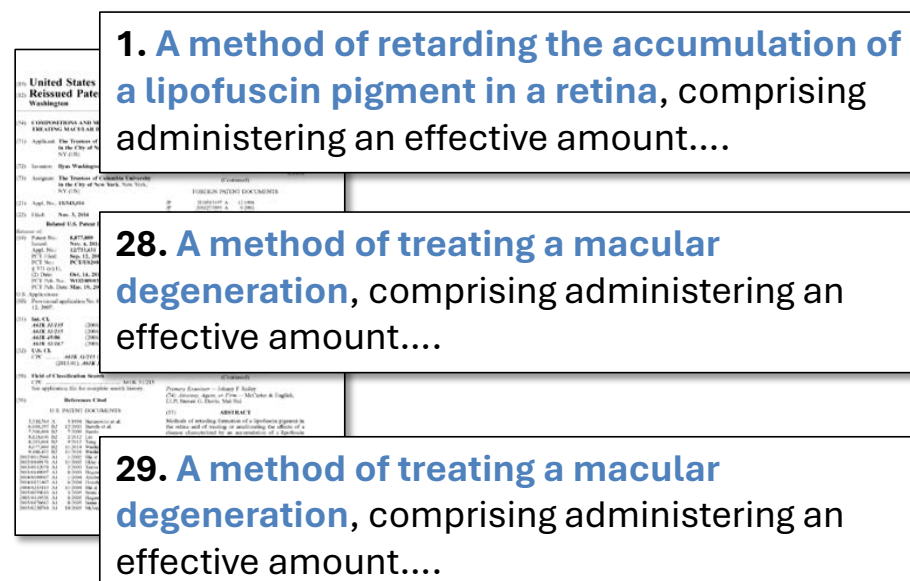
Petitioner Does Not Challenge ID Finding

Institution Decision

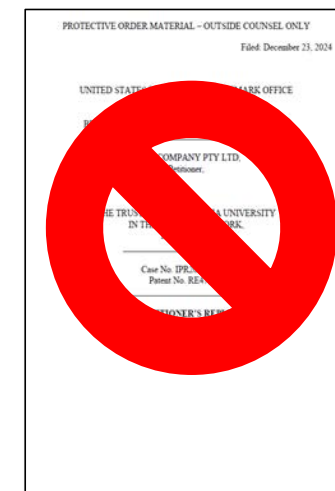


ID, 31

'045 Patent (EX1001)



Petitioner Reply



Dr. Guengerich Lacks Lipofuscin and Ophthalmology Experience



“A scientist... is not permitted to be the mouthpiece of a scientist in a different specialty”

Dura Auto. Sys. of Indiana, Inc. v. CTS Corp., 285 F.3d 609, 614 (7th Cir. 2002)

Dr. Guengerich (EX2103)



Q. You **don’t** have an **opinion** specific to the treatment of **Stargardt’s disease** different from the treatment of age-related **macular degeneration**, correct?

A. I **do not**. There’s another expert that’s filed a report in this case. I believe Dr. Calman, and he’s actually practicing – practicing clinician, and **he’s the expert and I’m not on that**.

EX2103, 36:12-37:7

Dr. Guengerich (EX2209)



Q. Did you **review Exhibit 2154**?
A. If I did, it’s not in my exhibit binders. I don’t know the name either.

Q. So that quote is **Mr. Mills** reading **Exhibit 2154**?

A. **That seems to be the case, yes.**

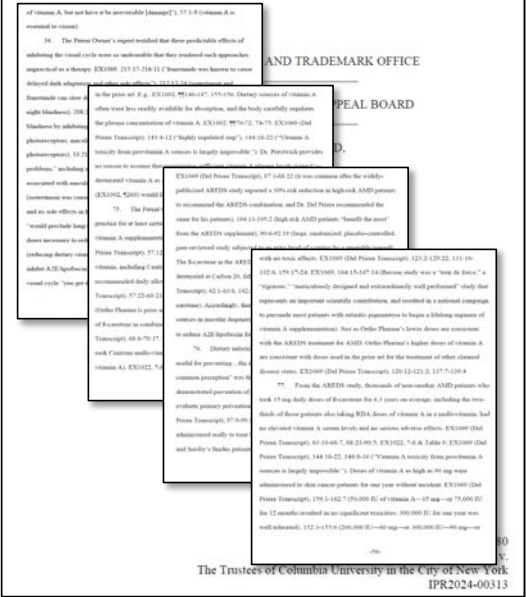
Q. So what you’re quoting in paragraph 76 is **Mr. Mills** reading **Exhibit 2153**; is that right?

A. **Yes, that’s my understanding of the discourse here.**

EX2209, 77:9-11, 78:15-17, 80:18-22

Dr. Guengerich (EX1080)

Citing pages of Dr. Del Priore
Dep. Tr. on ophthalmology



EX1080 pgs. 20, 48-51

Dr. Calman Is An Unqualified Generalist And Professional Witness

- Lacks experience concerning methods to slow lipofuscin formation or accumulation to treat an ophthalmologic disorder.

EX2104, 10:20-11:13

- Does not treat Stardgart's patients.

EX2104, 11:15-13:14, 21:8-21, 48:24-50:25

- Clinical research experience limited to diabetes, glaucoma, and monitoring ocular side effects.

EX2104, 146:6-25; EX1005, 11-12

- Professional Witness

- **79 depositions** vs. 21 publications

EX2104, 144:15-146:5, 152:25-153:14

Andrew F. Calman, MD, PhD
San Francisco, California



Specialties & Experience of this Expert Witness

General Specialties: Ophthalmology and Optometry

Keywords/Search Terms: Cataract, Glaucoma, Diabetic Retinopathy, eye, vision, eye injury, eye injuries, retina, macula, eye surgery, vision loss, patent, antitrust, eyedrops, pharmaceuticals, coding, reimbursement

Has 11 depositions to the California Judicial Branch, 10 depositions to the Federal Judicial Branch, and 10 depositions to the California Judicial Branch. Dr. Calman brings comprehensive expertise in eye diseases, injuries and surgery, as well as outstanding availability and responsiveness. Attorneys have repeatedly praised Dr. Calman's deposition and courtroom skills. Most cases have settled favorably after his expert report or deposition. Dr. Calman is also knowledgeable about pharmacological patent and antitrust issues including Hatch-Waxman.

Paragraph IV

Dr. Calman has served as an Ophthalmology Expert for the Medical Board of California, Associate Examiner for the American Board of Ophthalmology, and has developed national eye care policy with the Medicare Carrier Advisory Committee and the American Academy of Ophthalmology. He has an active private practice.

<https://www.seekexpert.com/members/3430-andrew-f-calman>

The Trustees of Columbia Univ. Ex. 2071 - Page 1 of 2
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

EX2071, 1

Petition Failed to Identify Real Parties In Interest

The Petition concealed related and commonly represented Lin BioScience and Belite Bio.

➤ Statutory Requirement: “[T]he petition identifies all real parties in interest.” 35 U.S.C. §312(a)(2).

RPIs Lin BioSciences and Belite Bio

Undisputed evidence of overlapping management & control, vested interests, and common representation

- EX2027, 4;
- EX2028, 2-3;
- EX2029, 4;
- EX2030, 9;
- EX2031, 2, 19;
- EX2032, 6;
- EX2034, 1;
- EX2035, 1;
- EX2039, 1;
- EX2190.

POR, 63-64.

Petitioner Concedes “Potential” RPIs Not identified in Petition

Petitioner Pre-Institution Reply

Paper No. _____
Filed: April 19, 2024

Petitioner requests Board authorization to identify Belite Bio and Lin Biosciences as potential real parties-in-interest to eliminate an unnecessary controversy. IPR2020-00734, Paper 11 (Oct. 6, 2020) (precedential). While PO did not raise its RPI allegation in IPR2025-00312, **Petitioner will update both cases for consistency.**

Paper 11, 5

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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