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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/510,975	11/08/2016	9486432	126277-00103	6583

86738 7590 10/19/2016
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Ilyas Washington, New York, NY;
The Trustees of Columbia University in the City of New York, New York, NY;

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/510,975	10/09/2014	Ilyas Washington	126277-00103	6583

86738 7590 10/13/2016
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER
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1621

NOTIFICATION DATE	DELIVERY MODE
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10/13/2016

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@mccarter.com

Response to Rule 312 Communication	Application No. 14/510,975	Applicant(s) WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621
-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address -- 1. ☒ The amendment filed on <u>13 September 2016</u> under 37 CFR 1.312 has been considered, and has been: a) ☒ entered. b) ☐ entered as directed to matters of form not affecting the scope of the invention. c) ☐ disapproved because the amendment was filed after the payment of the issue fee. Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue. d) ☐ disapproved. See explanation below. e) ☐ entered in part. See explanation below.		
		/ZOHREH FAY/ Primary Examiner, Art Unit 1621

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/510,975	10/09/2014	Ilyas Washington	126277-00103	6583

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480.00			\$480.00	09/15/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
Z. A. Fay	1621	

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached. ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.	2. For printing on the patent front page, list (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.	1 <u>McCarter & English, LLP</u> 2 <u>Steven G. Davis, Ph.D.</u> 3 <u>Mei Bai, Ph.D.</u>
--	---	--

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

The Trustees of Columbia University in the City of New York

New York, New York

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
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4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

☐ A check is enclosed.
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☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 50-4876 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Mei Bai/

Date September 13, 2016

Typed or printed name Mei Bai, Ph.D.

Registration No. 64,507

Certificate of Electronic Filing Under 37 C.F.R. § 1.8

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4):

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on September 13, 2016
Date

/Mei Bai/

Signature

Mei Bai, Ph.D.

Typed or printed name of person signing Certificate

64,507

Registration Number, if applicable

(617) 449-6590

Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Issue Fee Transmittal (1 page)
Charge \$480.00 to deposit account 50-4876

Electronic Patent Application Fee Transmittal				
Application Number:		14510975		
Filing Date:		09-Oct-2014		
Title of Invention:		Compositions and Methods for Treating Macular Degeneration		
First Named Inventor/Applicant Name:		Ilyas Washington		
Filer:		Mei Bai		
Attorney Docket Number:		126277-00103		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				480

Electronic Acknowledgement Receipt

EFS ID:	26909410
Application Number:	14510975
International Application Number:	
Confirmation Number:	6583
Title of Invention:	Compositions and Methods for Treating Macular Degeneration
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	86738
Filer:	Mei Bai
Filer Authorized By:	
Attorney Docket Number:	126277-00103
Receipt Date:	13-SEP-2016
Filing Date:	09-OCT-2014
Time Stamp:	15:14:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 480
RAM confirmation Number	1854
Deposit Account	504876
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment after Notice of Allowance (Rule 312)	Amendment_After_Allowance_Under_37_CFR__1.pdf	36116	no	7
			e5722c6448594f8e2a6197b2b188641c8f68410e		
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	Issue_Fee_Transmittal.pdf	42483	no	2
			96c2bd2b198b72d899a5810d83f5514f775396c3		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30307	no	2
			0efdb7cdeca44c29e542bb7a0981948c279f2b8f		
Warnings:					
Information:					
Total Files Size (in bytes):			108906		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 13, 2016 Signature: /Mei Bai/
(Mei Bai, Ph.D.)

Docket No.: 126277-00103
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Ilyas Washington

Application No.: 14/510,975

Confirmation No.: 6583

Filed: October 9, 2014

Art Unit: 1621

For: COMPOSITIONS AND METHODS FOR
TREATING MACULAR DEGENERATION

Examiner: Z. A. Fay

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312

MS Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to issuance of the patent, applicant respectfully requests entry of this amendment under 37 C.F.R. 1.312 for the above-captioned patent application.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please delete paragraph [0001] on page 1 of the specification as follows:

~~GOVERNMENT SUPPORT~~

~~This invention was made with government support under Grant EY T32 013933 awarded by the National Eye Institute of the National Institutes of Health. The government has certain rights in the invention.~~

AMENDMENTS TO THE CLAIMS

1-49. (Cancelled)

50. (Previously presented) A pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid and a pharmaceutically acceptable carrier, wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

51. (Currently Amended) The pharmaceutical composition according to Claim 50, wherein the substituted C₂₀-D₁₋₃-retinoid is ~~C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid~~ selected from the group consisting of C₂₀-D₃-retinol, C₂₀-D₃-retinol ester, C₂₀-D₃-retinal and a C₂₀-D₃-pro-vitamin A carotenoid.

52. (Currently Amended) The pharmaceutical composition according to Claim 51, wherein the C₂₀-D₁₋₃-retinoid is ~~C₂₀-D₁₋₃-retinol~~ C₂₀-D₃-retinol acetate.

53. (Previously presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is in unit dosage form.

54. (Original) The pharmaceutical composition according to Claim 50, wherein the C₂₀-D₁₋₃-retinoid, corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

55. (Previously presented) The pharmaceutical composition according to Claim 50, wherein the C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

56. (Previously presented) The pharmaceutical composition according to Claim 50, further comprising an effective amount of a supplement selected from the group consisting of (2E,6E)-N-

hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine, (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one, 13-cis-retinoic acid, all-trans-retinylamine, and fenretinide, and combinations thereof.

57-58. (Cancelled)

59. (Previously presented) The pharmaceutical composition according to Claim 50, further comprising one or more additives.

60. (Previously presented) The pharmaceutical composition according to Claim 59, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.

61. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 80 mg.

62. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 10 mg.

63. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 10 to about 80 mg.

64. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 3,000 mg.

65. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 15 mg.

66. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the

vitamin E is present in the pharmaceutical composition at between about 15 to about 3,000 mg.

67. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.1 mg.

68. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.015 mg.

69. (Previously presented) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.015 to about 0.1 mg.

70. (Previously presented) The pharmaceutical composition according to Claim 50, wherein the substituted C₂₀-D₁₋₃-retinoid is present in the pharmaceutical composition at a level sufficient to deliver on average about 0.1 to about 90 mg/day to a patient.

71. (Previously presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition comprises an additional active.

72. (Previously presented) The pharmaceutical composition according to Claim 71, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

73. (Previously presented) The pharmaceutical composition according to Claim 72, wherein the eye antioxidant is selected from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a trolox analog (PNU-83836-E), bilberry extract, and combinations thereof.

74. (Previously presented) The pharmaceutical composition according to Claim 72, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing

compounds, and combinations thereof.

75. (Previously presented) The pharmaceutical composition according to Claim 72, wherein the negatively-charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

76. (Previously presented) The pharmaceutical composition according to Claim 50, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

77. (Previously presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is suitable for administration directly to the eye.

78. (Previously presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is suitable for use as nutraceutical composition.

79. (New) The pharmaceutical composition according to Claim 52, wherein the C₂₀-D₁₋₃-retinoid, corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

REMARKS

Applicant has amended the Specification to delete the Government Support Statement, which is erroneously included.

Claims 51 and 52 have been amended to replace “C₂₀-D₁₋₃” with “C₂₀-D₃”. Support for this amendment is found in original Claims 51 and 52 as filed. This amendment corrects an obvious error.

New Claim 79 has been added, which is identical to current Claim 54 except that new Claim 79 depends on Claim 52. It is submitted that no new examination is required by this amendment.

If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 50-4876, under Order No. 126277-00103 from which the undersigned is authorized to draw.

Dated: September 13, 2016

Respectfully submitted,

By: /Mei Bai/
Mei Bai, Ph.D.
Registration No.: 64,507
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500
(617) 607-9200 (Fax)
Attorney/Agent For Applicant

Issue Classification 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

CPC					
Symbol				Type	Version
A61K	31	215		F	2013-01-01
A61K	31	135		I	2013-01-01
A61K	31	167		I	2013-01-01
A61K	45	06		I	2013-01-01

CPC Combination Sets				
Symbol	Type	Set	Ranking	Version

NONE		Total Claims Allowed:	
(Assistant Examiner)		27	
(Date)			
/ZOHREH FAY/		O.G. Print Claim(s)	O.G. Print Figure
Primary Examiner.Art Unit 1621		1	none
7/12/2016			
(Primary Examiner)			
(Date)			

Issue Classification 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION													
CLASS		SUBCLASS				CLAIMED					NON-CLAIMED								
514		546				A	6	1	K	31 / 135 (2006.01.01)									
CROSS REFERENCE(S)																			
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)																		
514	613																		
514	671																		
514	703																		

NONE		Total Claims Allowed:	
		27	
(Assistant Examiner)	(Date)		
/ZOHREH FAY/ Primary Examiner.Art Unit 1621	7/12/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	50	17	68												
2	51	18	69												
3	52	19	70												
4	53	20	71												
5	54	21	72												
6	55	22	73												
7	56	23	74												
8	59	24	75												
9	60	25	76												
10	61	26	77												
11	62	27	78												
12	63														
13	64														
14	65														
15	66														
16	67														

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 27	
/ZOHREH FAY/ Primary Examiner.Art Unit 1621 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1	O.G. Print Figure none

Search Notes 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/135	5/25/2016	ZF
A61K 31/215	5/25/2016	ZF
A61K31/167	5/25/2016	ZF

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	10/28/2015	ZF
Inventor search	10/28/2015	ZF
updated	5/25/2016	ZF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/135	5/25/2016	ZF
A61K	31/215	5/25/2016	ZF
A61K	31/167	5/25/2016	ZF

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/510,975	10/09/2014	Ilyas Washington	126277-00103	6583

86738 7590 08/03/2016
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER
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1621

NOTIFICATION DATE	DELIVERY MODE
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08/03/2016

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@mccarter.com

Notice of Allowability	Application No. 14/510,975	Applicant(s) WASHINGTON, ILYAS	
	Examiner ZOHREH FAY	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the amendments and remarks filed on 2/4/2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 50-56 and 59-78. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|---|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☐ Examiner's Amendment/Comment |
| 2. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 6. ☐ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other _____. |
| 4. ☐ Interview Summary (PTO-413),
Paper No./Mail Date _____. | |

/ZOHREH FAY/
Primary Examiner, Art Unit 1621



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

86738 7590 06/15/2016
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER

FAY, ZOHREH A

ART UNIT

PAPER NUMBER

1621

DATE MAILED: 06/15/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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14/510,975

10/09/2014

Ilyas Washington

126277-00103

6583

TITLE OF INVENTION: Compositions and Methods for Treating Macular Degeneration

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	09/15/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

86738 7590 06/15/2016
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/510,975	10/09/2014	Ilyas Washington	126277-00103	6583

TITLE OF INVENTION: Compositions and Methods for Treating Macular Degeneration

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	09/15/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
FAY, ZOHREH A	1621	514-546000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached. ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.	2. For printing on the patent front page, list (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____ (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____ 3 _____
---	---

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____
 Typed or printed name _____ Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/510,975	10/09/2014	Ilyas Washington	126277-00103	6583

86738 7590 06/15/2016
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER
----------	--------------

1621

DATE MAILED: 06/15/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/510,975	Applicant(s) WASHINGTON, ILYAS	
	Examiner ZOHREH FAY	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the amendments and remarks filed on 2/4/2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 50-57 and 59-78. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☐ Examiner's Amendment/Comment |
| 2. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other _____. |
| 4. ☐ Interview Summary (PTO-413),
Paper No./Mail Date _____. | |

/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Art Unit: 1621

Reasons for Allowance:

Applicant by amending claim 56 and cancelling claim 57 has overcome the 112 (a) and 112 (b) rejection. Applicant by filing a terminal Disclaimer has overcome the double patenting rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie McCormick can be reached on (571) 272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF

Application/Control Number: 14/510,975

Page 3

Art Unit: 1621

/ZOHREH FAY/

Primary Examiner, Art Unit 1621



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
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BIB DATA SHEET

CONFIRMATION NO. 6583

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
14/510,975	10/09/2014	514	1621	126277-00103		
RULE						
APPLICANTS The Trustees of Columbia University in the City of New York, New York, NY; INVENTORS Ilyas Washington, New York, NY; ** CONTINUING DATA ***** This application is a DIV of 12/733,631 10/14/2010 PAT 8877809 which is a 371 of PCT/US08/10676 09/12/2008 which claims benefit of 60/993,379 09/12/2007 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 10/16/2014						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged <u>/ZOHREH A FAY/</u> Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY NY	SHEETS DRAWINGS 15	TOTAL CLAIMS 29	INDEPENDENT CLAIMS 1
ADDRESS MCCARTER & ENGLISH, LLP BOSTON 265 Franklin Street Boston, MA 02110 UNITED STATES						
TITLE Compositions and Methods for Treating Macular Degeneration						
FILING FEE RECEIVED 1160	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		

Issue Classification 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

CPC						
Symbol					Type	Version
A61K		31	/	215	F	2013-01-01
A61K		31	/	135	I	2013-01-01
A61K		31	/	167	I	2013-01-01
A61K		45	/	06	I	2013-01-01
			/			
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CPC Combination Sets				
Symbol	Type	Set	Ranking	Version

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 26	
/ZOHREH FAY/ Primary Examiner.Art Unit 1621 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

☐ Claims renumbered in the same order as presented by applicant															
☐ CPA															
☒ T.D.															
☐ R.1.47															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	50	17	69												
2	51	18	70												
3	53	19	71												
4	55	20	72												
5	56	21	73												
6	57	22	74												
7	59	23	75												
8	60	24	76												
9	61	25	77												
10	62	26	78												
11	63														
12	64														
13	65														
14	66														
15	67														
16	68														

NONE	Total Claims Allowed: 26	
(Assistant Examiner)	(Date)	
/ZOHREH FAY/ Primary Examiner.Art Unit 1621	O.G. Print Claim(s) 1	O.G. Print Figure none
(Primary Examiner)	(Date)	

Search Notes 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/135	5/25/2016	ZF
A61K 31/215	5/25/2016	ZF
A61K31/167	5/25/2016	ZF

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	10/28/2015	ZF
Inventor search	10/28/2015	ZF
updated	5/25/2016	ZF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/135	5/25/2016	ZF
A61K	31/215	5/25/2016	ZF
A61K	31/167	5/25/2016	ZF

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:

Application No.: 14/510,975

Confirmation No.: 6583

Filed: October 9, 2014

Art Unit: 1621

For: COMPOSITIONS AND METHODS FOR
TREATING MACULAR DEGENERATION

Examiner: Zohreh A. FAY

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Dear Sir:

INTRODUCTORY COMMENTS

This paper is responsive to the non-final Office Action dated November 5, 2015. Please amend the above-identified application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims

The following **Listing of Claims** will replace all prior versions, and listings, of claims in the application.

Listings of claims

1-49. (Canceled)

50. (Previously Presented) A pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid and a pharmaceutically acceptable carrier, wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

51. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the substituted C₂₀-D₁₋₃-retinoid is C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

52. (Previously Presented) The pharmaceutical composition according to Claim 51, wherein the C₂₀-D₁₋₃-retinoid is C₂₀-D₁₋₃-retinol acetate.

53. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is in unit dosage form.

54. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the C₂₀-D₁₋₃-retinoid, corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

55. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

56. (Currently Amended) The pharmaceutical composition according to Claim 50, further

comprising an effective amount of a supplement selected from the group consisting of (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine, (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one, 13-cis-retinoic acid, all-trans-retinylamine, and fenretinide, a visual cycle antagonist, a molecule that inhibits influx of a retinoid into an eye, and combinations thereof.

57. (Canceled)

58. (Canceled)

59. (Previously Presented) The pharmaceutical composition according to Claim 50, further comprising one or more additives.

60. (Previously Presented) The pharmaceutical composition according to Claim 59, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.

61. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 80 mg.

62. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 10 mg.

63. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 10 to about 80 mg.

64. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 3,000 mg.

65. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 15 mg.

66. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein

the vitamin E is present in the pharmaceutical composition at between about 15 to about 3,000 mg.

67. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.1 mg.

68. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.015 mg.

69. (Previously Presented) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.015 to about 0.1 mg.

70. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the substituted C₂₀-D₁₋₃-retinoid is present in the pharmaceutical composition at a level sufficient to deliver on average about 0.1 to about 90 mg/day to a patient.

71. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition comprises an additional active.

72. (Previously Presented) The pharmaceutical composition according to Claim 71, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

73. (Previously Presented) The pharmaceutical composition according to Claim 72, wherein the eye antioxidant is selected from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a trolox analog (PNU-83836-E), bilberry extract, and combinations thereof.

74. (Previously Presented) The pharmaceutical composition according to Claim 72, wherein

the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

75. (Previously Presented) The pharmaceutical composition according to Claim 72, wherein the negatively-charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

76. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

77. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is suitable for administration directly to the eye.

78. (Previously Presented) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is suitable for use as nutraceutical composition.

REMARKS**Support for Claim Amendments**

Applicant respectfully requests entrance of the present Amendment, as described in further detail below. Applicant submits that after entrance of the current amendment, claims 50-56 and 59-78 are pending and under consideration. Claims 57 and 58 have been cancelled without prejudice. Claim 56 was amended to add in the limitations of claims 57 and 58. Applicant submits that no new matter has been added by this Amendment.

Response to Rejections**35 USC § 112 – 2nd Paragraph**

The examiner rejected claim 57 as indefinite under 35 USC 112 second paragraph for containing the abbreviations “TDH”, “TDT”, and “ret-NH2”. Claim 57 has been canceled, thus making the rejection moot. Withdrawal is respectfully requested.

35 USC § 112 – 1st Paragraph

Claim 56 was rejected as lacking written description under 35 USC 112 first paragraph for containing the terms “visual cycle antagonist” and “a molecule that inhibits the influx of retinoid into the eye”.

Without agreeing to the merit of the rejection, and solely to advance prosecution of the present application, Applicants have amended claim 56 to incorporate the specific “visual cycle antagonist” and “a molecule that inhibits the influx of retinoid into the eye” compounds which were contained in claims 57 and 58, neither of which were rejected under this basis, and both of which therefore have proper written description support. Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting

The presently pending claims have been rejected based on the nonstatutory double patenting grounds in view of US Patent 8,877,809. Without agreeing to the merit of the rejection, and solely to advance prosecution of the present application, Applicants are filing

herewith a Terminal Disclaimer over the cited patent. Reconsideration and withdrawal of the rejection is respectfully requested.

Applicants believe after entry of the present amendments that the application is in condition for allowance, which action is respectfully requested.

SUMMARY

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 50-4876, under Order No. 126277-00103, from which the undersigned is authorized to draw.

Dated: February 4, 2015

Respectfully submitted,

Electronic signature: /Kathryn M. Kizer/
Kathryn M. Kizer, Esq.

Registration No.: 51,628
McCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500
(617) 607-9200 (Fax)
Attorney/Agent For Applicants

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 126277-00103
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In re Application of: Ilyas Washington

Application No.: 14/510,975

Filed: October 9, 2014

For: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

The applicant, The Trustees of Columbia University in the City of New York, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8,877,809 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 51,628

<u>/Kathryn M. Kizer/</u> Signature	<u>February 4, 2016</u> Date
<u>Kathryn M. Kizer</u> Typed or printed name	
<u>Attorney for Applicant(s)</u> Title	<u>(617) 449-6500</u> Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

AMENDMENT TRANSMITTAL LETTER			Docket No. 126277-00103	
Application No. 14/510,975	Filing Date October 9, 2014	Examiner Z. A. Fay	Art Unit 1621	

Applicant(s): Ilyas Washington

Invention: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.
The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED					
	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims	27	- 29 =	0	x	
Independent Claims	1	- 3 =	0	x	
Multiple Dependent Claims (check if applicable) ☐					
Other fee (please specify): Statutory Disclaimer					160.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					160.00

☐ Large Entity
 ☒ Small Entity

☒ No additional fee is required for this amendment.

☐ Please charge Deposit Account No. _____ in the amount of \$ _____.

☐ A check in the amount of \$ _____ to cover the filing fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge and credit Deposit Account No. 50-4876 as described below. A duplicate copy of this sheet is enclosed.

☒ Credit any overpayment.

☒ Charge any additional filing or application processing fees required under 37 C.F.R. § 1.16 and 1.17.

/Kathryn M. Kizer/
Kathryn M. Kizer
Attorney/Agent Reg. No.: 51,628
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500

Dated: February 4, 2016

Electronic Patent Application Fee Transmittal				
Application Number:		14510975		
Filing Date:		09-Oct-2014		
Title of Invention:		Compositions and Methods for Treating Macular Degeneration		
First Named Inventor/Applicant Name:		Ilyas Washington		
Filer:		Kathryn Mary Kizer/Barbara Johnston		
Attorney Docket Number:		13533/541US2		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Statutory or Terminal Disclaimer	2814	1	160	160
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	24821139
Application Number:	14510975
International Application Number:	
Confirmation Number:	6583
Title of Invention:	Compositions and Methods for Treating Macular Degeneration
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	86738
Filer:	Kathryn Mary Kizer
Filer Authorized By:	
Attorney Docket Number:	13533/541US2
Receipt Date:	04-FEB-2016
Filing Date:	09-OCT-2014
Time Stamp:	14:04:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	312
Deposit Account	504876
Authorized User	DAVIS, STEVEN G.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	0202.pdf	37777	no	7
			420c90e75820c84c9fb50a68f653aca61d4c743b		

Warnings:

Information:

2	Terminal Disclaimer Filed	Terminal_Disclaimer.pdf	20103	no	1
			7b2c3b3ad9855c51ac370dfe6e5f44e069ce2fa3		

Warnings:

Information:

3	Miscellaneous Incoming Letter	Amendment_Transmittal.pdf	21746	no	1
			aed30e3e7b96acae6924b93ae1ef54dbd5c70ae8		

Warnings:

Information:

4	Fee Worksheet (SB06)	fee-info.pdf	30456	no	2
			9e383357a20c90ab528f3546e14d02ded8082c3b		

Warnings:

Information:

Total Files Size (in bytes):	110082
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/510,975	Filing Date 10/09/2014	☐ To be Mailed
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ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO**APPLICATION AS FILED – PART I**

(Column 1)

(Column 2)

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

(Column 1)

(Column 2)

(Column 3)

	02/04/2016	CLAIMS REMAINING AFTER AMENDMENT	Minus	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT	Total (37 CFR 1.16(i))	* 27	Minus	** 29	= 0	X \$40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X \$210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
TOTAL ADD'L FEE							0

(Column 1)

(Column 2)

(Column 3)

		CLAIMS REMAINING AFTER AMENDMENT	Minus	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
TOTAL ADD'L FEE							

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/VERONICA DAY EVERETT/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Application Number 	Application/Control No. 14/510,975	Applicant(s)/Patent under Reexamination WASHINGTON, ILYAS	
Document Code - DISQ		Internal Document – DO NOT MAIL	

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 04 February, 2016	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
<u>/PAMELA YOUNG/</u> Technology Center: <u>PLRC</u> Telephone: _____



UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/510,975	10/09/2014	Ilyas Washington	13533/541US2

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

CONFIRMATION NO. 6583
POA ACCEPTANCE LETTER



Date Mailed: 12/08/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/01/2015.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/yfeferra/

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
14/510,975	October 9, 2014

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 86738

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name			
Address			
City	State	Zip	
Country			
Telephone	Email		

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

The Trustees of Columbia University in the City of New York

☐ Inventor or Joint Inventor (title not required below)

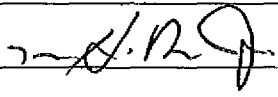
☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	11/24/2015
Name			
Title			

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of 1 forms are submitted.

Thomas H. Burrows Jr., J.D.
Associate General Counsel
Columbia University
New York, N.Y. U.S.A.
(212) 654-0681

Electronic Acknowledgement Receipt

EFS ID:	24213383
Application Number:	14510975
International Application Number:	
Confirmation Number:	6583
Title of Invention:	Compositions and Methods for Treating Macular Degeneration
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	26646
Filer:	Kathryn Mary Kizer
Filer Authorized By:	
Attorney Docket Number:	13533/541US2
Receipt Date:	01-DEC-2015
Filing Date:	09-OCT-2014
Time Stamp:	09:19:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	TRANSMITTAL_OF_POA.pdf	16460 3b0d0a7e596ffe65d96af6cda487cf7d3a4b36db	no	1

Warnings:

Information:

2	Power of Attorney	POA_executed.PDF	80658	no	1
			776ead131addca5de9c5e63d9c0241aa9f1d330		
Warnings:					
Information:					
Total Files Size (in bytes):			97118		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA/82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/510,975		
Filing Date	October 9, 2014		
First Named Inventor	Ilyas Washington		
Title	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION		
Art Unit	1621		
Examiner Name	Z. A. Fay		
Attorney Docket Number	126277-00103		
SIGNATURE of Applicant or Patent Practitioner			
Signature	/Kathryn M. Kizer/	Date (Optional)	November 30, 2015
Name	Kathryn M. Kizer	Registration Number	51,628
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			
NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.			
☐	*Total of <u>1</u> forms are submitted.		



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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/510,975	10/09/2014	Ilyas Washington	13533/541US2	6583

26646 7590 11/05/2015
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER

FAY, ZOHREH A

ART UNIT	PAPER NUMBER
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1621

NOTIFICATION DATE	DELIVERY MODE
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11/05/2015

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@kenyon.com

Office Action Summary	Application No. 14/510,975	Applicant(s) WASHINGTON, ILYAS	
	Examiner ZOHREH FAY	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 50-78 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 50-78 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☐ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date <u>1/20/2015</u> | 4) ☐ Other: _____ |

DETAILED ACTION

Claims 50-78 are presented for examination.

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 57 is indefinite as to the terms “TDH”, “TDT” and “ret-NH2” rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 27 is indefinite in failing to set forth the components encompassed by the above terms.

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56 is rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is drawn to the phrases “a visual cycle antagonist” and “a molecule that inhibits the influx of retinoid into the eye”. The instant specification discloses a few compounds within the scope of what is claimed. However, there is no evidence that there is any per se structure/function relationship between the disclosed visual cycle antagonists and molecules that inhibit the influx of retinoid into an eye and any others that might be found using the claimed method. Structural identifying characteristics of group of visual cycle antagonists and the molecules that inhibit the influx of a retinoid into the eye are not disclosed. Therefore the claimed invention is not supported by an adequate written description. To provide adequate written description an evidence of possession of the claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, Functional characteristics, structure/function correlation, or any combination thereof.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double

Art Unit: 1621

patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all

Art Unit: 1621

requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to

<http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

Claims 50-78 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 8,877,809. Although the claims at issue are not identical, they are not patentably distinct from each other because they overlap. The claims of the instant application are drawn to a composition having the same components as the claims of the U.S. Patent 8,877,809. The composition of the instant application is within the scope of the claims of the U.S. Patent. It would have been obvious to a person skilled in the art to use the claimed composition for the treatment of disorders claimed by the U.S. Patent, considering that instant specification discloses the use of the composition for the treatment of the same disorders as the U.S. Patent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie McCormick can be reached on (571) 272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1621

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF
/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Search Notes 	Application/Control No. 14510975	Applicant(s)/Patent Under Reexamination WASHINGTON, ILYAS
	Examiner ZOHREH FAY	Art Unit 1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	10/28/2015	ZF
Inventor search	10/28/2015	ZF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14510975	
	Filing Date		2014-10-09	
	First Named Inventor	Ilyas Washington		
	Art Unit	TBA		
	Examiner Name	TBA		
	Attorney Docket Number	13533-541US2		

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**INFORMATION DISCLOSURE
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Application Number	14510975
Filing Date	2014-10-09
First Named Inventor	Ilyas Washington
Art Unit	TBA
Examiner Name	TBA
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1	SAKAI, et al. "Ocular Age Pigment 'A2-E': An Unprecedented Pyridinium Bisretinoid," J. Am. Chem. Soc. (1996), Vol. 118, pp.1559-1560.	☐
2	SCHUTT, et al. "Accumulation of A2-E in mitochondrial membranes of cultured RPE cells," Graefe's Arch. Clin. Exp. Ophthalmol. (2007), Vol. 245, pp. 391-398.	☐
3	SCHUTT, et al. "Photodamage to human RPE cells by A2-E, a retinoid component of lipofuscin," Invest. Ophthalmol. Vis. Sci. (2000), Vol. 41, pp. 2303-2308.	☐
4	SHABAN, et al., "A2E and blue light in the retina: the paradigm of age-related macular degeneration," Bioi. Chem. (2002), Vol. 383, pp. 537-545.	☐
5	SHABAN, et al., "Phosphatidylglycerol potently protects human retinal pigment epithelial cells against apoptosis induced by A2E, a compound suspected to cause age-related macula degeneration," Exp. Eye Res. (2002), Vol. 75, pp. 99-108.	☐
6	SMITH, "Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration," Invest Ophthalmol Vis Sci. (2006), Vol. 47, pp. 5495-5504.	☐
7	UM, et al. "Synthesis and Biological Activity of Novel Retinamide and Retinoate Derivatives," Chemical & Pharmaceutical Bulletin (2004), Vol. 52, pp. 501-506.	☐
8	SORIATANE, [online], [retrieved July 05, 2012] Retrieved from RXList: The Internet Drug Index using Internet <URL: http://www.rxlist.com/cgi/generic/acitretin.htm >.	☐
9	SPARROW, et al. "A2E, a Lipofuscin Fluorophore, in Human Retinal Pigmented Epithelial Cells in Culture, Invest. Ophthalmol Vis Sci (1999), Vol. 40, pp. 2988-2995.	☐
10	SPARROW, et al. "The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells," Invest. Ophthalmol. Vis. Sci. (2000), Vol. 41, pp. 1981-1989.	☐
11	SPARROW, et al., "A2E-epoxides damage DNA in retinal pigment epithelial cells. Vitamin E and other antioxidants inhibit A2E-epoxide formation," J. Bioi. Chem. (2003), Vol. 278, pp. 18207-18213.	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Z.F./

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12	SREEKUMAR et al. "Protection from oxidative stress by methionine sulfoxide reductases in RPE cells," Biochem Biophys Res Commun (2005), Vol. 334:1, pp. 245-253.	☐
13	SUTER, et al. "Age-related Macular Degeneration: The lipofuscin component n-retinyl-n-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells," J. Bio. Chem. (2000), Vol. 275, pp. 39625-39630.	☐
14	TARGRETIN, [online], [retrieved July 05, 2012] Retrieved from RXlist: The Internet Drug Index using Internet <URL: http://www.rxlist.com/cgi/generic/bexarotene.htm >.	☐
15	TOTH, "Functional changes of the aging rat retina in relation to the modifications of the ERG components," Aktuelle Gerontol (1976), Vol. 6, pp. 79-86.	☐
16	TRAVIS, G. H. et al., Diseases caused by defects in the visual cycle: retinoids as potential therapeutic agents," Annual Review of Pharmacology and Toxicology, Annual Review Inc., Palo Alto, CA (2007), Vol. 47, pp. 469-512 (NIH Public Access Author manuscript, pages 1-38).	☐
17	VILLABLANCA, et al. "Phase I trial of 13-cis-retinoic acid in children with neuroblastoma following bone marrow transplantation," J Clin Oncol. (1995), Vol. 13, pp. 894-901.	☐
18	WASELL, et al. "A role for vitamin A in the formation of ocular lipofuscin," Br J Ophthalmol (1997), Vol. 81, pp. 911-918.	☐
19	WATSON, et al. "Comparison of low-vision reading with spectacle-mounted magnifiers," J. Rehabil Res Dev. (2005), Vol. 42:4, pp. 459-470.	☐
20	WENG, et al. "Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in abcr knockout mice," Cell (1999), Vol. 98, pp. 13-23.	☐
21	WRIGHT, et al. "Hybrid eye tracking for computer-aided retinal surgery," Biomed Sci Instrum (1996), Vol. 32, pp. 225-235.	☐
22	WALKER, "New/Old Findings on Unique Vitamin E," [online], [retrieved on Sep 5 2012] retrieved from the Internet: < http://www.enerex.ca/en/articles/new-old-findings-on-unique-vitamin-e.htm >.	☐

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23	Japanese Office Action with English translation from counterpart Japanese Application No.: 2012-260971 dated February 7, 2014.	☐
24	"What is Deuterium?" [retrieved on 2/11/2013], <URL: http://www.innovateus.net/printscience/what-deuterium >. 4 pages.	☐
25	FOSTER, Allan, "Deuterium Isotope Effects in Studies of Drug Metabolism," TIPS-- December 1984.	☐
26	HANDELMAN et al., "An Improved Protocol for Determining Ratios of Retinol-d4 to Retinol Isolated from Human Plasma", Anal. Chem. (1993), Vol. 65, pp. 2024-2028.	☐
27	HASKINS, N.J., "The Application of Stable Isotopes in Biomedical Research", Biomedical Mass Spectrometry (1982), Vol. 9:7, pp. 269-277.	☐
28	KUSHNER et al., "Pharmacological uses and perspectives of heavy water and deuterated compounds," Can. J. Physiol. Pharmacol. (1999), Vol. 77, pp. 79-88.	☐
29	PARK, et al. "Metabolism of Fluorine-Containing Drugs," Annu. Rev. Pharmacol. Toxicol. (2001), Vol. 41, pp. 443-470.	☐
30	TANG, G. et al., "Deuterium enrichment of retinol in humans determined by gas chromatography electron capture negative chemical ionization mass spectrometry", J. Nutr. Biochem (1998), Vol. 9, pp. 408-414.	☐
31	TUNG, Office Action for US Patent Application 12/874,783, Dated 08/16/2011.	☐
32	WOLEN, R., "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence", The Journal of Clinical Pharm. (1986), Vol. 26, pp. 419-424.	☐

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Examiner Name	TBA
Attorney Docket Number	13533-541US2

EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/	Date Considered	10/28/2015
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

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Examiner Name	TBA
Attorney Docket Number	13533-541US2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

- ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

- ☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

- ☐ See attached certification statement.
- ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Joseph A. Coppola/	Date (YYYY-MM-DD)	2015-01-20
Name/Print	Joseph A. Coppola	Registration Number	38,413

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Z.F./

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	Art Unit	TBA	
	Examiner Name	TBA	
	Attorney Docket Number	13533-541US2	

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Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5310764		1994-05-10	Baranowitz et al.	
	2	6660297		2003-12-09	Bartels et al.	
	3	7566808		2009-07-28	Rando	
	4	8124646	B2	2012-02-28	Liu	
	5	8263601	B2	2012-09-11	Tung et al.	
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	1	20020012966		2002-01-31	Shi et al.	

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Application Number		14510975
Filing Date		2014-10-09
First Named Inventor	Ilyas Washington	
Art Unit		TBA
Examiner Name	TBA	
Attorney Docket Number		13533-541US2

	2	20020169176	A1	2002-11-14	Elder et al.	
	3	20030032078		2003-02-13	Travis	
	4	20030149997		2003-08-07	Hageman	
	5	20040009907		2004-01-15	Alsobrook et al.	
	6	20040121407		2004-06-24	Distefano et al.	
	7	20040235113		2004-11-25	Shi et al.	
	8	20050059010		2005-03-17	Stone et al.	
	9	20050119536		2005-06-02	Hageman	
	10	20050176662		2005-08-11	Inana et al.	
	11	20050220768		2005-10-06	McVey et al.	
	12	20050256207		2005-11-17	McGrath	
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13	20060089411	A1	2006-04-27	Gierhart	
14	20060094063		2006-05-04	Mata et al.	
15	20060099714		2006-05-11	Mata et al.	
16	20060135460		2006-06-22	Widder et al.	
17	20060292099		2006-12-28	Milburn et al.	
18	20070014833		2007-01-18	Milburn et al.	
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2	1996024344	WO	A1	1996-08-15	Warner Lambert Co		☐
3	H10513197	JP	A	1998-12-15	Warner Lambert Co.		☐
4	2002072528	WO	B2	2002-09-19	Lilly Co Eli		☐
5	2002275095	JP	A	2002-09-25	Warner Lambert Co		☐
6	2004526725	JP	A	2004-09-02	Eli Lily & Co. et al		☐
7	2005000230	WO	A2	2005-01-06	Achkar, Charles et al.		☐
8	2005065669	WO	B3	2005-07-21	Alcon, Inc		☐
9	05087210	WO	A2	2005-09-22	Larsen, Lars		☐
10	0719503	WO	A2	2007-02-15	Harvard College		☐
11	2006526662	JP	A	2006-11-24	ACHKAR, Charles et al.		☐

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	1	Acutane [online], [retrieved on July 05, 2012] Retrieved from RXlist: The Internet Drug Index using Internet <URL: http://www.rxlist.com/cgi/generic/isotret.htm >.	☐
	2	Age-Related Eye Disease Study Research Group, "A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss," Arch. Ophthalmol. (2001) Vol. 119, 1417-1436.	☐
	3	ALIKMETS, et al. "A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy," Nat. Genet (1997), Vol. 15, pp. 236-246.	☐
	4	ASHMARIN, et al. "Thyroliberin: new physiological effects and prospects of clinical use," Vestn Ross Akad Med X Nauk (1992), VOL. 6, PP. 40-44. (with abstract translation)	☐
	5	BAEHR, et al. "The Retinoid Cycle and Retina Disease," Vision Research (2003) Vol. 43, pp. 2957-2958.	☐
	6	BAILLIE, T., "The Use of Stable Isotopes in Pharmacological Research", Pharmacological Reviews(1981), Vol. 33, No. 2, pp. 81-132.	☐
	7	BARRETT, et al. "Hybrid Tracking System for Retinal Photocoagulation Prototype II," Biomed Sci Instrum (1999) Vol. 35, pp. 259-64.	☐
	8	BAUSCH, et al. "Method for the Assessment of Vitamin A Liver Stores," Acta Vitaminol Enzymol31 (1977,) pp. 99-112.	☐
	9	BEN-SHABAT, et al. "Fluorescent pigments of the retinal pigment epithelium and age-related macular degeneration," Bioorg Med Chem Lett. 11(2001), pp. 1533-1540.	☐
	10	BERGEN, et al. "Synthesis of Tri-, Tetra-, and Penta-Deuterated Forms of Vitamin A," Journal of Labelled compounds and Radiopharmaceuticals (1998), vol. 25:1, pp. 11-21.	☐

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11	BERGMANN, et al. "Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration," FASEB J.18 (2004), pp. 562-564.	☐
12	CAMERINI, et al. "Safety of the Synthetic Retinoid Fenretinide: Long-Term Results From a Controlled Clinical Trial for the Prevention of Contralateral Breast Cancer," J. Clin. Oncol. (2001), Vol. 19, pp. 1664-1670.	☐
13	CAPON, et al. "Sorsby's fundus dystrophy: a light and electron microscopic study," Ophthalmology 96 (1989), pp.1769-1777.	☐
14	Isotretinoin, [online], [retrieved on July 05, 2012] Retrieved from Chemocare.com using Internet <URL: http://www.chemocare.com/bio/isotretinoin.asp >.	☐
15	CHONG, et al. "TIMP-3 collagen, and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy," Invest Ophthalmol Vis Sci (2000), Vol. 41, pp. 898-902.	☐
16	DE, et al. "Interaction of A2E with model membranes. Implications to the pathogenesis of age-related macular degeneration," J Gen Physiol. (2002), Vol. 120, pp. 147-157.	☐
17	DOWLING, "Neural and Photochemical Mechanisms of Visual Adaptation in the Rat," J. Gen. Physio. (1963), pp. 1287-1301	☐
18	DRAGNEV, et al. "The Retinoids and Cancer Prevention Mechanisms," Oncologist 5 (2000), pp. 361-368.	☐
19	FINE, et al. "Age-related macular degeneration," N Engl J Med. (2000), Vol. 342, pp. 483-492.	☐
20	FINNEMANN, et al. "The lipofuscin component A2E selectively inhibits phagolysosomal degradation of photoreceptor phospholipid by the retinal pigment epithelium," Proc Natl Acad Sci. (2002), Vol. 99, pp. 3842-3847.	☐
21	FISHKIN, et al. "Isolation and characterization of retinal pigment epithelial cell fluorophore: An all-trans-retinal dimer conjugate," Proc. Natl. Acad. Sci. (2005), Vol. 102, pp. 7091-7096.	☐
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22	FREEMANTLE, et al. "Retinoids in cancer therapy and chemoprevention: promise meets resistance," Oncogene (2003), Vol. 22, pp. 7305-7315.	☐
23	FRIEDMAN, et al. "Prevalence of age related macular degeneration in the United States," Arch. Ophthalmol. (2004) Vol. 122, pp. 564-572.	☐
24	GOLCZAK, et al. "Metabolic Basis of Visual Cycle Inhibition by Retinoid and Non retinoid Compounds in the Vertebrate Retina," J. Biol. Chem. (2008), Vol. 283, pp. 9543-9554.	☐
25	GOLLAPALLI, et al. "The specific binding of retinoic acid to RPE65 and approaches to the treatment of macular degeneration," PNAS. (2004), Vol. 101:27, pp. 10030-10035.	☐
26	GUDAS, et al. "Cellular biology and biochemistry of retinoids"; The retinoids, Biology, Chemistry and Medicine (1994), Raven Press Ltd., New York, pp. 443-520.	☐
27	HARALAMPUS-GRYNAVSKI, et al. "Spectroscopic and morphological studies of human retinal lipofuscin granules," Proc. Natl. Acad. Sci. (2003), Vol. 100, pp. 3179-3184.	☐
28	HASKELL, et al. "Use of deuterated-retinol-dilution technique to assess total body vitamin A stores of adult volunteers consuming different amounts of vitamin A1-3", Amer. J. of Clinical Nutrition (1999), Vol. 70, pp. 874-880.	☐
29	JARC-VIDMAR, et al. "Fundus autofluorescence imaging in Best's vitelliform dystrophy," Klinische Monatsblätter Fur Augenheilkunde (2003), Vol.220, pp. 861-867.	☐
30	JONG, "Age-related macular degeneration," N. Engl J Med 355 (2006), pp. 1474-1485.	☐
31	KATZ, et al. "Relationship between dietary retinol and lipofuscin in the retinal pigment epithelium," Mech Age. Dev. (1986), Vol. 35, pp. 291-305.	☐
32	KIM, et al. "Rpe65 Leu450Met variant is associated with reduced levels of the retinal pigment epithelium lipofuscin fluorophores A2E and iso-A2E," Proc. Nat. Acad. Sci. (2004), Vol. 101, pp. 11668-11672.	☐
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33	MAEDA, et al. "Effects of potent inhibitors of the retinoid cycle on visual function and photoreceptor protection from light damage in mice," Mol. Pharmacol. (2006), Vol. 70, pp. 1220-1229.	☐
34	MAITI, et al. "Small molecule RPE65 antagonists limit the visual cycle and prevent lipofuscin formation," Biochemistry (2006), Vol. 45, pp. 852-860.	☐
35	MARMORSTEIN, et al. "Spectral Profiling of Autofluorescence Associated with Lipofuscin, Bruch's Membrane, and Sub-RPE Deposits in Normal and AMD Eyes," Invest. Ophthalmol. Vis. Sci. (2002), Vol. 43, pp.2435-2441.	☐
36	MURATA, et al. "Suppression of laser-induced choroidal neovascularization by subconjunctival injection of 9alpha-fluoromedroxyprogesterone acetate (FMPA), an anti-angiogenic agent, in rats," Biol. Pharm Bull (2006), Vol. 29:12, pp. 2410-2414.	☐
37	NASON-BURCHENAL, et al. "The retinoids: cancer therapy and prevention mechanisms," Retinoids: The Biochemical and Molecular Basis of Vitamin A and Retinoid Action (1999), Berlin, pp. 301-322.	☐
38	OWSLEY, et al. "Aging and scotopic dysfunction," Perception 29 (2000), Abstract Supplement.	☐
39	OWSLEY, et al. "Delays in rod-mediated dark adaptation in early age-related maculopathy," Ophthalmology (2001), Vol.108, pp. 1196-1202.	☐
40	PAPADAKI et al. "Somatostatin for Uveitic Cystoid Macular Edema (CME)," Ocul ImmunolInflamm (2005), Vol. 13:6, pp. 469-470.	☐
41	PARDOEN, et al. "Synthesis of 8-, 9-, 12-, and 13-mono-13C-retinal," Canadian Journal of Chemistry (1985), Vol. 63, pp. 1431-1435.	☐
42	PARDOEN, et al. "Synthesis of retina is isotopically labeled at positions 11, 12, 14 and 20," Recueil des Travaux Chimiques des Pays-Bas (1986), Vol. 105, pp. 92-98.	☐
43	HALPERN, et al. "Cystoid macular edema in aphakia and pseudophakia after use of prostaglandin analogs," Semin Ophthalmol (2002), Vol. 17(3-4) pp. 181-186.	☐
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44	PUDUVALLI, et al. "Phase II Study of Fenretinide (NSC 374551) in Adults With Recurrent Malignant Gliomas: A North American Brain Tumor Consortium Study," J. Clin. Oncol. (2004), Vol. 22, pp. 4282-4289.	☐
45	RADU, et al. "Reductions in serum vitamin A arrest Accumulation of toxic retinal fluorophores: A potential therapy for treatment of lipofuscin based retinal diseases," Invest Ophthalmol Vis Sci (2005), Vol. 46, pp. 4393-4401.	☐
46	RATTNER, et al. "Macular degeneration: recent advances and therapeutic opportunities," Nat. Rev. Neurosci. (2006), Vol. 7, pp. 860-872.	☐
47	RADU, et al. "Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargardt's macular degeneration" Proc Natl Acad Sci (2003), Vol. 100, pp. 4742-4747.	☐
48	RADU, et al. "Light exposure stimulates formation of A2E oxiranes in a mouse model of Stargardt's macular degeneration," Proc Natl Acad Sci (2004), Vol. 101, pp. 5928-5933.	☐
49	ROBISON, et al. "Deficiencies of vitamins E and A in the rat. Retinal damage and lipofuscin accumulation," Invest Ophthalmol Vis Sci (1980), Vol. 19, pp. 1030-1037.	☐
50	SAETTEL, et al. "Ab initio studies of [1 ,5]-H Shifts: pentadiene and beyond," J. Org. Chem. (2000), Vol. 65, pp. 2331-2336.	☐

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Signature	/Joseph A. Coppola/	Date (YYYY-MM-DD)	2015-01-20
Name/Print	Joseph A. Coppola	Registration Number	38413

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/510,975	10/09/2014	Ilyas Washington	13533/541US2

CONFIRMATION NO. 6583

PUBLICATION NOTICE



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KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

Title:Compositions and Methods for Treating Macular Degeneration

Publication No.US-2015-0133549-A1

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APPLICATION AS FILED - PART I									
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)	RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70	N/A				
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	300	N/A				
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360	N/A				
TOTAL CLAIMS (37 CFR 1.16(j))	29	minus 20 = * 9	x 40 =	360					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 = *	x 210 =	0.00					
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MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			TOTAL		TOTAL				
			1090						
* If the difference in column 1 is less than zero, enter "0" in column 2.									
APPLICATION AS AMENDED - PART II									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)		
	Total (37 CFR 1.16(i))	*	Minus **	=	x =	x =	x =		
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	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE		TOTAL ADD'L FEE			
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)		
	Total (37 CFR 1.16(i))	*	Minus **	=	x =	x =	x =		
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =	x =	x =		
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
				TOTAL ADD'L FEE		TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.									



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
14/510,975	10/09/2014	1629	1160	13533/541US2	29	1

CONFIRMATION NO. 6583

UPDATED FILING RECEIPT

26646
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004



Date Mailed: 02/03/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Ilyas Washington, New York, NY;

Applicant(s)

The Trustees of Columbia University in the City of New York, New York, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a DIV of 12/733,631 10/14/2010 PAT 8877809
which is a 371 of PCT/US08/10676 09/12/2008
which claims benefit of 60/993,379 09/12/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/510,975**

Projected Publication Date: 05/14/2015

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

Compositions and Methods for Treating Macular Degeneration

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application Serial No. 14/510,975

Filed: October 9, 2014

Art Unit: To be determined

For: Compositions and Methods for Treating Macular
Degeneration

Examiner: To be determined

VIA EFS-Web
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I hereby certify that this correspondence is being electronically transmitted to the United States Patent and Trademark Office via the Office Electronic Filing System on January 20, 2015.

Signature: /Loretta E. Charles/
Loretta E. Charles

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Dear Sir/Madam:

In response to the Notice to File Corrected Application Papers dated October 20, 2014, Applicants hereby submit replacement drawings sheets for Fig. 3A, 3B, 3C, 4A, 4B, 4C, 5A, 5B, 6A, 6B, 6C, 6D, 7A, 7B, and 7C. A clean and marked version of a Substitute Specification is also submitted. In the Substitute Specification:

- the priority information in paragraph [0002] has been updated;
- the list of "Cited Documents" at pages 31-36 is 1½ spaced;
- the Brief Description of the Drawings section has been amended to clarify the descriptions of Fig. 4A and Fig 4B in paragraph [0036]; Fig. 5A and Fig 5B in paragraph [0037]; and Fig. 6A-D in paragraph [0038];
- references to Fig. 5A and Fig. 5B has also been clarified in paragraph [0094].

The Substitute Specification contains no new matter.

The Notice dated October 20, 2014 set a two-month period for response expiring on December 20, 2015. Filed concurrently herewith is a Petition for the Extension of Time for a period sufficient to permit the filing of this response.

The Office is authorized to charge any fees necessary for the filing of this response and/or to credit any overpayment in connection with this response to **Kenyon & Kenyon LLP's** deposit account number **11-0600**.

Respectfully submitted,

Date: January 20, 2015

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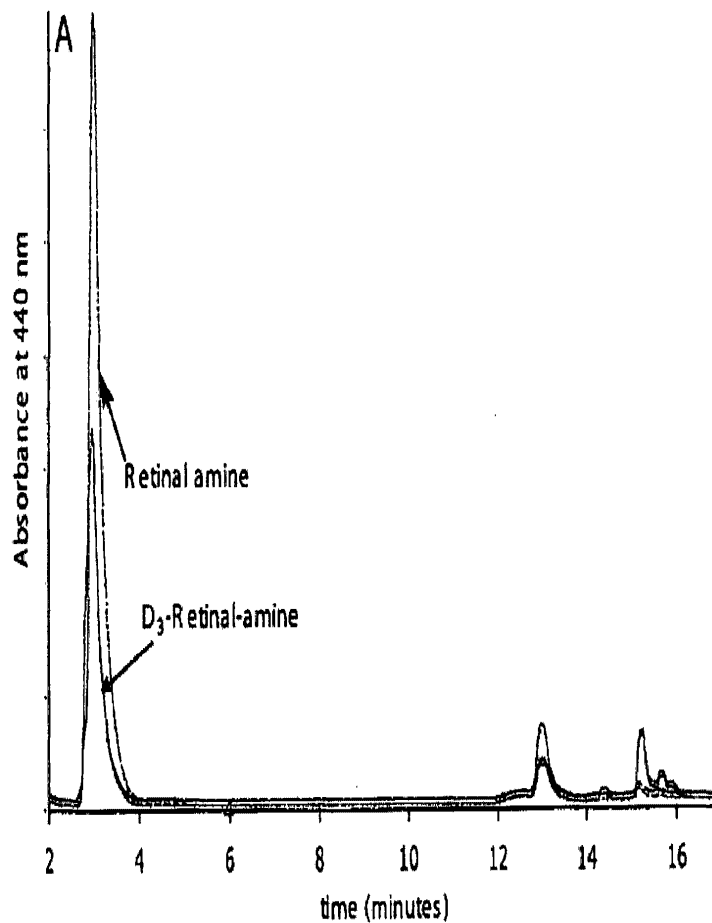


FIG. 3A

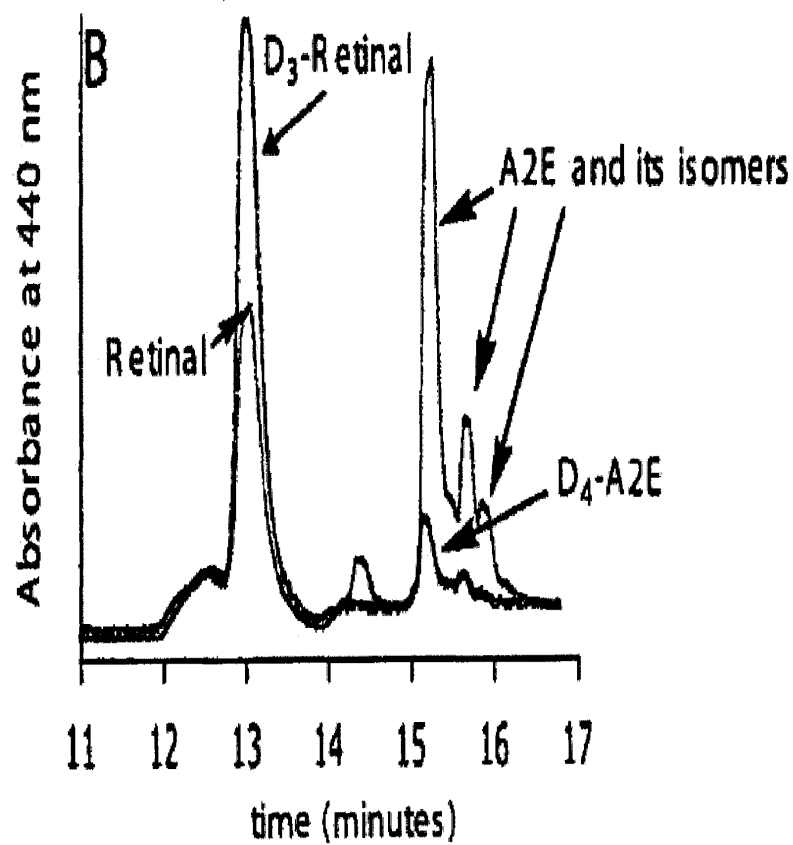


FIG. 3B

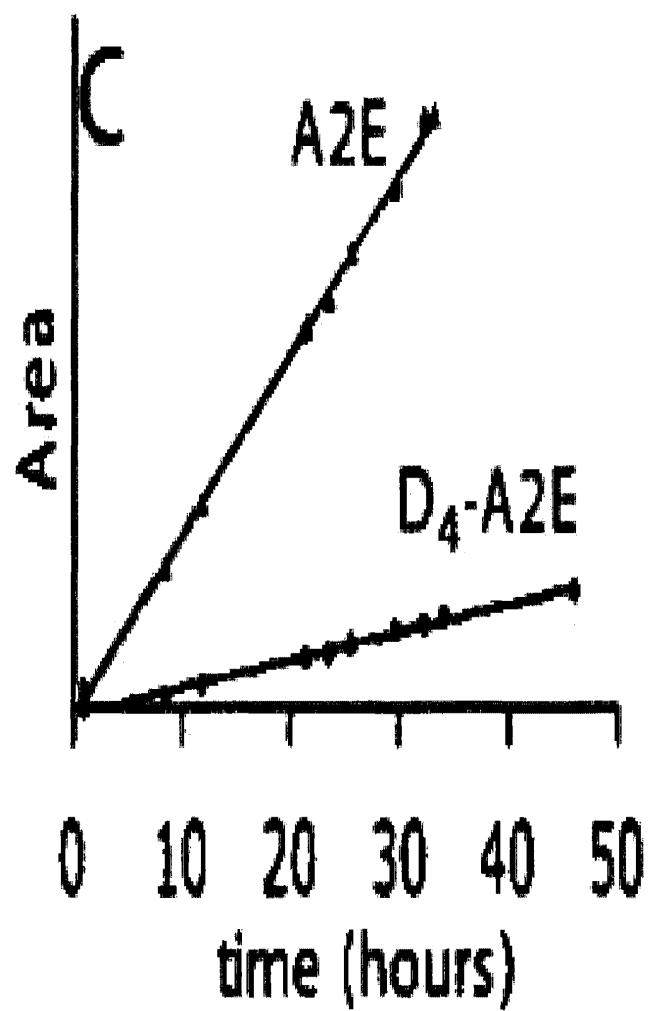


FIG. 3C

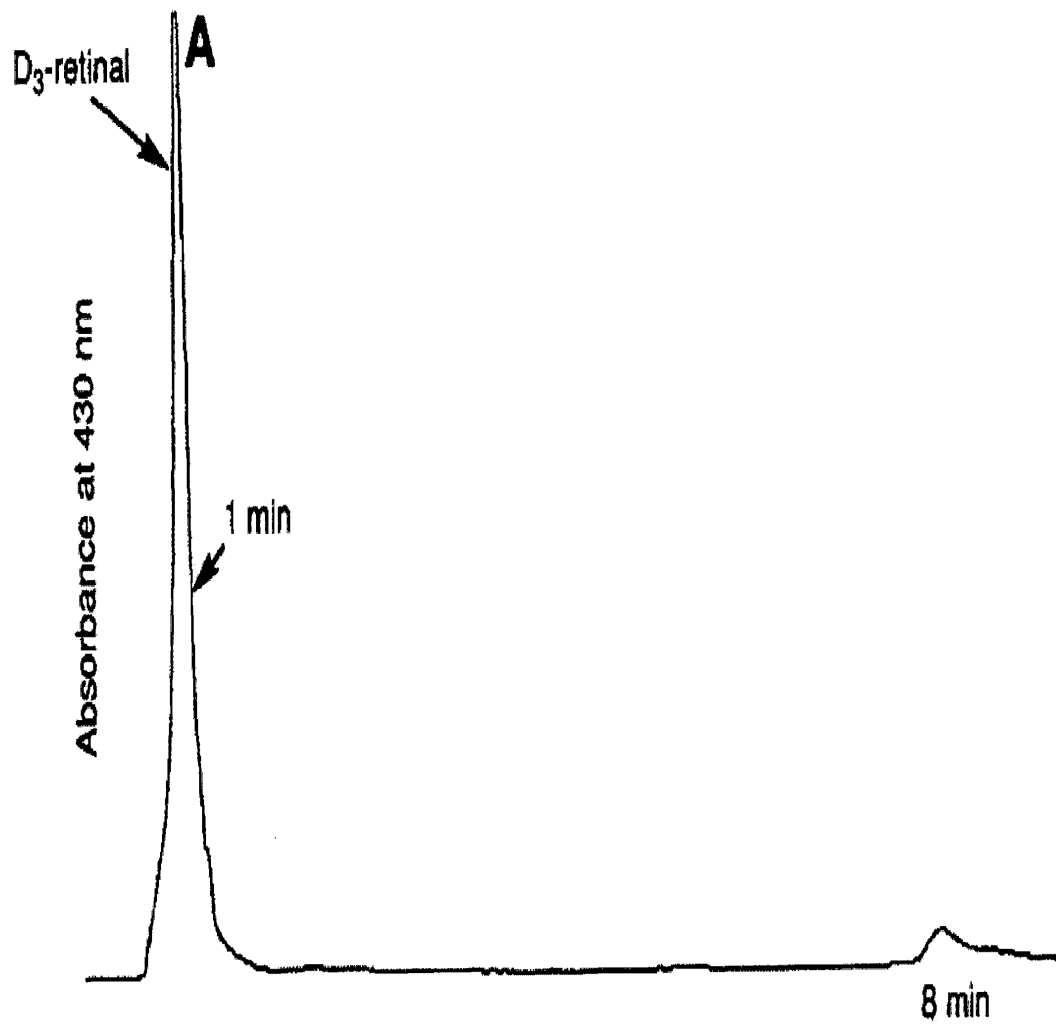


FIG. 4A

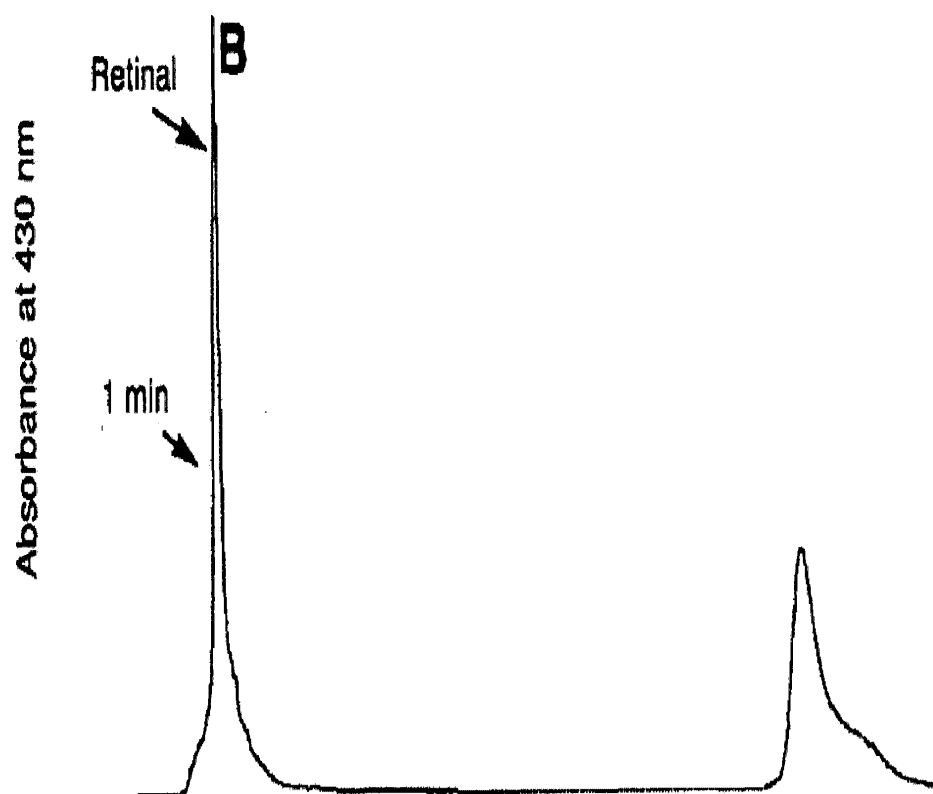


FIG. 4B

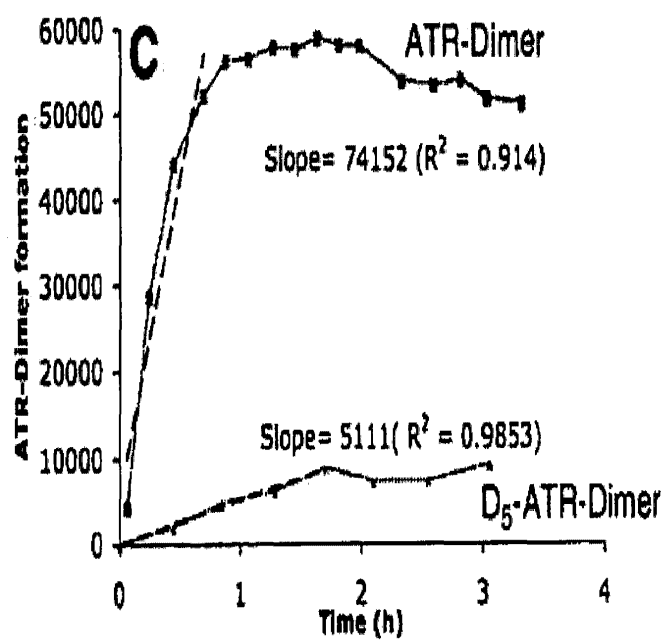


FIG. 4C

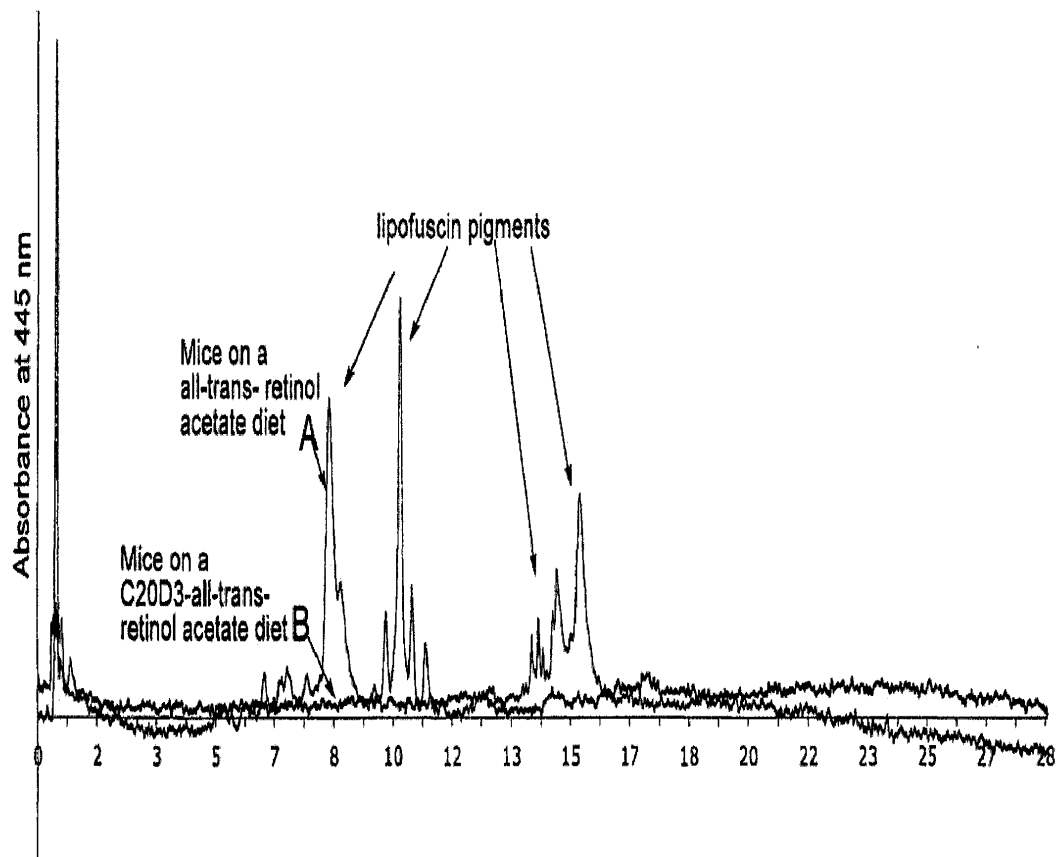


FIG. 5A

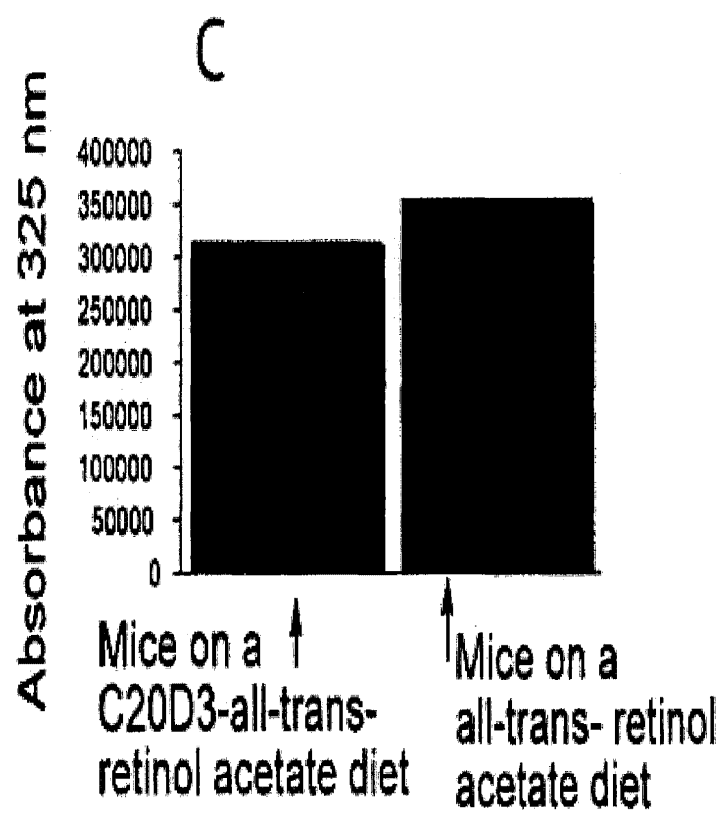


FIG. 5B

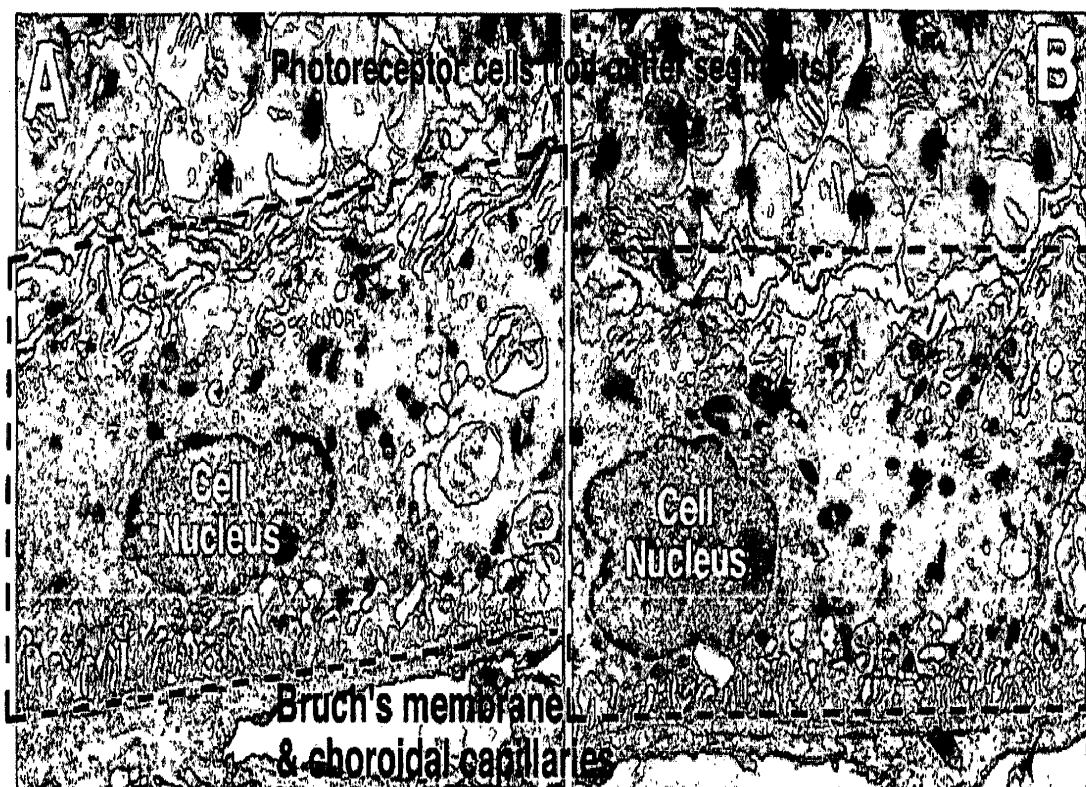


FIG. 6A

FIG. 6B

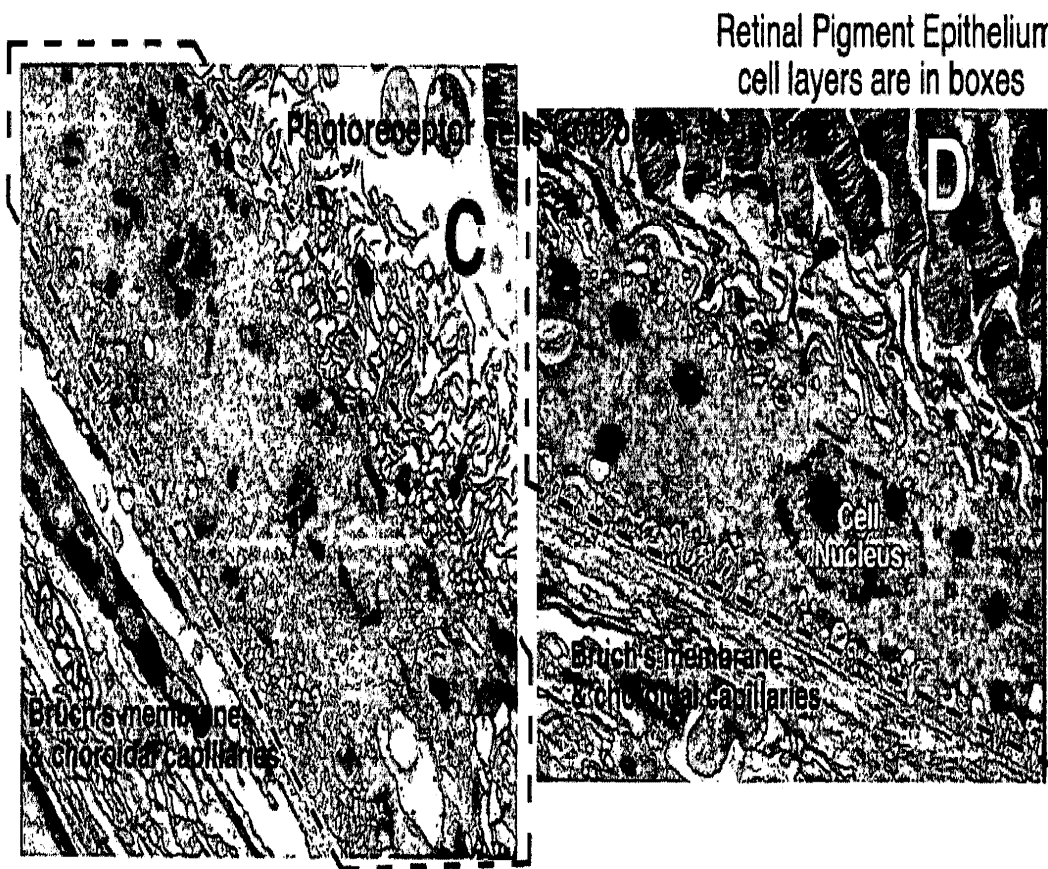


FIG. 6C

FIG. 6D

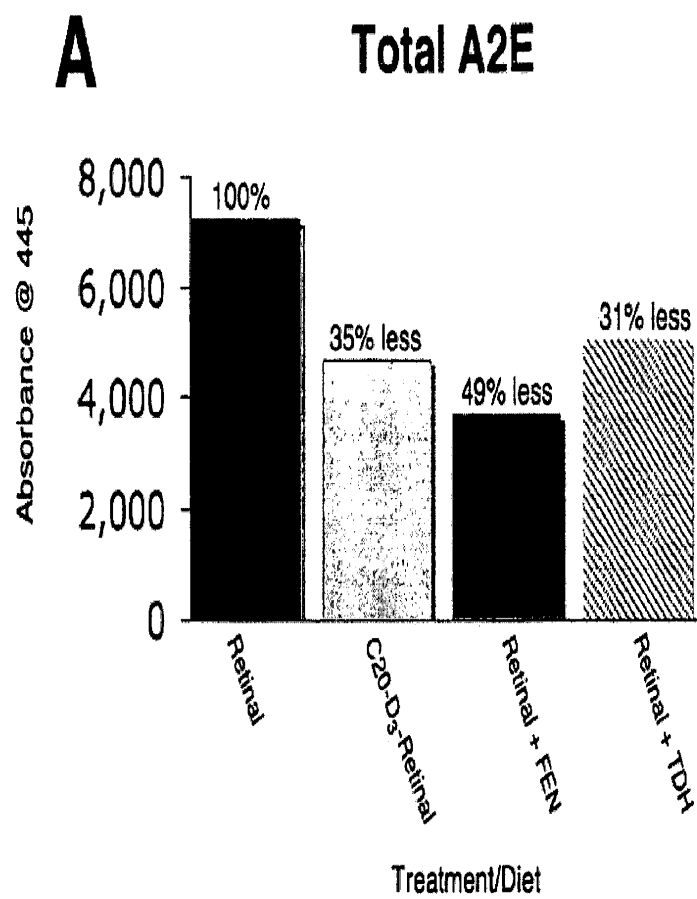


FIG. 7A

B

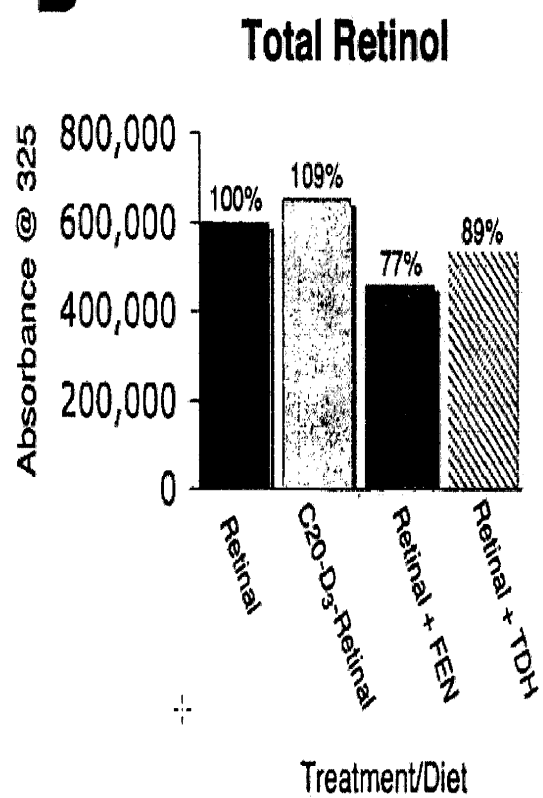


FIG. 7B

C

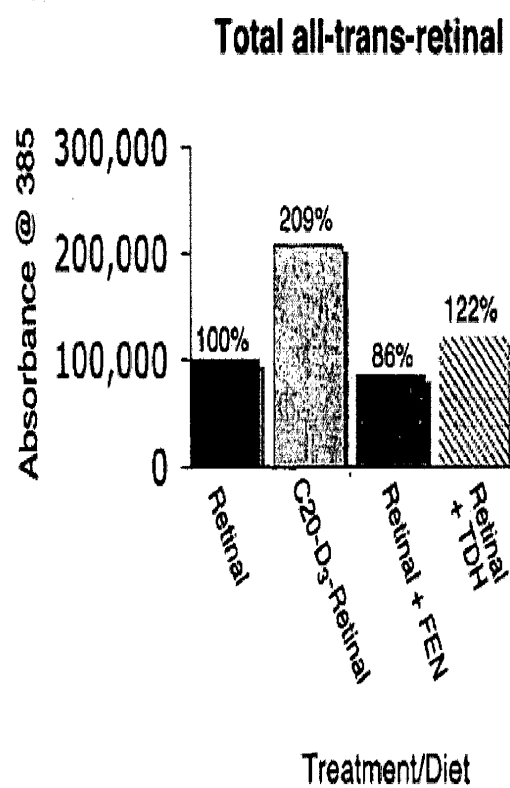


FIG. 7C

COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

GOVERNMENT FUNDING

[0001] This invention was made with government support under Grant EY T32 013933 awarded by the National Eye Institute of the National Institutes of Health. The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] The present application is a divisional of U.S. Patent Application Serial No. 12/733,631, which is a U.S. National Stage Application of International Application No. PCT/2008/010676, which was filed on September 12, 2008, and claims the benefit of U.S. provisional patent application no. 60/993,379, filed 12 September 2007, the disclosures of each of which is are incorporated by reference as if recited in full herein.

FIELD OF THE INVENTION

[0003] The present invention relates, inter alia, to compounds, compositions, and methods to slow lipofuscin formation/accumulation in order to treat or ameliorate an ophthalmologic disorder, such as, e.g., macular degeneration, without, or with reduced, adverse visual effects. More particularly, the present invention relates to compounds and compositions that may be used to treat or ameliorate an ophthalmologic disorder, such as, e.g., macular degeneration, by slowing or limiting the accumulation of age pigments or lipofuscin in the retinal pigment epithelium ("RPE") cells of the retina. The present invention also relates to methods of treating or ameliorating an ophthalmologic disorder, such as, e.g., macular degeneration, in a mammal by administering to a mammal in need of such treatment an effective amount of the compounds and/or compositions disclosed herein.

BACKGROUND OF THE INVENTION

[0004] The macula is located at the back of the eye in the center of the retina. When the millions of cells in this light-sensitive, multilayer tissue deteriorate, central vision is lost along with the ability to perform tasks such as reading, writing, driving, and

seeing color. This “macular degeneration” principally affects the elderly and has a prevalence of about 3% in populations between 75-79 years of age and about 12% for populations over 80 years of age.(1) In younger populations, macular degeneration is found in individuals with genetic disorders, such as Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy and Malattia Leventinese (Dojne Honeycomb or Dominant Radial Drusen). Stargardt Disease is the most common form of inherited juvenile macular degeneration, affecting about 1 in 10,000 children.

[0005] There are no therapies currently available for genetic or dry (non-neovascular) age related macular degeneration. Vitamin supplements such as antioxidants, and diet changes, such as low fat diets, have been shown to slow disease progression in some clinical studies. However, for the majority of patients, diagnosis is followed by the progressive loss of central vision.(2-4)

[0006] The above listed macular dystrophies are all marked by the accumulation of lipofuscin, fluorescent deposits, in the retinal pigment epithelium (RPE) cell layer (5-11). The only compounds that have been characterized to date from RPE lipofuscin, A2E (N-retinylidene-N-retinylethanolamine) and ATR-dimer (all-*trans*-retinal dimer), are derived from reactions of all-*trans*-retinal, an isomer of 11-*cis*-retinal, the chromophore of the visual pigments (12, 13). These toxic retinal dimers have been shown to cause RPE cell death, which is thought to lead to photoreceptor cell degeneration and vision loss (2, 14-22). Slowing the visual cycle using RPE 65 antagonists (23-25) or retarding the delivery of vitamin A (retinol) to the RPE by, *e.g.*, limiting dietary intake of vitamin A (26) or blocking serum retinol binding proteins (27) have been shown to impede or abolish RPE lipofuscin formation in animal models. Conversely, increasing the amount of all-*trans*-retinal in outer segments, such as occurs with the mutations in *abcr*^{+/−} (responsible for recessive Stargardt disease), leads to the rapid accumulation of lipofuscin pigments (8).

[0007] The above cited evidence leads to the conclusion that lipofuscin and/or A2E and ATR-dimer in RPE cells may reach levels that contribute to a decline in cell function followed by vision loss and that vitamin A plays an important role in ocular lipofuscin formation. (28)

[0008] Several vitamin A analogs have been shown to limit lipofuscin formation in a mouse model by slowing down the visual cycle. The ABCR^{-/-} mouse model has been used to test approaches to limit RPE lipofuscin formation. Mice lacking the ABCR (also known as ABCA4) gene encoding a photoreceptor-specific adenosine triphosphate (ATP)-binding cassette transporter, lack the ability to properly shuttle vitamin A (in the form of retinal) in the eye. ABCR^{-/-} mice were developed as an animal model of human recessive Stargardt's Disease (8). As in humans with recessive Stargardt's disease, ABCR^{-/-} mice accumulate large lipofuscin deposits in RPE cells of their eyes, as shown in FIG. 1, and eventually experience delayed dark adaptation. Lipofuscin accumulation and vision loss observed in this mouse model is also thought to be relevant to age-related macular degeneration (AMD) and other macular dystrophies.

[0009] In attempts to slow down the visual cycle, visual cycle enzymes have been targeted. In such approaches, small molecules have been proposed as antagonists to visual cycle enzymes. In this methodology, the drug (often a vitamin A derivative) binds to visual cycle proteins, which blocks participation by the proteins in the visual cycle, and slows the visual cycle. Another approach to slowing the visual cycle includes impeding the delivery of vitamin A from the blood to the eye.

[0010] Drug candidates for inhibiting lipofuscin formation by slowing down the visual cycle have been evaluated by their ability to cause delayed dark adaptation (a side effect of an impaired visual cycle) and their ability to impede the age related accumulation of eye lipofuscin as measured by the concentration of A2E and other byproducts of the visual cycle, e.g., ATR-dimer. Examples of such drug candidates and their corresponding mechanisms of action to slow the visual cycle are summarized below:

[0011] 13 *cis*-retinoic acid (Acutane or isotretinoin) is thought to inhibit the enzymes 11-*cis*-retinol dehydrogenase and RPE65 involved in the visual cycle.(19, 24) When administered, 13 *cis*-retinoic acid has been shown to cause delayed dark adaptation. When 3-month-old ABCR knockout mice (n=3) were administered 13-*cis*-retinoic acid at 40 mg/kg/day for one month, the mice showed a decrease in A2E formation by about 40-50% compared to control ABCR knockout mice (n=3).(24) Furthermore, when 2-month-old ABCR knockout mice were administered 13-*cis*-retinoic

acid at 20 mg/kg/day for two months, the mice also showed a decrease in lipofuscin formation in the RPE cell layer as judged by electron microscopy.

[0012] (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one (TDT) is thought to inhibit RPE65.(23) When TDT is administered to mice, delayed dark adaptation is observed. When 2-month-old ABCR knockout mice (n=2) were administered TDT at 50 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50-85% compared to control ABCR knockout mice (n=2).(23)

[0013] (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine (TDH) is also thought to inhibit RPE65 and when given to mice, causes delayed dark adaptation.(23) When 2-month-old ABCR knockout mice (n=2) were administered TDH at 50 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50% compared to control ABCR knockout mice (n=2).(23)

[0014] All-*trans*-retinylamine (Ret-NH₂) is thought to inhibit RPE65 and when administered to mice results in severe delayed dark adaptation. When 1-month-old ABCA4 knockout mice were given Ret-NH₂ at 40 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50% compared to control ABCA4 knockout mice.(25)

[0015] N-(4-hydroxyphenyl) retinamide (Fenretinide) slows the influx of retinol into the eyes by reducing levels of vitamin A bound to serum retinol-binding protein. Thus, treatment with Fenretinide lowers the levels of vitamin A in the eye which leads to delayed dark adaptation. When 2-month-old ABCA4 knockout mice (n=3) were administered Fenretinide at 20 mg/kg/day for one month, they showed a decrease in A2E formation by about 40-50% compared to control ABCA4 knockout mice (n=3).(27)

[0016] Thus, recently proposed therapeutic approaches to limit lipofuscin formation are based upon slowing the visual cycle (1, 10, 11, 12). There are, however, disadvantages to slowing the visual cycle as a means to impede lipofuscin formation in order to prevent, e.g., macular degeneration. Four of these disadvantages are detailed below.

[0017] 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. Poor night vision (Scotopic dysfunction) is already a functional marker of early age-related maculopathy

(ARM), and has been linked to the occurrence of falls and vehicle collisions.(29, 30) A further slowing down of the visual cycle is expected to make night vision worse in patients who already suffer from poor night vision.

[0018] Second, in order to sufficiently impede lipofuscin formation, one would have to slow down the visual cycle for a prolonged period of time. But, long-term slowing of the visual cycle leads to photoreceptor cell death and loss of vision.(31, 32) In fact, impairment of the visual cycle is the cause of various retinal diseases such as Stargardt's disease, retinitis pigmentosa, Lebers Congenital Amaurosis, Fundus Albipunctatus, age-related macular degeneration and Congenital Stationary Night Blindness.

[0019] Third, the above methodology often uses vitamin A analogs to impede proteins involved in vitamin A processing in the eye. However, vitamin A analogs of diverse structures, pharmacological profiles, receptor affinities, and biologic activities have been shown to be toxic. Indeed, numerous vitamin A analogs have been shown in experimental animal models, cellular models, epidemiological data and clinical trials to inhibit or retard various biological functions such as, for example, bone growth, reproduction, cell division, cell differentiation and regulation of the immune system.(33-37). Thus, inhibiting vitamin A processing in the eye is also expected to retard some of these basic bodily functions, which may lead to significant adverse side effects.

[0020] For example, vitamin A analogs that are currently used to treat certain cancers and/or psoriasis such as, e.g., Bexarotene (Targretin), Etretinate (Tegison) Acitretin (Soriatane), Fenretinide (*N*-(4-hydroxyphenyl) retinamide or 4-HPR) and 13 *cis*-retinoic acid (Accutane or isotretinoin) have side effects, which include, e.g., dry nose, nosebleeds, chapped lips, mouth sores, increased thirst, sore tongue, bleeding gums, dry mouth, cold sores, dry or irritated eyes, dry skin, peeling or scaly skin, hair loss, easy bruising, muscle aches, nausea, stomach upset, cough or swelling of the hands or feet, vision problems, chest pain, tightness in the chest, abnormal pulse, dizziness, vomiting, severe headache, and yellowing of the eyes/skin (jaundice).(38-40)

[0021] Fourth, in animal models, candidate drugs for limiting lipofuscin formation have been shown to be effective only in relatively large doses. For example, studies in mouse models typically use doses around 11-40 mg/kg/day. But, current vitamin A

analogs are typically used in the clinic at doses of 1-3 mg/kg/day to minimize side effects. Larger dosing regimes will lead to increased side effects.

[0022] For example, Fenretinide (*N*-(4-hydroxyphenyl) retinamide or 4-HPR) is currently used to treat cancer and clinical trials are in progress for AMD. The most common adverse effects reported among 1,432 patients who underwent treatment with this drug at a dosage of 200 mg/day for a five year period were: diminished dark adaptation, cumulative incidence (16%) and dermatologic disorders (16%). Less common effects were gastrointestinal symptoms (8%) and disorders of the ocular surface (8%).(41) At this relatively low dose a delay in dark adaptation, an assessment of the effectiveness of a drug to impede lipofuscin formation, was only observed in 16% of patients. In another study when patients were administered larger oral doses of 600 or 900 mg/m² bid in 6-week cycles, mild to moderate adverse effects were reported in 43 (95%) of the 45 patients that were possibly linked to Fenretinide. These side effects included: fatigue, headache, skin changes (dry skin, pruritus, and rash) and digestive tract symptoms (abdominal pain, cramping, diarrhea, stomatitis, and xerostomia). Grade 2 toxicities reported as possibly linked to Fenretinide treatment included seizures and confusion.(42)

[0023] A patient with an anaplastic astrocytoma who had been receiving treatment with Fenretinide at the 600 mg/m² bid dose for one cycle presented with headaches, nausea, and vomiting, and was found to have a small intracranial bleed in the region of the basal ganglia. He recovered without deficits and continued treatment without further events. Another patient, who was also undergoing treatment at the 600 mg/m² bid dosage and was receiving oral anticoagulation with warfarin for deep venous thrombosis, died after developing an uncontrollable nasal bleed (international normalized ratio > 6.0). Of the four patients treated at the 900 mg/m² bid dose, one had grade 3 vomiting, grade 2 speech impairment, and grade 1 memory impairment, which improved without residual symptoms.(42)

[0024] A typical dose of 13 *cis*-retinoic acid (Accutane or isotretinoin) for treatment of acne is 0.5 to 1 mg/kg/day for children and 2.0 mg/kg/day for adults for fourteen days in a row, followed by a 14-day break. This twenty-eight day course is usually repeated five more times.(40) These doses are about 10 to 80 times less than

what was used in mice to impede A2E formation.(24) For larger doses of 13 *cis*-retinoic acid used to treat cancer, side effects occurring in more than 30% of users included headache, fever, dry skin, dry mucous membranes (mouth, nose), bone pain, nausea and vomiting, rash, mouth sores, itching, sweating, and eyesight changes.(43, 44)

[0025] Side effects occurring in 10-29% of users of 13 *cis*-retinoic acid include back pain, muscle and joint pain, allergic reaction, abdominal pain, poor appetite, dizziness, drowsiness, insomnia, anxiety, numbness and tingling of hands and feet, weakness, depression, hair loss (thinning), dry eyes, sensitivity to light (see eye problems), decreased night vision, which may persist after treatment is stopped, feet or ankle swelling, and low blood counts.(44) In addition, it has been observed that white and red blood cells and platelets may temporarily decrease, which may put a patient at increased risk for infection, anemia and/or bleeding. Side effects also include abnormal blood tests: increased triglyceride, cholesterol and/or blood sugar levels.

[0026] The above disadvantages make slowing of the visual cycle a difficult methodology to adapt alone for the clinical treatment of ophthalmologic disorders, e.g., macular degeneration.

SUMMARY OF THE INVENTION

[0027] Accordingly, it would be advantageous to provide treatments for ophthalmologic disorders, e.g., macular degeneration, that do not have, or limit one or more of, the side effects summarized above. In particular, it would be advantageous to provide compounds, compositions, and methods for impeding or halting the accumulation of lipofuscin or age pigments in the RPE cells of the retina without slowing, or slowing minimally, the visual cycle.

[0028] In this regard, one embodiment of the present invention is a method of retarding formation of a lipofuscin pigment in the retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

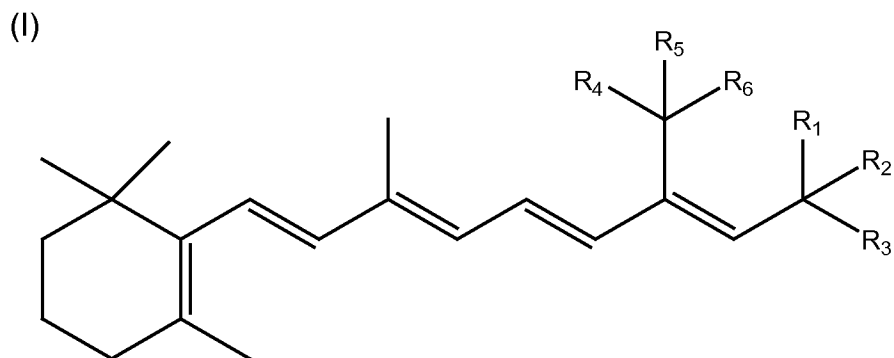
[0029] Another embodiment of the present invention is method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina. This method includes the step of administering to a patient in need

thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

[0030] A further embodiment of the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate in a patient under conditions sufficient to impede the formation of A2E.

[0031] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina containing a substituted C₂₀-retinoid and pharmaceutically acceptable carrier.

[0032] A further embodiment of the invention is a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I:



wherein:

R₁ is oxo or H;

R₂ is H or nothing;

R₃ is hydroxy or oxo or CHR₇ where R₇ forms a carotenoid and

R₄, R₅, and R₆ are independently selected from the group consisting of ¹H, ²H, ³H, halogen, and C₁₋₈alkyl.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1 shows HPLC and UV-vis profiles of lipofuscin pigments extracted from the eyecups (six of them minus the retina) of 5.5-6 month old, ABCR^{-/-} mice. Lipofuscin pigments such A2E and ATR dimer, represented by peaks 2, 3 and 4 have

been characterized and are derived from all-*trans*-retinal. Other lipofuscin pigments such as peaks 1 and 5 are also derived from all-*trans*-retinal, however, they have not been fully characterized. The above pigments are also found in humans and are thought to contribute to the macular degeneration.

[0034] FIG. 2 is a reaction scheme showing the biosynthesis of A2E and ATR-dimer from all-*trans*-retinal and a biological amine.

[0035] FIG. 3A shows HPLC profiles of reaction mixtures of C₂₀-D₃-all-*trans*-retinal and all-*trans*-retinal with ethanolamine for the formation of A2E. FIG. 3B is an expanded view of FIG. 3A. A2E formation was monitored over time by measuring the appearance of peaks starting at around 15 min. Both HPLC traces were measured about 30 hours into the reactions. For all-*trans*-retinal, a considerable amount of A2E has formed as well as an unidentified compound with a retention time at around 14.5 min as seen in the expanded view. On the other hand, for C₂₀-D₃-all-*trans*-retinal A2E formation is much slower and the peak at 14.5 min is almost absent. FIG. 3C is a plot of A2E formation over time for the above reactions. C₂₀-D₃-all-*trans*-retinal forms A2E about 7-times slower than all-*trans*-retinal.

[0036] FIG. 4A and 4B shows HPLC profiles of reaction mixtures of C₂₀-D₃-all-*trans*-retinal (Fig. 4A) and all-*trans*-retinal (Fig. 4B) with proline for the formation of ATR-dimer. ATR-dimer formation was monitored over time by measuring the appearance of peaks starting at around 8 min. Both HPLC traces were measured about 1 hour into the reactions. For all-*trans*-retinal, a considerable amount of ATR-dimer has formed. On the other hand, for C₂₀-D₃-all-*trans*-retinal ATR-dimer formation is much slower. FIG. 4C is a plot of ATR-dimer formation over time for the above reactions. C₂₀-D₃-all-*trans*-retinal forms A2E about 14-times slower than all-*trans*-retinal.

[0037] FIG. 5A shows HPLC profiles of lipofuscin pigments extracted from the eyecups (six of them minus the retina) of 5.5-6 month old, ABCR^{-/-} mice raised on a diet of either retinol acetate (trace A (FIG. 5A)) or C₂₀-D₃-all-*trans*-retinol acetate (trace B (FIG. 5B)). Mice raised on retinol acetate show considerable accumulation of lipofuscin pigments as shown by the HPLC peaks. On the other hand, lipofuscin pigments were undetectable in mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet. FIG. 5B shows plots of total retinol and retinol ester or D₃-retinol and D₃-retinol ester

concentrations in the above mice raised on either the retinol acetate or C₂₀-D₃-all-*trans*-retinol acetate diets, respectively. Both groups had roughly the same amount of retinol in the eye, despite having different concentrations of lipofuscin pigments.

[0038] FIG. 6A-D shows electron micrographs of RPE layers from 5.5-6 month old, ABCR^{-/-} mice raised on a diet of either retinol acetate (FIGs. 6A and 6B) or C₂₀-D₃-all-*trans*-retinol acetate (FIGs. 6C and 6D). Due to the uncertainty in distinguishing lipofuscin from melanin bodies. Comparisons were made between the numbers of all dark, electron dense bodies found in the RPE between mice on the retinol acetate diet vs. those on the C₂₀-D₃-all-*trans*-retinol acetate diet. In addition to the electron dense lipofuscin and melanin bodies, RPE phagosomes, mitochondria, and lipid droplets are also present but were ultrastructurally distinct. Mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet have considerably less electron dense bodies (i.e. lipofuscin bodies) compared to mice raised on the retinol acetate diet.

[0039] FIG. 7A shows total A2E, as measured by HPLC peak area at 445 nm, for rats (three females per group) treated/raised on either retinal, C₂₀-D₃-retinal, retinal plus Fenretinide (FEN) or retinal plus TDH. Animals treated with retinal had the greatest amount of A2E-lipofuscin (normalized to 100%). Whereas, animals treated with C₂₀-D₃-retinal or retinal plus Fenretinide or the RPE65 antagonist, TDH, showed less A2E-lipofuscin. FIG. 7B shows that all four groups of animals had roughly the same amount of eye retinol. FIG. 7C shows that levels of eye all-*trans*-retinal were increased in the C₂₀-D₃-retinal group.

DETAILED DESCRIPTION OF THE INVENTION

[0040] In the present invention, methods are provided to slow lipofuscin formation that do not rely on slowing the visual cycle or small molecules that inhibit the visual cycle (i.e., visual cycle antagonists). Thus, many of the disadvantages, such as, delayed dark adaptation, unformed visual pigment, which can leading to vision impairment and loss, high drug doses, and the potentially adverse side effects of prior methods are avoided.

[0041] More particularly, in the present invention provides methods for selectively replacing atoms on vitamin A in order to hamper its intrinsic reactivity to form vitamin A

derived lipofuscin pigments, such as, A2E and ATR dimer, while at the same time preserving the chemical structure of vitamin A such that participation in the visual cycle (binding to visual cycle proteins) is minimally disturbed. Because such changes to the structure of vitamin A do not interfere with normal vitamin A metabolism or function, one of the utilities of the present invention is that many potential side effects are avoided. Furthermore, because the compounds of the present invention (disclosed in more detail below) do not compete with natural retinoids for protein binding (because, e.g., they can perform the job of natural retinoids), smaller doses are needed for treatment of e.g., macular degeneration, compared to previous treatments using, e.g., visual cycle antagonists.

[0042] In the present invention, when the C₂₀ hydrogens of all-*trans*-retinoids are replaced by fluorine atoms (F₃), the formation of A2E is eliminated, as measured by monitoring the disappearance of C₂₀-F₃-all-*trans*-retinal and the absence of the corresponding fluorinated A2E by HPLC. A2E and the ATR-dimer are believed to be formed *in vivo* by a multi-step reaction sequence involving two molecules of all-*trans*-retinal, as shown in FIG. 2. In the first step, all-*trans*-retinal condenses with a biological amine to form the imine. This imine is then thought to undergo a [1,5] hydrogen shift involving a hydrogen atom at carbon C₂₀ (step 2). Subsequent reaction (step 3) with another molecule of retinal either by 1,2- or 1,4-addition followed by cyclizations (step 4) yields A2E or ATR-dimer precursors, respectively. A2E is subsequently formed after spontaneous oxidation in air, and ATR dimer, after elimination (step 4).

[0043] It has been shown that replacing certain C-H bonds with C-F bonds in retinal (*i.e.*, C₂₀-F₁₋₃-retinal) hampers the reactivity of all-*trans*-retinal, and, thus slows or eliminates the formation of A2E *in vitro*. By replacing hydrogen atoms at C₂₀ with fluorine, the [1,5] hydrogen shift step is blocked. Accordingly, C₂₀-F₁₋₃-retinal is expected to appreciably slow A2E and ATR-dimer biosynthesis.

[0044] A small change in the reaction rate of all-*trans*-retinal to form its toxic dimers is expected to translate into a large decrease in RPE lipofuscin formation over a lifetime. The methods of the present invention will slow the formation of the toxic pigments and will not slow (or will not slow significantly) visual cycle kinetics, because the regeneration of 11-*cis*-retinal does not involve the breaking of the C₂₀ hydrogen

bond. Therefore, treatment with a C₂₀-F₁₋₃-retinoid (which may be transformed into C₂₀-F₁₋₃-retinal in the body) will be particularly useful in impeding lipofuscin formation in humans who suffer from Stargardt Disease or other diseases or conditions associated with lipofuscin formation and/or macular degenerations.

[0045] C₂₀-D₁₋₃-retinoid according to the present invention will also be useful as a therapy to treat or ameliorate macular degeneration without adverse (or significantly adverse) visual effects. When C₂₀ hydrogens are replaced by deuteriums, A2E formation is about seven times slower (FIG. 3) and ATR-dimer formation is about 15 times slower (FIG. 4). This kinetic isotope effect will slow A2E and ATR-dimer formation *in vivo*. Deuterated vitamin A is widely used in humans and shows no toxicity (45, 46). Thus, a treatment using a C₂₀-D₁₋₃-retinoid should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects.

[0046] In view of the foregoing, one embodiment of the present invention is a method of retarding formation of a lipofuscin pigment in the retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of a C₂₀-D₁₋₃-retinoid and a C₂₀-F₁₋₃-retinoid. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, all-*trans*-retinoid (ATR)-dimer, and combinations thereof.

[0047] Preferably, the substituted C₂₀-retinoid is administered to the patient as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C₂₀-retinoid is administered as a unit dosage form.

[0048] In the present invention, the patient may be a mammal, preferably a human. In this embodiment, the substituted C₂₀-retinoid is a compound or combination of compounds disclosed herein, preferably compounds of Formula I, including Formulae Ic-Ie and Formula II, which are defined below.

[0049] In this embodiment, an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina will vary by patient and the particular substituted C₂₀-retinoid used. Typically, such amount will be about 0.05 to about 300 mg/day, including, e.g., 0.5-50, 1-25, and 3-10 mg/day.

[0050] Another embodiment of the present invention is method of treating or ameliorating the effects of an ophthalmologic disorder, such as, e.g. a disease characterized by an accumulation of a lipofuscin pigment in a retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinoids and C₂₀-F₁₋₃-retinoids. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

[0051] Preferably, the substituted C₂₀-retinoid is administered as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C₂₀-retinoid is administered as a unit dosage form.

[0052] In this embodiment, the disease maybe selected from the group consisting of Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy, age related macular degeneration, and Malattia Leventinese. Preferably, the disease is macular degeneration.

[0053] In this embodiment, the administration step includes replacing a component of the patient's diet that contains retinoid(s) or Vitamin A with a component that contains a substituted C₂₀-retinoid. By "replacing a component of a patient's diet" it is meant that a part of the diet that contains vitamin A or its precursors (including, but not limited to carotenoids) is replaced with a component that contains a substituted C₂₀-retinoid. Preferably, from about 1% to about 95%, including, e.g., from about 5-75%, 10-50%, or 20-30%, of the retinoid(s) in the patient's diet is replaced with a substituted C₂₀-retinoid. The replacement may be through, e.g., administering substituted C₂₀-retinoid containing foods or through treatment with compositions of the present invention, including pharmaceuticals or nutraceuticals, in lieu of consuming retinoid- or Vitamin A-containing foods that would have otherwise been consumed.

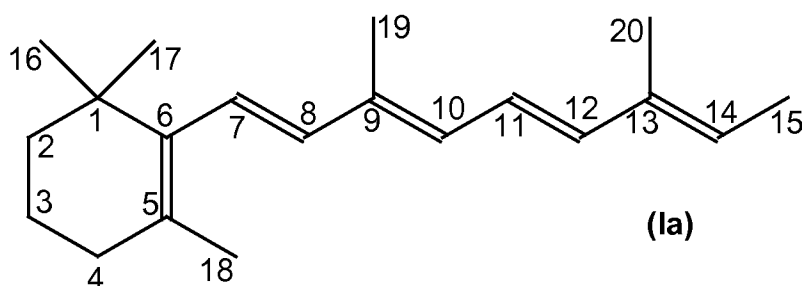
[0054] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina, which composition contains a substituted C₂₀-retinoid and a pharmaceutically acceptable carrier. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinoid and

C₂₀-F₁₋₃-retinoid. Preferably, the composition is in a unit dosage form. Preferably, the composition is a vitamin supplement or a pharmaceutical formulation.

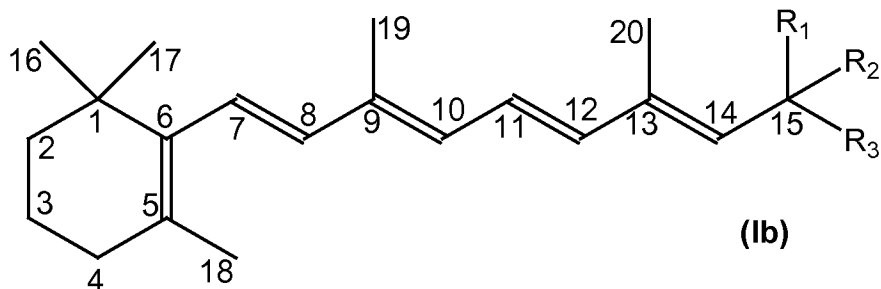
[0055] A further embodiment of the present invention is a method of retarding formation of a lipofuscin pigment selected from the group consisting of an A2E, an ATR dimer, and combinations thereof. This method comprises replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate under conditions sufficient to impede the formation of A2E, ATR dimer, or both, or an A2E and/or an ATR-dimer derivative. As used in the present invention, “conditions sufficient to impede the formation of A2E, ATR dimer, or both are well known in the art or may be determined empirically, if desired. The replacing step in this embodiment is described in more detail below.

[0056] A further embodiment of the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate under conditions sufficient to impede the formation of A2E. The replacing step in the last two embodiments may be accomplished using known method, including the methods disclosed above. For example, the substrate replacement may take place in the eye of the patient, e.g., the substrate may be administered directly to the eye via eye drops, ointment, or injection. Alternatively, the substrate may be administered systemically via, e.g., ingestion of a pill or capsule or absorption through a patch or by injection.

[0057] In the present invention, the “substituted C₂₀-retinoid” includes all retinols, retinol acetates, retinol esters, and retinoic acids as defined below as well as pharmaceutical salts thereof and metabolites thereof. For purposes of the present invention, the number scheme set forth in formula 1a for retinoids shall be used:



Thus, retinol, retinol acetate, retinol palmitate, retinoic acid, and beta-carotene have the following structures:



wherein

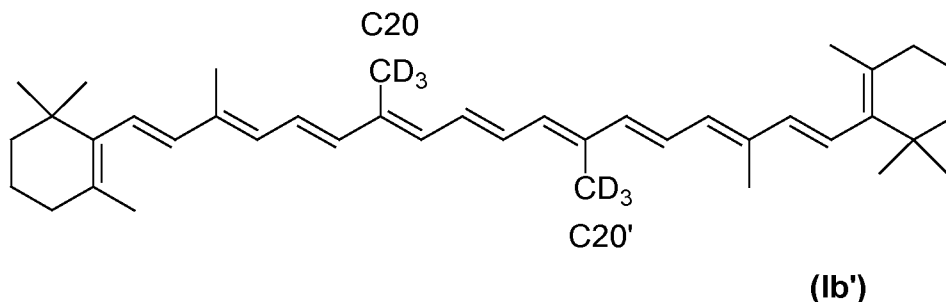
R_1 and R_2 are both H and R_3 is OH (retinol); or

R_1 and R_2 are both H and R_3 is OCOCH_3 (retinol acetate); or

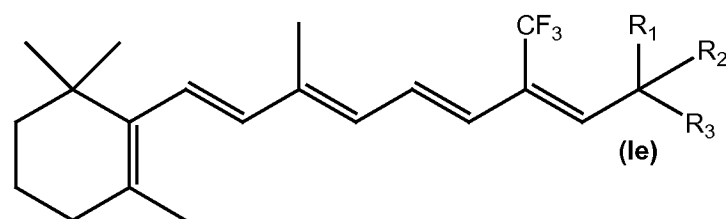
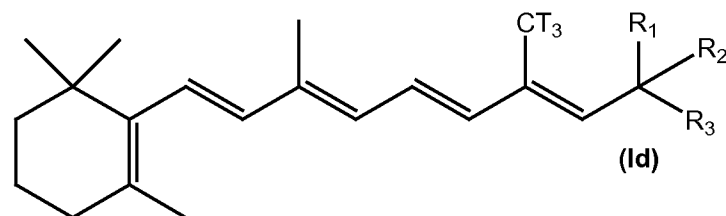
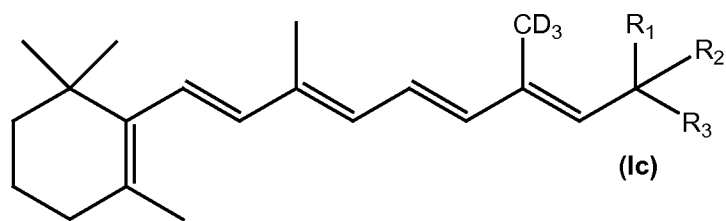
R_1 and R_2 are both H and R_3 is OCOR (retinol ester such as, e.g., retinol palmitate) or

R_1 is $=\text{O}$, R_2 is nothing and R_3 is OH (retinoic acid) or

R_1 is H, R_3 is nothing, and R_2 is $=\text{CH-R}_7$, where R_7 forms a carotenoid. In this embodiment, R_7 together with the rest of the compound forms, e.g., a beta-carotene or another pro-vitamin A carotenoid such as the deuterated beta-carotene shown in formulae Ib' below:

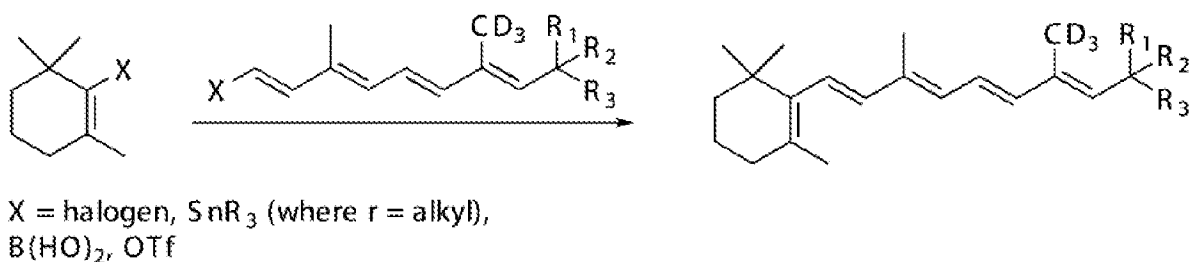
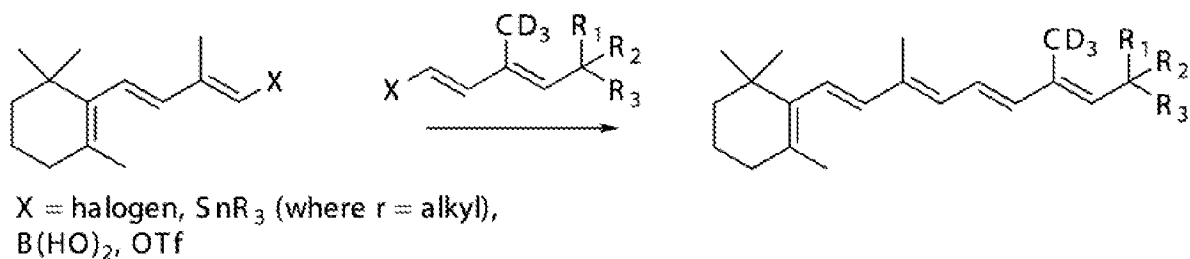
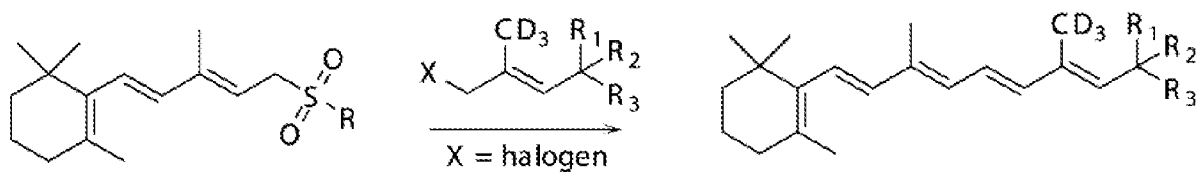
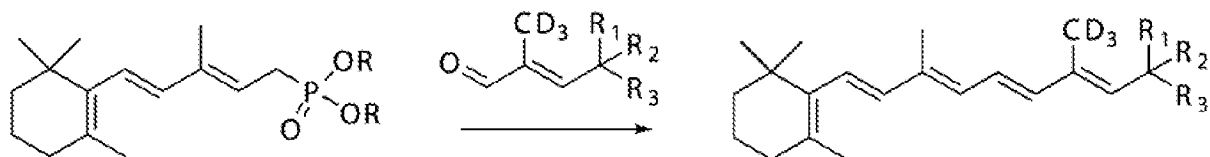
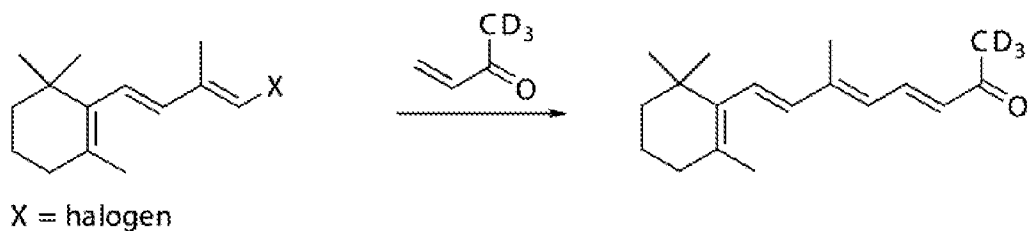


[0058] Exemplary substituted C_{20} -retinoid compounds that may be used in the compositions of the present invention include the following (compounds Ic-Ie):

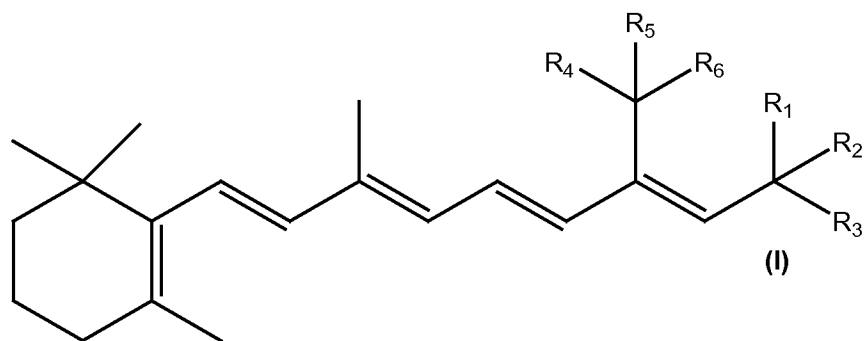


wherein R_1 , R_2 , and R_3 are as defined in Formula Ib.

[0059] Exemplary methods and reaction schemes for making substituted C20-retinoid compounds according to the present invention are set forth below:



[0060] In another embodiment, the invention is a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I:



wherein:

R_1 is oxo or H;

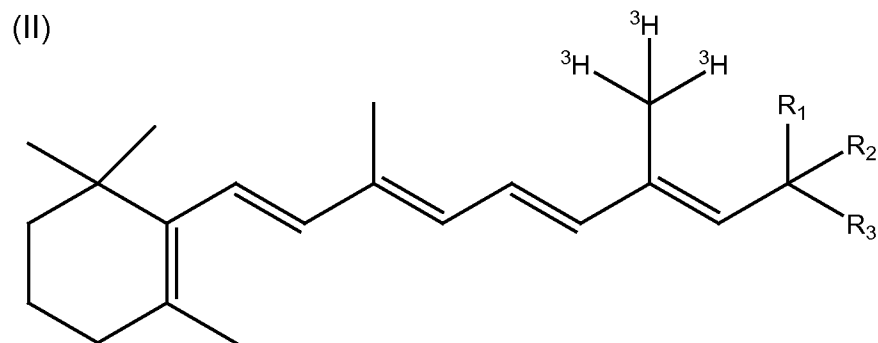
R_2 is H or nothing;

R_3 is hydroxy or oxo or $=CH-R_7$, where R_7 forms a carotenoid; and

R_4 , R_5 , and R_6 are independently selected from the group consisting of ^2H (D), ^3H (T), halogen, and C_{1-8} alkyl. Preferably, the halogen is fluorine (F).

[0061] In this embodiment, R_4 , R_5 , and R_6 may also be independently selected from H or a substituent that slows lipofuscin formation, a substituent that slows the formation of at least one of A2E or ATR dimer formation, or a substituent that slows hydrogen abstraction or migration at the C_{20} position compared to a retinoid that is not substituted at the C_{20} position, e.g. a $C_{20}-H_3$ retinoid. The present invention further contemplates any combination of the foregoing substituents at R_4 , R_5 , and R_6 .

[0062] Preferably, in the composition of the present invention the compound has the structure of formula II:



wherein:

R₁ is oxo or H;

R₂ is H or nothing; and

R₃ is hydroxy or oxo or =CH-R₇, where R₇ forms a carotenoid.

[0063] In the present invention, the compositions may further contain a supplement. Representative, non-limiting examples of a supplement according to the present invention are visual cycle antagonists, molecules that inhibit influx of a retinoid into an eye, or combinations thereof.

[0064] Exemplary, non-limiting visual cycle antagonists according to the present invention include TDH, TDT, 13-*cis*-retinoic acid, ret-NH₂, and combinations thereof. An exemplary, non-limiting visual cycle antagonist according to the present invention is fenretinide. Other visual cycle antagonists within the scope of the present invention include those disclosed in R. Rando, U.S. Application Serial No. 11/199,594 filed August 8, 2005, which application is incorporated by reference as if recited in full herein.

[0065] In the present invention, one or more additives may be included in the compositions. Exemplary, non-limiting additives that may be included in the compositions of the present invention include zinc, vitamin E, vitamin D, and combinations thereof.

[0066] The zinc, vitamin E, and vitamin D additives may be present in the compositions of the present invention in amounts that are effective to, e.g., enhance the bioavailability of the substituted C₂₀-retinoid compounds of the present invention,

including Formula I, Formulae Ic-e, and Formula II. Thus, in the present invention, zinc may be present in the composition at between about 3 to about 80 mg, preferably between about 3 to about 10 mg or between about 10 to about 80 mg. Vitamin E may be present in the composition at between about 3 to about 3,000 mg, preferably between about 3 to about 15 mg or between about 15 to about 3,000 mg. Vitamin D may be present in the composition at between about 0.005 to about 0.1 mg, preferably between about 0.005 to about 0.015 mg or between about 0.015 to about 0.1 mg.

[0067] The compositions of the present invention may also include one or more additional additives, including, for example, eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof. The use of antioxidants has been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Arch. Ophthalmol., 119: 1417-36 (2001); Sparrow, et al., J. Biol. Chem., 278:18207-13 (2003). Examples of suitable anti-oxidants that could be used in a composition of the present invention in combination with a compound of formulae I, including formulae Ic-le and II, include vitamin C, vitamin E, beta-carotene and other carotenoids, coenzyme Q, OT-551 (Othera Pharmaceuticals Inc.), 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (also known as Tempol), butylated hydroxytoluene, resveratrol, a trolox analogue (PNU-83836-E), bilberry extract, and combinations thereof.

[0068] The use of certain minerals has also been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Arch. Ophthalmol., 119: 1417-36 (2001). Thus, the present invention contemplates the optional inclusion of one or more of such minerals. Examples of suitable minerals that could be used in a composition of the present invention include copper-containing minerals, such as cupric oxide (by way of example only); zinc-containing minerals, such as zinc oxide (by way of example only); and selenium-containing compounds, and combinations thereof.

[0069] The use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Shaban & Richter, Biol. Chem., 383:537-45 (2002); Shaban, et al., Exp. Eye Res., 75:99-108 (2002). Examples of suitable negatively charged phospholipids that could optionally be used in a composition of the present invention include cardiolipin, phosphatidylglycerol,

and combinations thereof. Positively-charged and/or neutral phospholipids may also provide benefit for patients with macular degenerations and dystrophies when used in combination with a composition of the present invention.

[0070] The use of certain carotenoids has been correlated with the maintenance of photoprotection necessary in photoreceptor cells. Carotenoids are naturally-occurring yellow to red pigments of the terpenoid group that can be found in plants, algae, bacteria, and certain animals, such as birds and shellfish. Carotenoids are a large class of molecules in which more than 600 naturally occurring carotenoids have been identified. Carotenoids include hydrocarbons (carotenes) and their oxygenated, alcoholic derivatives (xanthophylls). They include actinioerythrol, astaxanthin, canthaxanthin, capsanthin, capsorubin, beta-8'-apo-carotenal (apo-carotenal), beta-12'-apo-carotenal, alpha-carotene, beta-carotene, "carotene" (a mixture of alpha- and beta-carotenes), gamma-carotenes, beta-cyrtloxanthin, lutein, lycopene, violerythrin, zeaxanthin, and esters of hydroxyl- or carboxyl-containing members thereof. Many of the carotenoids occur in nature as cis- and trans-isomeric forms, while synthetic compounds are frequently racemic mixtures.

[0071] In humans, the retina selectively accumulates mainly two carotenoids: zeaxanthin and lutein. These two carotenoids are thought to aid in protecting the retina because they are powerful antioxidants and absorb blue light. Examples of suitable carotenoids for optional use in a composition of the present invention include lutein and zeaxanthin, as well as any of the aforementioned carotenoids and combinations thereof.

[0072] Effective dosage forms, modes of administration, and dosage amounts, in addition to those disclosed above, may be determined empirically, and making such determinations is within the skill of the art. It is understood by those skilled in the art that the dosage amount will vary with the route of administration, the rate of excretion, the duration of the treatment, the identity of any other drugs being administered, the age, size, and species of mammal, e.g., human patient, and like factors well known in the arts of medicine and veterinary medicine. In general, a suitable dose of a compound according to the invention will be that amount of the compound, which is the lowest dose effective to produce the desired effect. For example, a compound of the

invention is present in the composition at a level sufficient to deliver about 0.1 to about 90 mg/day to a patient. The effective dose of a compound maybe administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

[0073] A compound of the present invention may be administered in any desired and effective manner: as pharmaceutical compositions for oral ingestion, or as an ointment or drop for local administration to the eyes, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous, topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. Further, a compound of the present invention may be administered in conjunction with other treatments. A compound or composition of the present invention maybe encapsulated or otherwise protected against gastric or other secretions, if desired.

[0074] While it is possible for a compound of the invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition) or a vitamin supplement or a nutraceutical. The pharmaceutically acceptable compositions of the invention comprise one or more compounds as an active ingredient in admixture with one or more pharmaceutically-acceptable carriers and, optionally, one or more other compounds, drugs, ingredients and/or materials. Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art. See, *e.g.*, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.).

[0075] Pharmaceutically acceptable carriers are well known in the art (*see, e.g.*, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (*e.g.*, lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (*e.g.*, dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, water, aqueous solutions (*e.g.*, saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (*e.g.*, ethyl alcohol, propyl

alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and tryglycerides), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, oils (e.g., corn, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, *etc.* Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Carriers suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

[0076] The pharmaceutical compositions or vitamin supplements or nutraceuticals of the invention may, optionally, contain additional ingredients and/or materials commonly used in such pharmaceutical compositions or vitamin supplements or nutraceuticals. These ingredients and materials are well known in the art and include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, sucrose and acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate; (10) suspending agents, such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth; (11) buffering agents; (12) excipients, such as lactose, milk sugars, polyethylene glycols, animal and vegetable fats, oils, waxes, paraffins, cocoa butter, starches, tragacanth, cellulose derivatives, polyethylene glycol, silicones, bentonites, silicic acid, talc, salicylate, zinc oxide,

aluminum hydroxide, calcium silicates, and polyamide powder; (13) inert diluents, such as water or other solvents; (14) preservatives; (15) surface-active agents; (16) dispersing agents; (17) control-release or absorption-delaying agents, such as hydroxypropylmethyl cellulose, other polymer matrices, biodegradable polymers, liposomes, microspheres, aluminum monostearate, gelatin, and waxes; (18) opacifying agents; (19) adjuvants; (20) wetting agents; (21) emulsifying and suspending agents; (22), solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; (23) propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane; (24) antioxidants; (25) agents which render the formulation isotonic with the blood of the intended recipient, such as sugars and sodium chloride; (26) thickening agents; (27) coating materials, such as lecithin; and (28) sweetening, flavoring, coloring, perfuming and preservative agents. Each such ingredient or material must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Ingredients and materials suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable ingredients and materials for a chosen dosage form and method of administration may be determined using ordinary skill in the art.

[0077] Pharmaceutical compositions or vitamin supplements or nutraceuticals suitable for oral administration may be in the form of capsules, cachets, pills, tablets, powders, granules, a solution or a suspension in an aqueous or non-aqueous liquid, an oil-in-water or water-in-oil liquid emulsion, an elixir or syrup, a pastille, a bolus, an electuary or a paste. These formulations may be prepared by methods known in the art, e.g., by means of conventional pan-coating, mixing, granulation or lyophilization processes.

[0078] Solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like) may be prepared by mixing the active ingredient(s) with one or more pharmaceutically-acceptable carriers and, optionally, one

or more fillers, extenders, binders, humectants, disintegrating agents, solution retarding agents, absorption accelerators, wetting agents, absorbents, lubricants, and/or coloring agents. Solid compositions of a similar type maybe employed as fillers in soft and hard-filled gelatin capsules using a suitable excipient. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using a suitable binder, lubricant, inert diluent, preservative, disintegrant, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine. The tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein. They may be sterilized by, for example, filtration through a bacteria-retaining filter. These compositions may also optionally contain opacifying agents and may be of a composition such that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. The active ingredient can also be in microencapsulated form.

[0079] Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. The liquid dosage forms may contain suitable inert diluents commonly used in the art. Besides inert diluents, the oral compositions may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents. Suspensions may contain suspending agents.

[0080] Pharmaceutical compositions for rectal or vaginal administration may be presented as a suppository, which maybe prepared by mixing one or more active ingredient(s) with one or more suitable nonirritating carriers which are solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound. Pharmaceutical compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such pharmaceutically-acceptable carriers as are known in the art to be appropriate.

[0081] Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, drops and inhalants. The active compound may be mixed under sterile conditions with a suitable pharmaceutically-acceptable carrier. The ointments, pastes, creams and gels may contain excipients. Powders and sprays may contain excipients and propellants.

[0082] Pharmaceutical compositions suitable for parenteral administrations comprise one or more compound in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain suitable antioxidants, buffers, solutes which render the formulation isotonic with the blood of the intended recipient, or suspending or thickening agents. Proper fluidity can be maintained, for example, by the use of coating materials, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. These compositions may also contain suitable adjuvants, such as wetting agents, emulsifying agents and dispersing agents. It may also be desirable to include isotonic agents. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption.

[0083] In some cases, in order to prolong the effect of a drug (e.g., pharmaceutical formulation or vitamin supplement or nutraceutical), it is desirable to slow its absorption from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility.

[0084] The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug may be accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms may be made by forming microencapsule matrices of the active ingredient in biodegradable polymers. Depending on the ratio of the active ingredient to polymer, and the nature of the particular polymer employed, the rate of active ingredient release can be controlled. Depot injectable formulations are also prepared by entrapping the

drug in liposomes or microemulsions which are compatible with body tissue. The injectable materials can be sterilized for example, by filtration through a bacterial-retaining filter.

[0085] The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

[0086] The following examples are provided to further illustrate the methods of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

EXAMPLES

EXAMPLE 1

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E *in vitro*

[0087] C₂₀-D₃-retinal was prepared according to the literature procedure(47) and its *in vitro* ability to form A2E as compared to all-*trans*-retinal was measured by HPLC.

[0088] FIG. 3A plots the formation of all A2E for two reaction mixtures containing either all-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal (16 mg), ethanolamine (0.5 equivalents) and acetic acid (1.2 equivalents). A typical HPLC trace is shown in FIG. 3B for the all-*trans*-retinal and C₂₀-D₃-all-*trans*-retinal reaction mixtures. The area under the curve corresponds to the amount of A2E: the larger the area the more A2E. The concentrations of A2E in the two reactions mixtures were measured about every 8 hours for 50 hours. The concentrations at each time point was plotted and the data points fit to a line for each reaction mixture. A comparison of the slopes of the two lines for the two reaction revealed that A2E formation occurred 7-times faster for all-*trans*-retinal compared to C₂₀-D₃-all-*trans*-retinal. Hydrogen deuterium exchange was not observed during the reaction with the labeled retinal, as measured by mass spectrometry of the reaction mixture after 50 hours, which clearly showed the presence

of the tri-deuterated retinal, tri-deuterated retinal hydroxylamine Schiff base and tetra-deuterated A2E.

EXAMPLE 2

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of ATR-dimer *in vitro*

[0089] C₂₀-D₃-all-*trans*-retinal was prepared as described in Example 1 and its *in vitro* ability to form ATR-dimer as compared to all-*trans*-retinal was measured by HPLC. All-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal (10 mg) and proline (2 equivalents) in ethanol were mixed, and the reaction was followed by HPLC, the results of which are depicted in FIG. 4A. A typical HPLC trace is shown in FIG. 4B for the all-*trans*-retinal and C₂₀-D₃-all-*trans*-retinal reaction mixtures at the same time points. The concentrations of ATR-dimer in the two reaction mixtures were measured about every 15 min for 3 hours. The concentration at each time point was plotted and the data points fit to a line for each reaction mixture. A comparison of the slopes of the two lines showed that C₂₀-D₃-all-*trans*-retinal formed ATR-dimer 15 times slower than the unlabeled retinal as shown in FIG. 4C.

EXAMPLE 3

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E-lipofuscin in CD-1 (ICR) mice

[0090] C₂₀-D₃-all-*trans*-retinal was administered to mice in order to measure its ability to form A2E in the eye compared to all-*trans*-retinal. Nine, 8-week old, CD-1 (ICR) mice (from Charles River, Wilmington, MA) were divided up into two groups of five and administered 1.5 mg of ether all-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal by intraperitoneal injection (IP) injection in a 10% solution of Tween-20 in saline bi-weekly for 6 weeks. At the end of this six-week period, each mouse was given a total of 60,000 I.U. (18 mg) or about 28-times the original amount of vitamin A in the mouse's body. Massive dosing with C₂₀-D₃-all-*trans*-retinal quickly replaces normal vitamin A stores with the C₂₀-D₃-analog. And, the injected retinal rapidly accumulates in the eye

(rod outer segments), where at high enough concentrations it will react to form lipofuscin pigments. This is similar to the accumulation of *all-trans*-retinal in the ABCR^{-/-} mice and in patients with Stargardt's disease.

[0091] At the end of the six week period, the eyes were dissected, the retinas and eyecups pooled into groups of 4 or 5, and homogenated with 50 μ L ethanol. The homogenate was centrifuged at 13,000 rpm for 5 minutes and 40 μ L of the supernatant was drawn off and analyzed for A2E-lipofuscin by HPLC. Retinol and retinol esters were analyzed at 325 nm and A2E-lipofuscin was measured at 445 nm. Mice administered C₂₀-D₃-*all-trans*-retinal (n = 5) had 68% less A2E-lipofuscin as compared to mice administered *all-trans*-retinal (n = 4). Both groups of mice had roughly the same concentrations of retinol and retinol esters.

EXAMPLE 4

Replacing the C₂₀ hydrogens of *all-trans*-retinal with deuteriums reduces the formation of A2E in ABCR^{-/-} mice

[0092] C₂₀-D₃-*all-trans*-retinol acetate was prepared according to the literature procedure(47) and was administered to ABCR^{-/-} mice (48, 49) in order to measure its ability to lead to lipofuscin compared to that of *all-trans*-retinol acetate. Eight 2-month old, ABCR^{-/-} mice raised on a standard rodent diet were then fed a diet containing 20,000 I.U./kg of either C₂₀-D₃-*all-trans*-retinol acetate or *all-trans*-retinol acetate for 3 months. On this diet each mouse roughly received the daily-recommended amount of vitamin A or the same amount of the C₂₀-D₃-vitamin A drug, which was less than about 1mg/kg/day.

[0093] At the end of the 5 month period, the eyes were dissected, eyecups pooled into groups of six and homogenated with 80 μ L ethanol. The homogenate was centrifuged at 13000 rpm for 5 min and 30 μ L of the supernatant was drawn off and analyzed for A2E-lipofuscin by HPLC. A2E-lipofuscin was measured at 445 nm. Mice on the 3-month diet containing C₂₀-D₃-*all-trans*-retinol acetate had 44-58% less A2E-lipofuscin as compared to mice on a diet of *all-trans*-retinol acetate. This percentage of A2E reduction is on the same order of magnitude observed in similar studies in ABCR^{-/-} mice with the visual cycle antagonist TDH, TDT, Ret-NH₂, 13-*cis*-retinoic, acid and

fenretinide. However, in this example A2E reduction is achieved with doses of C₂₀-D₃-all-*trans*-retinol acetate that are 11- to 40-times less.

EXAMPLE 5

ABCR^{-/-} mice raised exclusively on a C₂₀-D₃-all-*trans*-retinol acetate diet show undetectable amounts of extractable lipofuscin pigments and reduced lipofuscin deposits.

[0094] As in Example 4, two groups of four ABCR^{-/-} mice were raised either on diets containing C₂₀-D₃-all-*trans*-retinol acetate or all-*trans*-retinol acetate. However, in this example the mice were offspring of mothers on the same diet, and thus were raised only on their respective vitamin A analogs. At 5.5-6 months of age the mice were sacrificed and the eyecups were analyzed for lipofuscin pigments as described in Example 4. The results are shown FIG 5. While both mice contained the same amount of eye retinol and retinol esters (FIG 5GB) lipofuscin pigments were undetectable in mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet (FIG 5BA) but were detectable in mice raised on the all-*trans*-retinol acetate diet (FIG 5A).

[0095] In order to measure the amount lipofuscin granules in the eyes of the above mice on a normal diet vs. the diet containing C₂₀D₃-all-*trans*-retinol acetate, eyecups from both groups of mice (2 from each group) were evaluated by electron microscopy. Mice on the C₂₀-D₃-all-*trans*-retinol acetate diet had less electron dense lipofuscin deposits compared to mice on a diet of all-*trans*-retinol acetate as shown in FIG. 6.

EXAMPLE 6

C₂₀-D₃-all-*trans*-retinal slows A2E-lipofuscin formation as well as Fenretinide and/or TDH in wild-type rats.

[0096] 45-50 day old, female, CD IGS rats (Charles River, Wilmington, MA) were divided up into four groups of three. Three of these groups were administered all-*trans*-retinal and the one group was given C₂₀-D₃-all-*trans*-retinal (IP injection in a 10%

solution of Tween-20 in saline) at 3 mg, bi- or tri-weekly for 8 weeks (20, 3 mg injections total). Thus, at the end of the 8-week period the animals received roughly 20 times their original stores of vitamin A, as retinal or C₂₀-D₃-all-*trans*-retinal. Massive dosing with C₂₀-D₃-all-*trans*-retinal quickly replaces normal vitamin A stores with the C₂₀-D₃-analog. Of the three groups administered all-*trans*-retinal, one group was given Fenretinide (50) and another TDH (23), at doses of roughly 1.5 mg/day/animal (both supplied in the drinking water emulsified with 1g/L of Nu-rice (RIBUS, Inc, St. Louis, MO)).

[0097] At the end of the 8 weeks, RPE, A2E-lipofuscin was evaluated in each of the four groups by HPLC as described in Example 3 and in FIG. 7. A2E-lipofuscin pigments were greatest in the animals receiving all-*trans*-retinal (the control group). While animals receiving C₂₀D₃-all-*trans*-retinal had 35% less A2E-lipofuscin than animals receiving all-*trans*-retinal. Likewise, animals receiving Fenretinide or TDH had 49% and 31% less A2E-lipofuscin compared to animals administered only all-*trans*-retinal.

CITED DOCUMENTS

[0098] The following documents, which have been cited above, are incorporated by reference as if recited in full herein:

1. Friedman, D.S.; O'Colmain, B.J.; Muñoz, B.; Tomany, S.C.; McCarty, C.; DeJong, P.T.V.M.; Nemesure, B.; Mitchell, P.; Kempen, J.; Congdon, N. Prevalence of age related macular degeneration in the United States. Arch. Ophthalmol. **2004**, 122, 564–572.
2. Rattner, A.; Nathans, J. Macular degeneration: recent advances and therapeutic opportunities. Nat. Rev. Neurosci. **2006**, 7, 860-872.
3. Jong, P.T.V.M.d. Age-related macular degeneration N. Engl J Med **2006**, 355, 478-485.
4. Fine, S.L.; Berger, J.W.; Maguire, M.G.; Ho, A.C. Age-related macular degeneration N Engl J Med **2007**, 342, 483-492.
5. Jarc-Vidmar, M.; Kraut, A.; Hawlina, M. Fundus autofluorescence imaging in Best's vitelliform dystrophy. Klinische Monatsblätter Fur Augenheilkunde **2003**, 220, 861-867.

6. Capon, M.; Marshall, J.; Krafft, J.; Alexander, R.; Hiscott, P.; Bird, A. Sorsby's fundus dystrophy: a light and electron microscopic study. *Ophthalmology* **1989**, *95*, 1969-1977.
7. Chong, N.; Alexander, R.; Gin, T.; Bird, A.; Luthert, P. TIMP-3 collagen, and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy *Invest Ophthalmol Vis Sci* **2000**, *41*, 898-902.
8. Alikmets, R.; Singh, N.; Sun, H.; Shroyer, N.F.; Hutchinson, A.; Chidambaram, A.; Gerrard, B.; Baird, L.; Stauffer, D.; Peiffer, A.; Rattner, A.; Smallwood, P.; Li, Y.; Anderson, K.L.; Lewis, R.A.; Nathans, J.; Leppert, M.; Dean, M.; R., L.J. A Photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat. Genet.* **1997**, *15*, 236-246.
9. Haralampus-Grynaviski, N.M.; Lamb, L.E.; Clancy, C.M.R.; Skumatz, C.; Burke, J.M.; Sarna, T.; Simon, J.D. Spectroscopic and morphological studies of human retinal lipofuscin granules. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*.
10. Marmorstein, A.D.; Marmorstein, L.Y.; Sakaguchi, H.; Hollyfield, J.G. Spectral Profiling of Autofluorescence Associated with Lipofuscin, Bruch's Membrane, and Sub-RPE Deposits in Normal and AMD Eyes. *Invest. Ophthalmol. Vis. Sci.* **2002**, *43*, 2435-2441.
11. Smith, R.T.; Chan, J.K.; Busuoic, M.; Sivagnanavel, V.; Bird, A.C.; Chong, N.V. Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration. *Invest Ophthalmol Vis Sci.* **2006**, *47*, 5495-5504.
12. Sakai, N.; Decatur, J.; Nakanishi, K.; Eldred, G.E. A2-E": An Unprecedented Pyridinium Bisretinoid. *J. Am. Chem. Soc.* **1996**, *118*, 1559-1560.
13. Fishkin, N.E.; Sparrow, J.R.; Allikements, R.; Nakanishi, K. Isolation and characterization of retinal pigment epithelial cell fluorophore: An all-*trans*-retinal dimer conjugate. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *100*, 7091-7096.
14. Sparrow, J.S.; Nakanishi, K.; Parish, C.A. The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells. *Invest. Ophthalmol. Vis. Sci.* **2000**, *41*, 1981-1989.

15. Suter, M.; Reme, C.E.; Christian Grimm; Wenzel, A.; Jaattela, M.; Esser, P.; Kociok, N.; Leist, M.; Richter, C. Age-related Macular Degeneration: The lipofuscin component n-retinyl-n-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells. *J. Bio. Chem.* **2000**, 275, 39625-39630.
16. Finnemann, S.; Leung, L.W.; Rodriguez-Boulan, E. The lipofuscin component A2E selectively inhibits phagolysosomal degradation of photoreceptor phospholipid by the retinal pigment epithelium. *Proc Natl Acad Sci U S A.* **2002**, 99, 3842-3847.
17. De, S.; Sakmar, T.P. Interaction of A2E with model membranes. Implications to the pathogenesis of age-related macular degeneration. *J Gen Physiol.* **2002**, 120, 147-157.
18. Bergmann, M.; Schütt, F.; Holz, F.G.; Kopitz, J. Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration. *FASEB J.* **2004**, 18, 562-564.
19. Radu, R.A.; Mata, N.L.; Bagla, A.; Travis, G.H. Light exposure stimulates formation of A2E oxiranes in a mouse model of Stargardt's macular degeneration. *Proc Natl Acad Sci U S A.* **2004**, 101, 5928–5933.
20. Ben-Shabat, S.; Parish, C.A.; Hashimoto, M.; Liu, J.; Nakanishi, K.; Sparrow, J.R. Fluorescent pigments of the retinal pigment epithelium and age-related macular degeneration. *Bioorg Med Chem Lett.* **2001**, 11, 1533-1540.
21. Schutt, F.; Bergmann, M.; Holz, F.G.; Dithmar, S.; Volcker, H.-E.; Kopitz, J. Accumulation of A2-E in mitochondrial membranes of cultured RPE cells. **2007**, 245, 391-398.
22. Schutt, F.; Davies, S.; Kopitz, J.; Holz, F.G.; Boulton, M.E. Photodamage to human RPE cells by A2-E, a retinoid component of lipofuscin. **41** **2000**, 2303-2308.
23. Maiti, P.; Kong, J.; Kim, S.A.; Sparrow, J.S.; Allikmets, R.; Rando, R.R. Small molecule RPE65 antagonists limit the visual cycle and prevent lipofuscin formation. *Biochemistry* **2006**, 45, 852-860.

24. Radu, R.A.; Mata, N.L.; Nusinowitz, S.; Liu, X.; Sieving, P.A.; Travis, G.H. Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargardt macular degeneration. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 4742-4747.
25. Golczak, M.; Maeda, A.; Bereta, G.; Maeda, T.; Kiser, P.D.; Hunzelmann, S.; Lintig, J.V.; Blaner, W.S.; Palczewski, K. Metabolic Basis of Visual Cycle Inhibition by Retinoid and Nonretinoid Compounds in the Vertebrate Retina. *J. Biol. Chem.* **2008**, *283*, 9543-9554.
26. Katz, M.L.; Drea, C.M.; Robison, W.G. Relationship between dietary retinol and lipofuscin in the retinal pigment epithelium. *Mech. Age. Dev.* **1986**, *35*, 291-305.
27. Radu, R.A.; Han, Y.; Bui, T.V.; Nusinowitz, S.; Bok, D.; Lichter, J.; Widder, K.; Travis, G.H.; Mata, N.L. Reductions in serum vitamin A arrest Accumulation of toxic retinal fluorophores: A potential therapy for treatment of lipofuscin based retinal diseases. *Invest Ophthalmol Vis Sci* **2005**, *46*, 4393-4401.
28. Wassell, J.; Boulton, M. A role for vitamin A in the formation of ocular lipofuscin. *Br J Ophthalmol* **1997**, *81*, 911-918.
29. Owsley, C.; Jackson, G.R. Aging and scotopic dysfunction. *Perception* **2000**, *29*, Abstract Supplement.
30. Owsley, C.; Jackson, G.R.; White, M.; Feist, R.; Edwards, D. Delays in rod-mediated dark adaptation in early age-related maculopathy. *Ophthalmology* **2001**, *108*, 1196-1202.
31. Baehr, W.; Wub, S.M.; Birdc, A.C.; Palczewski, K. The retinoid cycle and retina disease. *Vision Research* **2003**, *43*, 2957-2958.
32. Maeda, A.; Maeda, T.; Golczak, M.; Imanishi, Y.; Leahy, P.; Kubota, R.; Palczewski, K. Effects of potent inhibitors of the retinoid cycle on visual function and photoreceptor protection from light damage in mice. *Mol. Pharmacol.* **2006**, *70*, 1220-1229.
33. Hong, W.K.; Itri, L.M. *Retinoids and human cancer*, Second Edition Ed.; Raven Press Ltd: New York, 1994.
34. Gudas, L.J.; Sporn, M.B.; Roberts, A.B. *Cellular biology and biochemistry of retinoids*; Raven Press Ltd.: New York, 1994; 443-520 pp.

35. Nason-Burchenal, K.; Dmitrovsky, E. *The retinoids: cancer therapy and prevention mechanisms*: Berlin, 1999; 301-322 pp.
36. Dragnev, K.H.; Rigasa, J.R.; Dmitrovsky, E. The Retinoids and Cancer Prevention Mechanisms *Oncologist* **2003**, 5, 361-368.
37. Freemantle, S.J.; Spinella, M.J.; Dmitrovsky, E. Retinoids in cancer therapy and chemoprevention: promise meets resistance. *Oncogene* **2003**, 22, 7305–7315.
38. Soriatan, RXlist.com, <http://www.rxlist.com/cgi/generic/acitretin.htm#>, accessed Sept. 02, 2008. 2008.
39. Targretin, RXlist.com <http://www.rxlist.com/cgi/generic/bexarotene.htm>, accessed Sept. 02 2008.
40. Acutane, RXlist.com, <http://www.rxlist.com/cgi/generic/isotret.htm>, accessed Sept. 02 2008.
41. Camerini, T.; Mariani, L.; Palo, G.D.; Marubini, E.; Mauro, M.G.D.; Decens, A.; Costa, A.; Veronesi, U. Safety of the Synthetic Retinoid Fenretinide: Long-Term Results From a Controlled Clinical Trial for the Prevention of Contralateral Breast Cancer. *J. Clin. Oncol.* **2001**, 19, 1664-1670.
42. Puduvalli, V.K.; Yung, W.K.A.; Hess, K.R.; Kuhn, J.G.; Groves, M.D.; Levin, V.A.; Zwiebel, J.; Chang, S.M.; Cloughesy, T.F.; Junck, L.; Wen, P.; Lieberman, F.; Conrad, C.A.; Gilbert, M.R.; Meyers, C.A.; Liu, V.; Mehta, M.P.; Nicholas, M.K.; Prados, M. Phase II Study of Fenretinide (NSC 374551) in Adults With Recurrent Malignant Gliomas: A North American Brain Tumor Consortium Study. *J. Clin. Oncol.* **2004**, 22, 4282-4289.
43. Villablanca, J.G.; Khan, A.A.; Avramis, V.I.; Seeger, R.C.; Matthay, K.K.; Ramsay, N.K.; Reynolds, C.P. Phase I trial of 13-cis-retinoic acid in children with neuroblastoma following bone marrow transplantation. *J Clin Oncol.* **1995**, 13, 849-901.
44. Chemotherapy drugs, Isorettinoin, <http://www.chemocare.com/bio/isotretinoin.asp>, accessed September 8 2008.
45. Haskell, M.; Mazumder, R.M.; Peerson, J.M.; Jones, A.D.; Wahed, M.A.; Mahalanabis, D.; Brown, K.H. Use of deuterated-retinol-dilution technique to

- assess total body vitamin A stores of adult volunteers consuming different amounts of vitamin A1, 2, 3. *Amer. J. of Clinical Nutrition* **1999**, 70, 874-880.
46. Bausch, J.; Rietz, P. Method for the assessment of vitamin A liver stores. *Acta Vitaminol Enzymol* **1977**, 31, 99-112.
 47. Pardoen, J.A.; Mulder, P.P.J.; Van den Berg, E.M.M.; Lugtenburg, J. Synthesis of 8-, 9-, 12-, and 13-mono-¹³C-retinal. *Canadian Journal of Chemistry* **1985**, 63, 1431-1435.
 48. Weng, J.; Mata, N.L.; Azarian, S.M.; Tzekov, R.T.; Birch, D.G.; Travis, G.H. Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in abcr knockout mice. *Cell* **1999**, 9, 13-23.
 49. Kim, S.; Fishkin, N.; Kong, J.; Nakanishi, K.; Allikmets, R.; Sparrow, J.R. Rpe65 Leu450Met variant is associated with reduced levels of the retinal pigment epithelium lipofuscin fluorophores A2E and iso-A2E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 11668-11672.
 50. Soo-Jong; Kwon, Y.-J.; Han, H.-S.; Park, S.-H.; Park, M.-S.; Rho, Y.-S.; Sin, H.-S. Synthesis and Biological Activity of Novel Retinamide and Retinoate Derivatives. *Chemical & Pharmaceutical Bulletin* **2004**, 52, 501-506.

[0099] The scope of the present invention is not limited by the description, examples, and suggested uses herein and modifications can be made without departing from the spirit of the invention. Thus, it is intended that the present invention cover modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

GOVERNMENT FUNDING

[0001] This invention was made with government support under Grant EY T32 013933 awarded by the National Eye Institute of the National Institutes of Health. The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] The present application is a divisional of U.S. Patent Application Serial No. 12/733,631, which is a U.S. National Stage Application of International Application No. PCT/2008/010676, which was filed on September 12, 2008, and claims the benefit of U.S. provisional patent application no. 60/993,379, filed 12 September 2007, the disclosures of each of which are incorporated by reference as if recited in full herein.

FIELD OF THE INVENTION

[0003] The present invention relates, inter alia, to compounds, compositions, and methods to slow lipofuscin formation/accumulation in order to treat or ameliorate an ophthalmologic disorder, such as, e.g., macular degeneration, without, or with reduced, adverse visual effects. More particularly, the present invention relates to compounds and compositions that may be used to treat or ameliorate an ophthalmologic disorder, such as, e.g., macular degeneration, by slowing or limiting the accumulation of age pigments or lipofuscin in the retinal pigment epithelium ("RPE") cells of the retina. The present invention also relates to methods of treating or ameliorating an ophthalmologic disorder, such as, e.g., macular degeneration, in a mammal by administering to a mammal in need of such treatment an effective amount of the compounds and/or compositions disclosed herein.

BACKGROUND OF THE INVENTION

[0004] The macula is located at the back of the eye in the center of the retina. When the millions of cells in this light-sensitive, multilayer tissue deteriorate, central vision is lost along with the ability to perform tasks such as reading, writing, driving, and

seeing color. This “macular degeneration” principally affects the elderly and has a prevalence of about 3% in populations between 75-79 years of age and about 12% for populations over 80 years of age.(1) In younger populations, macular degeneration is found in individuals with genetic disorders, such as Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy and Malattia Leventinese (Dojne Honeycomb or Dominant Radial Drusen). Stargardt Disease is the most common form of inherited juvenile macular degeneration, affecting about 1 in 10,000 children.

[0005] There are no therapies currently available for genetic or dry (non-neovascular) age related macular degeneration. Vitamin supplements such as antioxidants, and diet changes, such as low fat diets, have been shown to slow disease progression in some clinical studies. However, for the majority of patients, diagnosis is followed by the progressive loss of central vision.(2-4)

[0006] The above listed macular dystrophies are all marked by the accumulation of lipofuscin, fluorescent deposits, in the retinal pigment epithelium (RPE) cell layer (5-11). The only compounds that have been characterized to date from RPE lipofuscin, A2E (N-retinylidene-N-retinylethanolamine) and ATR-dimer (all-*trans*-retinal dimer), are derived from reactions of all-*trans*-retinal, an isomer of 11-*cis*-retinal, the chromophore of the visual pigments (12, 13). These toxic retinal dimers have been shown to cause RPE cell death, which is thought to lead to photoreceptor cell degeneration and vision loss (2, 14-22). Slowing the visual cycle using RPE 65 antagonists (23-25) or retarding the delivery of vitamin A (retinol) to the RPE by, *e.g.*, limiting dietary intake of vitamin A (26) or blocking serum retinol binding proteins (27) have been shown to impede or abolish RPE lipofuscin formation in animal models. Conversely, increasing the amount of all-*trans*-retinal in outer segments, such as occurs with the mutations in *abcr*⁺ (responsible for recessive Stargardt disease), leads to the rapid accumulation of lipofuscin pigments (8).

[0007] The above cited evidence leads to the conclusion that lipofuscin and/or A2E and ATR-dimer in RPE cells may reach levels that contribute to a decline in cell function followed by vision loss and that vitamin A plays an important role in ocular lipofuscin formation. (28)

[0008] Several vitamin A analogs have been shown to limit lipofuscin formation in a mouse model by slowing down the visual cycle. The ABCR^{-/-} mouse model has been used to test approaches to limit RPE lipofuscin formation. Mice lacking the ABCR (also known as ABCA4) gene encoding a photoreceptor-specific adenosine triphosphate (ATP)-binding cassette transporter, lack the ability to properly shuttle vitamin A (in the form of retinal) in the eye. ABCR^{-/-} mice were developed as an animal model of human recessive Stargardt's Disease (8). As in humans with recessive Stargardt's disease, ABCR^{-/-} mice accumulate large lipofuscin deposits in RPE cells of their eyes, as shown in FIG. 1, and eventually experience delayed dark adaptation. Lipofuscin accumulation and vision loss observed in this mouse model is also thought to be relevant to age-related macular degeneration (AMD) and other macular dystrophies.

[0009] In attempts to slow down the visual cycle, visual cycle enzymes have been targeted. In such approaches, small molecules have been proposed as antagonists to visual cycle enzymes. In this methodology, the drug (often a vitamin A derivative) binds to visual cycle proteins, which blocks participation by the proteins in the visual cycle, and slows the visual cycle. Another approach to slowing the visual cycle includes impeding the delivery of vitamin A from the blood to the eye.

[0010] Drug candidates for inhibiting lipofuscin formation by slowing down the visual cycle have been evaluated by their ability to cause delayed dark adaptation (a side effect of an impaired visual cycle) and their ability to impede the age related accumulation of eye lipofuscin as measured by the concentration of A2E and other byproducts of the visual cycle, e.g., ATR-dimer. Examples of such drug candidates and their corresponding mechanisms of action to slow the visual cycle are summarized below:

[0011] 13 *cis*-retinoic acid (Acutane or isotretinoin) is thought to inhibit the enzymes 11-*cis*-retinol dehydrogenase and RPE65 involved in the visual cycle.(19, 24) When administered, 13 *cis*-retinoic acid has been shown to cause delayed dark adaptation. When 3-month-old ABCR knockout mice (n=3) were administered 13-*cis*-retinoic acid at 40 mg/kg/day for one month, the mice showed a decrease in A2E formation by about 40-50% compared to control ABCR knockout mice (n=3).(24) Furthermore, when 2-month-old ABCR knockout mice were administered 13-*cis*-retinoic

acid at 20 mg/kg/day for two months, the mice also showed a decrease in lipofuscin formation in the RPE cell layer as judged by electron microscopy.

[0012] (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one (TDT) is thought to inhibit RPE65.(23) When TDT is administered to mice, delayed dark adaptation is observed. When 2-month-old ABCR knockout mice (n=2) were administered TDT at 50 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50-85% compared to control ABCR knockout mice (n=2).(23)

[0013] (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine (TDH) is also thought to inhibit RPE65 and when given to mice, causes delayed dark adaptation.(23) When 2-month-old ABCR knockout mice (n=2) were administered TDH at 50 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50% compared to control ABCR knockout mice (n=2).(23)

[0014] All-*trans*-retinylamine (Ret-NH₂) is thought to inhibit RPE65 and when administered to mice results in severe delayed dark adaptation. When 1-month-old ABCA4 knockout mice were given Ret-NH₂ at 40 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50% compared to control ABCA4 knockout mice.(25)

[0015] N-(4-hydroxyphenyl) retinamide (Fenretinide) slows the influx of retinol into the eyes by reducing levels of vitamin A bound to serum retinol-binding protein. Thus, treatment with Fenretinide lowers the levels of vitamin A in the eye which leads to delayed dark adaptation. When 2-month-old ABCA4 knockout mice (n=3) were administered Fenretinide at 20 mg/kg/day for one month, they showed a decrease in A2E formation by about 40-50% compared to control ABCA4 knockout mice (n=3).(27)

[0016] Thus, recently proposed therapeutic approaches to limit lipofuscin formation are based upon slowing the visual cycle (1, 10, 11, 12). There are, however, disadvantages to slowing the visual cycle as a means to impede lipofuscin formation in order to prevent, e.g., macular degeneration. Four of these disadvantages are detailed below.

[0017] 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. Poor night vision (Scotopic dysfunction) is already a functional marker of early age-related maculopathy

(ARM), and has been linked to the occurrence of falls and vehicle collisions.(29, 30) A further slowing down of the visual cycle is expected to make night vision worse in patients who already suffer from poor night vision.

[0018] Second, in order to sufficiently impede lipofuscin formation, one would have to slow down the visual cycle for a prolonged period of time. But, long-term slowing of the visual cycle leads to photoreceptor cell death and loss of vision.(31, 32) In fact, impairment of the visual cycle is the cause of various retinal diseases such as Stargardt's disease, retinitis pigmentosa, Lebers Congenital Amaurosis, Fundus Albipunctatus, age-related macular degeneration and Congenital Stationary Night Blindness.

[0019] Third, the above methodology often uses vitamin A analogs to impede proteins involved in vitamin A processing in the eye. However, vitamin A analogs of diverse structures, pharmacological profiles, receptor affinities, and biologic activities have been shown to be toxic. Indeed, numerous vitamin A analogs have been shown in experimental animal models, cellular models, epidemiological data and clinical trials to inhibit or retard various biological functions such as, for example, bone growth, reproduction, cell division, cell differentiation and regulation of the immune system.(33-37). Thus, inhibiting vitamin A processing in the eye is also expected to retard some of these basic bodily functions, which may lead to significant adverse side effects.

[0020] For example, vitamin A analogs that are currently used to treat certain cancers and/or psoriasis such as, e.g., Bexarotene (Targretin), Etretinate (Tegison) Acitretin (Soriatane), Fenretinide (*N*-(4-hydroxyphenyl) retinamide or 4-HPR) and 13 *cis*-retinoic acid (Accutane or isotretinoin) have side effects, which include, e.g., dry nose, nosebleeds, chapped lips, mouth sores, increased thirst, sore tongue, bleeding gums, dry mouth, cold sores, dry or irritated eyes, dry skin, peeling or scaly skin, hair loss, easy bruising, muscle aches, nausea, stomach upset, cough or swelling of the hands or feet, vision problems, chest pain, tightness in the chest, abnormal pulse, dizziness, vomiting, severe headache, and yellowing of the eyes/skin (jaundice).(38-40)

[0021] Fourth, in animal models, candidate drugs for limiting lipofuscin formation have been shown to be effective only in relatively large doses. For example, studies in mouse models typically use doses around 11-40 mg/kg/day. But, current vitamin A

analogs are typically used in the clinic at doses of 1-3 mg/kg/day to minimize side effects. Larger dosing regimes will lead to increased side effects.

[0022] For example, Fenretinide (*N*-(4-hydroxyphenyl) retinamide or 4-HPR) is currently used to treat cancer and clinical trials are in progress for AMD. The most common adverse effects reported among 1,432 patients who underwent treatment with this drug at a dosage of 200 mg/day for a five year period were: diminished dark adaptation, cumulative incidence (16%) and dermatologic disorders (16%). Less common effects were gastrointestinal symptoms (8%) and disorders of the ocular surface (8%).(41) At this relatively low dose a delay in dark adaptation, an assessment of the effectiveness of a drug to impede lipofuscin formation, was only observed in 16% of patients. In another study when patients were administered larger oral doses of 600 or 900 mg/m² bid in 6-week cycles, mild to moderate adverse effects were reported in 43 (95%) of the 45 patients that were possibly linked to Fenretinide. These side effects included: fatigue, headache, skin changes (dry skin, pruritus, and rash) and digestive tract symptoms (abdominal pain, cramping, diarrhea, stomatitis, and xerostomia). Grade 2 toxicities reported as possibly linked to Fenretinide treatment included seizures and confusion.(42)

[0023] A patient with an anaplastic astrocytoma who had been receiving treatment with Fenretinide at the 600 mg/m² bid dose for one cycle presented with headaches, nausea, and vomiting, and was found to have a small intracranial bleed in the region of the basal ganglia. He recovered without deficits and continued treatment without further events. Another patient, who was also undergoing treatment at the 600 mg/m² bid dosage and was receiving oral anticoagulation with warfarin for deep venous thrombosis, died after developing an uncontrollable nasal bleed (international normalized ratio > 6.0). Of the four patients treated at the 900 mg/m² bid dose, one had grade 3 vomiting, grade 2 speech impairment, and grade 1 memory impairment, which improved without residual symptoms.(42)

[0024] A typical dose of 13 *cis*-retinoic acid (Accutane or isotretinoin) for treatment of acne is 0.5 to 1 mg/kg/day for children and 2.0 mg/kg/day for adults for fourteen days in a row, followed by a 14-day break. This twenty-eight day course is usually repeated five more times.(40) These doses are about 10 to 80 times less than

what was used in mice to impede A2E formation.(24) For larger doses of 13 *cis*-retinoic acid used to treat cancer, side effects occurring in more than 30% of users included headache, fever, dry skin, dry mucous membranes (mouth, nose), bone pain, nausea and vomiting, rash, mouth sores, itching, sweating, and eyesight changes.(43, 44)

[0025] Side effects occurring in 10-29% of users of 13 *cis*-retinoic acid include back pain, muscle and joint pain, allergic reaction, abdominal pain, poor appetite, dizziness, drowsiness, insomnia, anxiety, numbness and tingling of hands and feet, weakness, depression, hair loss (thinning), dry eyes, sensitivity to light (see eye problems), decreased night vision, which may persist after treatment is stopped, feet or ankle swelling, and low blood counts.(44) In addition, it has been observed that white and red blood cells and platelets may temporarily decrease, which may put a patient at increased risk for infection, anemia and/or bleeding. Side effects also include abnormal blood tests: increased triglyceride, cholesterol and/or blood sugar levels.

[0026] The above disadvantages make slowing of the visual cycle a difficult methodology to adapt alone for the clinical treatment of ophthalmologic disorders, e.g., macular degeneration.

SUMMARY OF THE INVENTION

[0027] Accordingly, it would be advantageous to provide treatments for ophthalmologic disorders, e.g., macular degeneration, that do not have, or limit one or more of, the side effects summarized above. In particular, it would be advantageous to provide compounds, compositions, and methods for impeding or halting the accumulation of lipofuscin or age pigments in the RPE cells of the retina without slowing, or slowing minimally, the visual cycle.

[0028] In this regard, one embodiment of the present invention is a method of retarding formation of a lipofuscin pigment in the retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

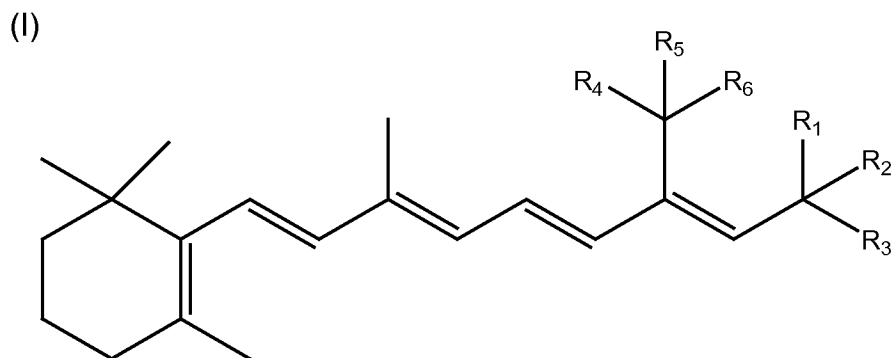
[0029] Another embodiment of the present invention is method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina. This method includes the step of administering to a patient in need

thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

[0030] A further embodiment of the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate in a patient under conditions sufficient to impede the formation of A2E.

[0031] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina containing a substituted C₂₀-retinoid and pharmaceutically acceptable carrier.

[0032] A further embodiment of the invention is a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I:



wherein:

R₁ is oxo or H;

R₂ is H or nothing;

R₃ is hydroxy or oxo or CHR₇ where R₇ forms a carotenoid and

R₄, R₅, and R₆ are independently selected from the group consisting of ¹H, ²H, ³H, halogen, and C₁₋₈alkyl.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1 shows HPLC and UV-vis profiles of lipofuscin pigments extracted from the eyecups (six of them minus the retina) of 5.5-6 month old, ABCR^{-/-} mice. Lipofuscin pigments such A2E and ATR dimer, represented by peaks 2, 3 and 4 have

been characterized and are derived from all-*trans*-retinal. Other lipofuscin pigments such as peaks 1 and 5 are also derived from all-*trans*-retinal, however, they have not been fully characterized. The above pigments are also found in humans and are thought to contribute to the macular degeneration.

[0034] FIG. 2 is a reaction scheme showing the biosynthesis of A2E and ATR-dimer from all-*trans*-retinal and a biological amine.

[0035] FIG. 3A shows HPLC profiles of reaction mixtures of C₂₀-D₃-all-*trans*-retinal and all-*trans*-retinal with ethanolamine for the formation of A2E. FIG. 3B is an expanded view of FIG. 3A. A2E formation was monitored over time by measuring the appearance of peaks starting at around 15 min. Both HPLC traces were measured about 30 hours into the reactions. For all-*trans*-retinal, a considerable amount of A2E has formed as well as an unidentified compound with a retention time at around 14.5 min as seen in the expanded view. On the other hand, for C₂₀-D₃-all-*trans*-retinal A2E formation is much slower and the peak at 14.5 min is almost absent. FIG. 3C is a plot of A2E formation over time for the above reactions. C₂₀-D₃-all-*trans*-retinal forms A2E about 7-times slower than all-*trans*-retinal.

[0036] FIG. 4A and 4B shows HPLC profiles of reaction mixtures of C₂₀-D₃-all-*trans*-retinal (Fig. 4A) and all-*trans*-retinal (Fig. 4B) with proline for the formation of ATR-dimer. ATR-dimer formation was monitored over time by measuring the appearance of peaks starting at around 8 min. Both HPLC traces were measured about 1 hour into the reactions. For all-*trans*-retinal, a considerable amount of ATR-dimer has formed. On the other hand, for C₂₀-D₃-all-*trans*-retinal ATR-dimer formation is much slower. FIG. 4C is a plot of ATR-dimer formation over time for the above reactions. C₂₀-D₃-all-*trans*-retinal forms A2E about 14-times slower than all-*trans*-retinal.

[0037] FIG. 5A shows HPLC profiles of lipofuscin pigments extracted from the eyecups (six of them minus the retina) of 5.5-6 month old, ABCR^{-/-} mice raised on a diet of either retinol acetate (trace A (FIG. 5A)) or C₂₀-D₃-all-*trans*-retinol acetate (trace B (FIG. 5A)). Mice raised on retinol acetate show considerable accumulation of lipofuscin pigments as shown by the HPLC peaks. On the other hand, lipofuscin pigments were undetectable in mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet. FIG. 5B shows plots of total retinol and retinol ester or D₃-retinol and D₃-retinol ester concentrations in

the above mice raised on either the retinol acetate or C₂₀-D₃-all-*trans*-retinol acetate diets, respectively. Both groups had roughly the same amount of retinol in the eye, despite having different concentrations of lipofuscin pigments.

[0038] FIG. 6A-D shows electron micrographs of RPE layers from 5.5-6 month old, ABCR^{-/-} mice raised on a diet of either retinol acetate (FIGs. 6A and 6B) or C₂₀-D₃-all-*trans*-retinol acetate (FIGs. 6C and 6D). Due to the uncertainty in distinguishing lipofuscin from melanin bodies. Comparisons were made between the numbers of all dark, electron dense bodies found in the RPE between mice on the retinol acetate diet vs. those on the C₂₀-D₃-all-*trans*-retinol acetate diet. In addition to the electron dense lipofuscin and melanin bodies, RPE phagosomes, mitochondria, and lipid droplets are also present but were ultrastructurally distinct. Mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet have considerably less electron dense bodies (i.e. lipofuscin bodies) compared to mice raised on the retinol acetate diet.

[0039] FIG. 7A shows total A2E, as measured by HPLC peak area at 445 nm, for rats (three females per group) treated/raised on either retinal, C₂₀-D₃-retinal, retinal plus Fenretinide (FEN) or retinal plus TDH. Animals treated with retinal had the greatest amount of A2E-lipofuscin (normalized to 100%). Whereas, animals treated with C₂₀-D₃-retinal or retinal plus Fenretinide or the RPE65 antagonist, TDH, showed less A2E-lipofuscin. FIG. 7B shows that all four groups of animals had roughly the same amount of eye retinol. FIG. 7C shows that levels of eye all-*trans*-retinal were increased in the C₂₀-D₃-retinal group.

DETAILED DESCRIPTION OF THE INVENTION

[0040] In the present invention, methods are provided to slow lipofuscin formation that do not rely on slowing the visual cycle or small molecules that inhibit the visual cycle (i.e., visual cycle antagonists). Thus, many of the disadvantages, such as, delayed dark adaptation, unformed visual pigment, which can leading to vision impairment and loss, high drug doses, and the potentially adverse side effects of prior methods are avoided.

[0041] More particularly, in the present invention provides methods for selectively replacing atoms on vitamin A in order to hamper its intrinsic reactivity to form vitamin A

derived lipofuscin pigments, such as, A2E and ATR dimer, while at the same time preserving the chemical structure of vitamin A such that participation in the visual cycle (binding to visual cycle proteins) is minimally disturbed. Because such changes to the structure of vitamin A do not interfere with normal vitamin A metabolism or function, one of the utilities of the present invention is that many potential side effects are avoided. Furthermore, because the compounds of the present invention (disclosed in more detail below) do not compete with natural retinoids for protein binding (because, e.g., they can perform the job of natural retinoids), smaller doses are needed for treatment of e.g., macular degeneration, compared to previous treatments using, e.g., visual cycle antagonists.

[0042] In the present invention, when the C₂₀ hydrogens of all-*trans*-retinoids are replaced by fluorine atoms (F₃), the formation of A2E is eliminated, as measured by monitoring the disappearance of C₂₀-F₃-all-*trans*-retinal and the absence of the corresponding fluorinated A2E by HPLC. A2E and the ATR-dimer are believed to be formed *in vivo* by a multi-step reaction sequence involving two molecules of all-*trans*-retinal, as shown in FIG. 2. In the first step, all-*trans*-retinal condenses with a biological amine to form the imine. This imine is then thought to undergo a [1,5] hydrogen shift involving a hydrogen atom at carbon C₂₀ (step 2). Subsequent reaction (step 3) with another molecule of retinal either by 1,2- or 1,4-addition followed by cyclizations (step 4) yields A2E or ATR-dimer precursors, respectively. A2E is subsequently formed after spontaneous oxidation in air, and ATR dimer, after elimination (step 4).

[0043] It has been shown that replacing certain C-H bonds with C-F bonds in retinal (*i.e.*, C₂₀-F₁₋₃-retinal) hampers the reactivity of all-*trans*-retinal, and, thus slows or eliminates the formation of A2E *in vitro*. By replacing hydrogen atoms at C₂₀ with fluorine, the [1,5] hydrogen shift step is blocked. Accordingly, C₂₀-F₁₋₃-retinal is expected to appreciably slow A2E and ATR-dimer biosynthesis.

[0044] A small change in the reaction rate of all-*trans*-retinal to form its toxic dimers is expected to translate into a large decrease in RPE lipofuscin formation over a lifetime. The methods of the present invention will slow the formation of the toxic pigments and will not slow (or will not slow significantly) visual cycle kinetics, because the regeneration of 11-*cis*-retinal does not involve the breaking of the C₂₀ hydrogen

bond. Therefore, treatment with a C₂₀-F₁₋₃-retinoid (which may be transformed into C₂₀-F₁₋₃-retinal in the body) will be particularly useful in impeding lipofuscin formation in humans who suffer from Stargardt Disease or other diseases or conditions associated with lipofuscin formation and/or macular degenerations.

[0045] C₂₀-D₁₋₃-retinoid according to the present invention will also be useful as a therapy to treat or ameliorate macular degeneration without adverse (or significantly adverse) visual effects. When C₂₀ hydrogens are replaced by deuteriums, A2E formation is about seven times slower (FIG. 3) and ATR-dimer formation is about 15 times slower (FIG. 4). This kinetic isotope effect will slow A2E and ATR-dimer formation *in vivo*. Deuterated vitamin A is widely used in humans and shows no toxicity (45, 46). Thus, a treatment using a C₂₀-D₁₋₃-retinoid should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects.

[0046] In view of the foregoing, one embodiment of the present invention is a method of retarding formation of a lipofuscin pigment in the retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of a C₂₀-D₁₋₃-retinoid and a C₂₀-F₁₋₃-retinoid. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, all-*trans*-retinoid (ATR)-dimer, and combinations thereof.

[0047] Preferably, the substituted C₂₀-retinoid is administered to the patient as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C₂₀-retinoid is administered as a unit dosage form.

[0048] In the present invention, the patient may be a mammal, preferably a human. In this embodiment, the substituted C₂₀-retinoid is a compound or combination of compounds disclosed herein, preferably compounds of Formula I, including Formulae Ic-Ie and Formula II, which are defined below.

[0049] In this embodiment, an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina will vary by patient and the particular substituted C₂₀-retinoid used. Typically, such amount will be about 0.05 to about 300 mg/day, including, e.g., 0.5-50, 1-25, and 3-10 mg/day.

[0050] Another embodiment of the present invention is method of treating or ameliorating the effects of an ophthalmologic disorder, such as, e.g. a disease characterized by an accumulation of a lipofuscin pigment in a retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinoids and C₂₀-F₁₋₃-retinoids. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

[0051] Preferably, the substituted C₂₀-retinoid is administered as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C₂₀-retinoid is administered as a unit dosage form.

[0052] In this embodiment, the disease maybe selected from the group consisting of Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy, age related macular degeneration, and Malattia Leventinese. Preferably, the disease is macular degeneration.

[0053] In this embodiment, the administration step includes replacing a component of the patient's diet that contains retinoid(s) or Vitamin A with a component that contains a substituted C₂₀-retinoid. By "replacing a component of a patient's diet" it is meant that a part of the diet that contains vitamin A or its precursors (including, but not limited to carotenoids) is replaced with a component that contains a substituted C₂₀-retinoid. Preferably, from about 1% to about 95%, including, e.g., from about 5-75%, 10-50%, or 20-30%, of the retinoid(s) in the patient's diet is replaced with a substituted C₂₀-retinoid. The replacement may be through, e.g., administering substituted C₂₀-retinoid containing foods or through treatment with compositions of the present invention, including pharmaceuticals or nutraceuticals, in lieu of consuming retinoid- or Vitamin A-containing foods that would have otherwise been consumed.

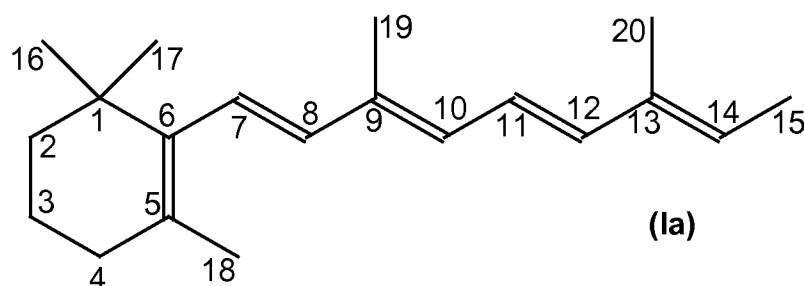
[0054] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina, which composition contains a substituted C₂₀-retinoid and a pharmaceutically acceptable carrier. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinoid and

C₂₀-F₁₋₃-retinoid. Preferably, the composition is in a unit dosage form. Preferably, the composition is a vitamin supplement or a pharmaceutical formulation.

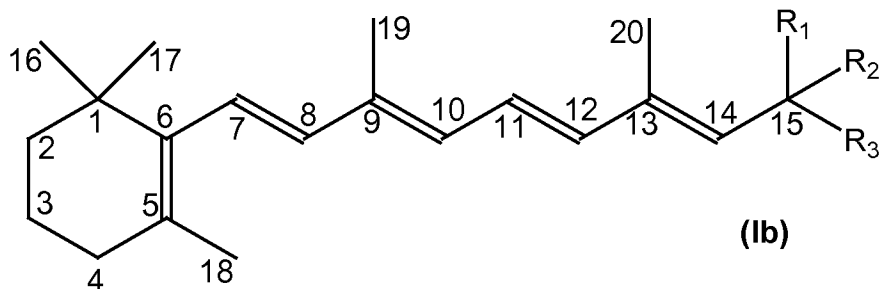
[0055] A further embodiment of the present invention is a method of retarding formation of a lipofuscin pigment selected from the group consisting of an A2E, an ATR dimer, and combinations thereof. This method comprises replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate under conditions sufficient to impede the formation of A2E, ATR dimer, or both, or an A2E and/or an ATR-dimer derivative. As used in the present invention, “conditions sufficient to impede the formation of A2E, ATR dimer, or both are well known in the art or may be determined empirically, if desired. The replacing step in this embodiment is described in more detail below.

[0056] A further embodiment of the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate under conditions sufficient to impede the formation of A2E. The replacing step in the last two embodiments may be accomplished using known method, including the methods disclosed above. For example, the substrate replacement may take place in the eye of the patient, e.g., the substrate may be administered directly to the eye via eye drops, ointment, or injection. Alternatively, the substrate may be administered systemically via, e.g., ingestion of a pill or capsule or absorption through a patch or by injection.

[0057] In the present invention, the “substituted C₂₀-retinoid” includes all retinols, retinol acetates, retinol esters, and retinoic acids as defined below as well as pharmaceutical salts thereof and metabolites thereof. For purposes of the present invention, the number scheme set forth in formula 1a for retinoids shall be used:



Thus, retinol, retinol acetate, retinol palmitate, retinoic acid, and beta-carotene have the following structures:



wherein

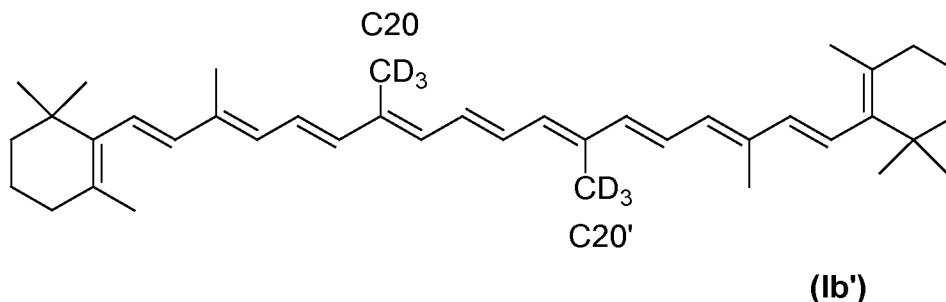
R_1 and R_2 are both H and R_3 is OH (retinol); or

R_1 and R_2 are both H and R_3 is OCOCH_3 (retinol acetate); or

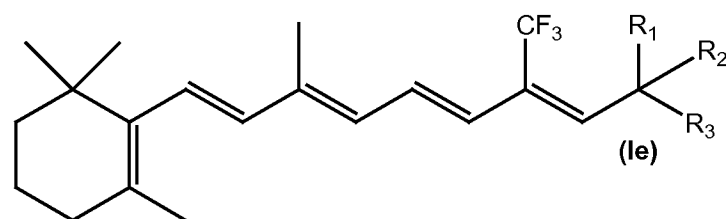
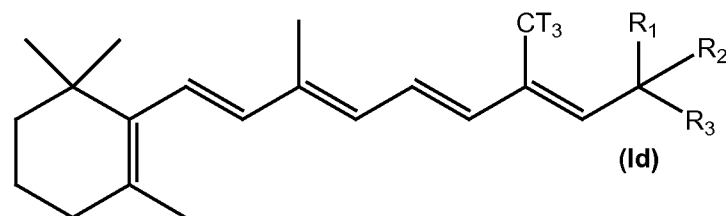
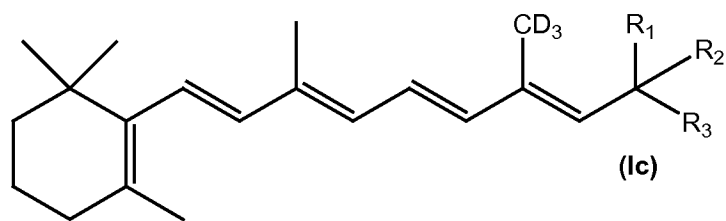
R_1 and R_2 are both H and R_3 is OCOR (retinol ester such as, e.g., retinol palmitate) or

R_1 is $=\text{O}$, R_2 is nothing and R_3 is OH (retinoic acid) or

R_1 is H, R_3 is nothing, and R_2 is $=\text{CH-R}_7$, where R_7 forms a carotenoid. In this embodiment, R_7 together with the rest of the compound forms, e.g., a beta-carotene or another pro-vitamin A carotenoid such as the deuterated beta-carotene shown in formulae Ib' below:

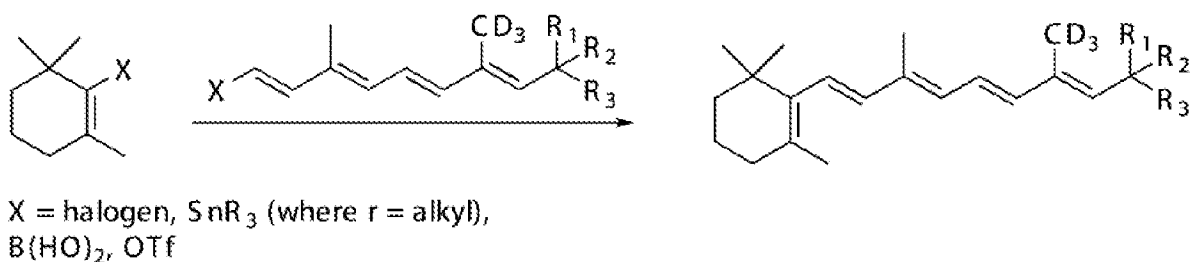
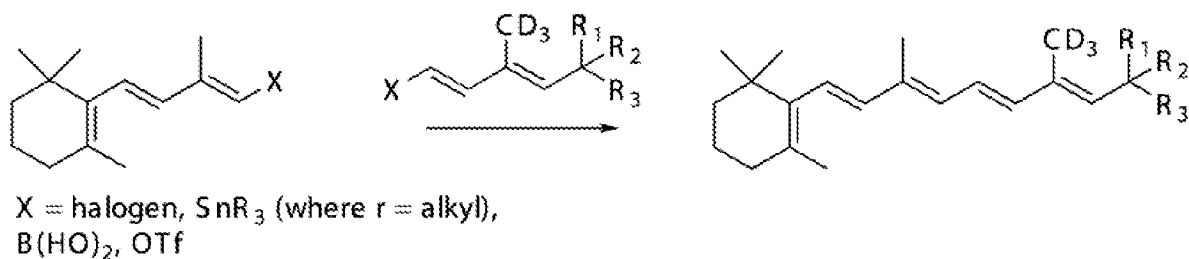
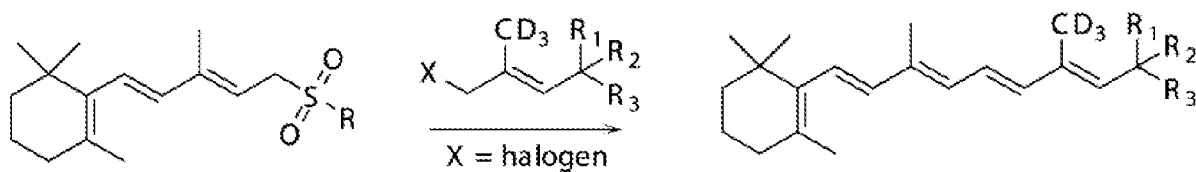
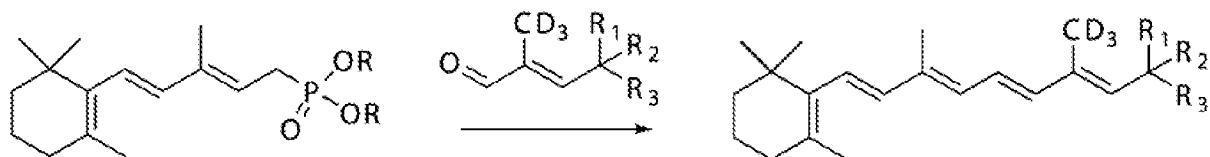
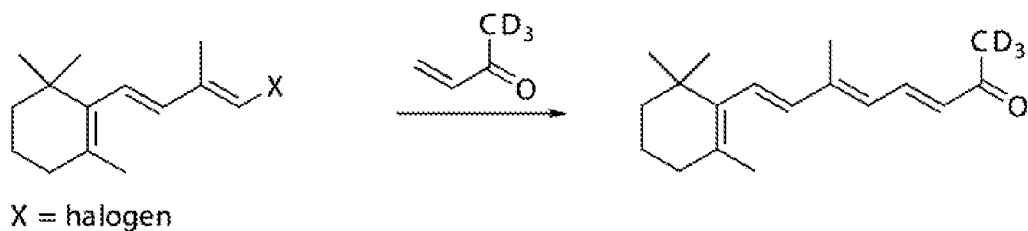


[0058] Exemplary substituted C_{20} -retinoid compounds that may be used in the compositions of the present invention include the following (compounds Ic-Ie):

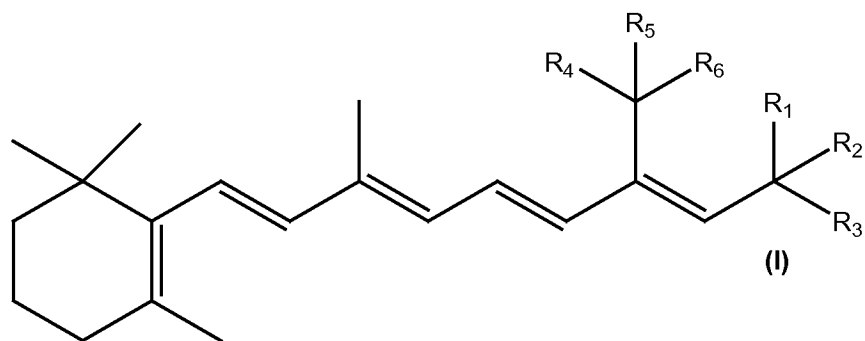


wherein R_1 , R_2 , and R_3 are as defined in Formula Ib.

[0059] Exemplary methods and reaction schemes for making substituted C20-retinoid compounds according to the present invention are set forth below:



[0060] In another embodiment, the invention is a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I:



wherein:

R_1 is oxo or H;

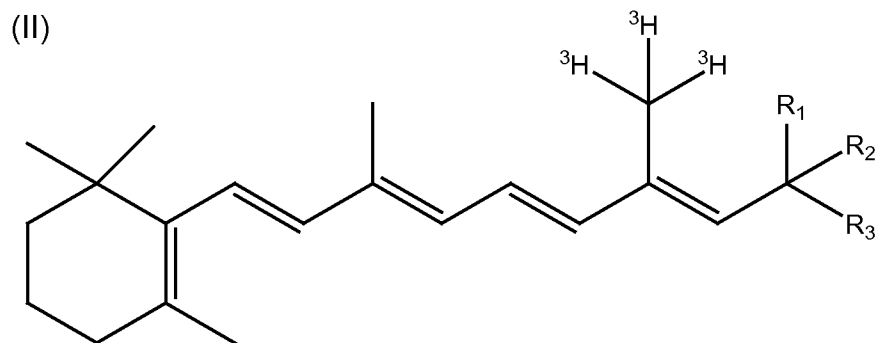
R_2 is H or nothing;

R_3 is hydroxy or oxo or $=CH-R_7$, where R_7 forms a carotenoid; and

R_4 , R_5 , and R_6 are independently selected from the group consisting of ^2H (D), ^3H (T), halogen, and C_{1-8} alkyl. Preferably, the halogen is fluorine (F).

[0061] In this embodiment, R_4 , R_5 , and R_6 may also be independently selected from H or a substituent that slows lipofuscin formation, a substituent that slows the formation of at least one of A2E or ATR dimer formation, or a substituent that slows hydrogen abstraction or migration at the C_{20} position compared to a retinoid that is not substituted at the C_{20} position, e.g. a $C_{20}-H_3$ retinoid. The present invention further contemplates any combination of the foregoing substituents at R_4 , R_5 , and R_6 .

[0062] Preferably, in the composition of the present invention the compound has the structure of formula II:



wherein:

R₁ is oxo or H;

R₂ is H or nothing; and

R₃ is hydroxy or oxo or =CH-R₇, where R₇ forms a carotenoid.

[0063] In the present invention, the compositions may further contain a supplement. Representative, non-limiting examples of a supplement according to the present invention are visual cycle antagonists, molecules that inhibit influx of a retinoid into an eye, or combinations thereof.

[0064] Exemplary, non-limiting visual cycle antagonists according to the present invention include TDH, TDT, 13-*cis*-retinoic acid, ret-NH₂, and combinations thereof. An exemplary, non-limiting visual cycle antagonist according to the present invention is fenretinide. Other visual cycle antagonists within the scope of the present invention include those disclosed in R. Rando, U.S. Application Serial No. 11/199,594 filed August 8, 2005, which application is incorporated by reference as if recited in full herein.

[0065] In the present invention, one or more additives may be included in the compositions. Exemplary, non-limiting additives that may be included in the compositions of the present invention include zinc, vitamin E, vitamin D, and combinations thereof.

[0066] The zinc, vitamin E, and vitamin D additives may be present in the compositions of the present invention in amounts that are effective to, e.g., enhance the bioavailability of the substituted C₂₀-retinoid compounds of the present invention,

including Formula I, Formulae Ic-e, and Formula II. Thus, in the present invention, zinc may be present in the composition at between about 3 to about 80 mg, preferably between about 3 to about 10 mg or between about 10 to about 80 mg. Vitamin E may be present in the composition at between about 3 to about 3,000 mg, preferably between about 3 to about 15 mg or between about 15 to about 3,000 mg. Vitamin D may be present in the composition at between about 0.005 to about 0.1 mg, preferably between about 0.005 to about 0.015 mg or between about 0.015 to about 0.1 mg.

[0067] The compositions of the present invention may also include one or more additional additives, including, for example, eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof. The use of antioxidants has been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Arch. Ophthalmol., 119: 1417-36 (2001); Sparrow, et al., J. Biol. Chem., 278:18207-13 (2003). Examples of suitable anti-oxidants that could be used in a composition of the present invention in combination with a compound of formulae I, including formulae Ic-le and II, include vitamin C, vitamin E, beta-carotene and other carotenoids, coenzyme Q, OT-551 (Othera Pharmaceuticals Inc.), 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (also known as Tempol), butylated hydroxytoluene, resveratrol, a trolox analogue (PNU-83836-E), bilberry extract, and combinations thereof.

[0068] The use of certain minerals has also been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Arch. Ophthalmol., 119: 1417-36 (2001). Thus, the present invention contemplates the optional inclusion of one or more of such minerals. Examples of suitable minerals that could be used in a composition of the present invention include copper-containing minerals, such as cupric oxide (by way of example only); zinc-containing minerals, such as zinc oxide (by way of example only); and selenium-containing compounds, and combinations thereof.

[0069] The use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Shaban & Richter, Biol. Chem., 383:537-45 (2002); Shaban, et al., Exp. Eye Res., 75:99-108 (2002). Examples of suitable negatively charged phospholipids that could optionally be used in a composition of the present invention include cardiolipin, phosphatidylglycerol,

and combinations thereof. Positively-charged and/or neutral phospholipids may also provide benefit for patients with macular degenerations and dystrophies when used in combination with a composition of the present invention.

[0070] The use of certain carotenoids has been correlated with the maintenance of photoprotection necessary in photoreceptor cells. Carotenoids are naturally-occurring yellow to red pigments of the terpenoid group that can be found in plants, algae, bacteria, and certain animals, such as birds and shellfish. Carotenoids are a large class of molecules in which more than 600 naturally occurring carotenoids have been identified. Carotenoids include hydrocarbons (carotenes) and their oxygenated, alcoholic derivatives (xanthophylls). They include actinioerythrol, astaxanthin, canthaxanthin, capsanthin, capsorubin, beta-8'-apo-carotenal (apo-carotenal), beta-12'-apo-carotenal, alpha-carotene, beta-carotene, "carotene" (a mixture of alpha- and beta-carotenes), gamma-carotenes, beta-cyrtloxanthin, lutein, lycopene, violerythrin, zeaxanthin, and esters of hydroxyl- or carboxyl-containing members thereof. Many of the carotenoids occur in nature as cis- and trans-isomeric forms, while synthetic compounds are frequently racemic mixtures.

[0071] In humans, the retina selectively accumulates mainly two carotenoids: zeaxanthin and lutein. These two carotenoids are thought to aid in protecting the retina because they are powerful antioxidants and absorb blue light. Examples of suitable carotenoids for optional use in a composition of the present invention include lutein and zeaxanthin, as well as any of the aforementioned carotenoids and combinations thereof.

[0072] Effective dosage forms, modes of administration, and dosage amounts, in addition to those disclosed above, may be determined empirically, and making such determinations is within the skill of the art. It is understood by those skilled in the art that the dosage amount will vary with the route of administration, the rate of excretion, the duration of the treatment, the identity of any other drugs being administered, the age, size, and species of mammal, e.g., human patient, and like factors well known in the arts of medicine and veterinary medicine. In general, a suitable dose of a compound according to the invention will be that amount of the compound, which is the lowest dose effective to produce the desired effect. For example, a compound of the

invention is present in the composition at a level sufficient to deliver about 0.1 to about 90 mg/day to a patient. The effective dose of a compound maybe administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

[0073] A compound of the present invention may be administered in any desired and effective manner: as pharmaceutical compositions for oral ingestion, or as an ointment or drop for local administration to the eyes, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous, topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. Further, a compound of the present invention may be administered in conjunction with other treatments. A compound or composition of the present invention maybe encapsulated or otherwise protected against gastric or other secretions, if desired.

[0074] While it is possible for a compound of the invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition) or a vitamin supplement or a nutraceutical. The pharmaceutically acceptable compositions of the invention comprise one or more compounds as an active ingredient in admixture with one or more pharmaceutically-acceptable carriers and, optionally, one or more other compounds, drugs, ingredients and/or materials. Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art. See, *e.g.*, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.).

[0075] Pharmaceutically acceptable carriers are well known in the art (*see, e.g.*, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (*e.g.*, lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (*e.g.*, dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, water, aqueous solutions (*e.g.*, saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (*e.g.*, ethyl alcohol, propyl

alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and tryglycerides), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, oils (e.g., corn, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, *etc.* Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Carriers suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

[0076] The pharmaceutical compositions or vitamin supplements or nutraceuticals of the invention may, optionally, contain additional ingredients and/or materials commonly used in such pharmaceutical compositions or vitamin supplements or nutraceuticals. These ingredients and materials are well known in the art and include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, sucrose and acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate; (10) suspending agents, such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth; (11) buffering agents; (12) excipients, such as lactose, milk sugars, polyethylene glycols, animal and vegetable fats, oils, waxes, paraffins, cocoa butter, starches, tragacanth, cellulose derivatives, polyethylene glycol, silicones, bentonites, silicic acid, talc, salicylate, zinc oxide, aluminum hydroxide,

calcium silicates, and polyamide powder; (13) inert diluents, such as water or other solvents; (14) preservatives; (15) surface-active agents; (16) dispersing agents; (17) control-release or absorption-delaying agents, such as hydroxypropylmethyl cellulose, other polymer matrices, biodegradable polymers, liposomes, microspheres, aluminum monostearate, gelatin, and waxes; (18) opacifying agents; (19) adjuvants; (20) wetting agents; (21) emulsifying and suspending agents; (22), solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; (23) propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane; (24) antioxidants; (25) agents which render the formulation isotonic with the blood of the intended recipient, such as sugars and sodium chloride; (26) thickening agents; (27) coating materials, such as lecithin; and (28) sweetening, flavoring, coloring, perfuming and preservative agents. Each such ingredient or material must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Ingredients and materials suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable ingredients and materials for a chosen dosage form and method of administration may be determined using ordinary skill in the art.

[0077] Pharmaceutical compositions or vitamin supplements or nutraceuticals suitable for oral administration may be in the form of capsules, cachets, pills, tablets, powders, granules, a solution or a suspension in an aqueous or non-aqueous liquid, an oil-in-water or water-in-oil liquid emulsion, an elixir or syrup, a pastille, a bolus, an electuary or a paste. These formulations may be prepared by methods known in the art, e.g., by means of conventional pan-coating, mixing, granulation or lyophilization processes.

[0078] Solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like) may be prepared by mixing the active ingredient(s) with one or more pharmaceutically-acceptable carriers and, optionally, one or more fillers, extenders, binders, humectants, disintegrating agents, solution retarding

agents, absorption accelerators, wetting agents, absorbents, lubricants, and/or coloring agents. Solid compositions of a similar type maybe employed as fillers in soft and hard-filled gelatin capsules using a suitable excipient. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using a suitable binder, lubricant, inert diluent, preservative, disintegrant, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine. The tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein. They may be sterilized by, for example, filtration through a bacteria-retaining filter. These compositions may also optionally contain opacifying agents and may be of a composition such that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. The active ingredient can also be in microencapsulated form.

[0079] Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. The liquid dosage forms may contain suitable inert diluents commonly used in the art. Besides inert diluents, the oral compositions may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents. Suspensions may contain suspending agents.

[0080] Pharmaceutical compositions for rectal or vaginal administration may be presented as a suppository, which maybe prepared by mixing one or more active ingredient(s) with one or more suitable nonirritating carriers which are solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound. Pharmaceutical compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such pharmaceutically-acceptable carriers as are known in the art to be appropriate.

[0081] Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, drops

and inhalants. The active compound may be mixed under sterile conditions with a suitable pharmaceutically-acceptable carrier. The ointments, pastes, creams and gels may contain excipients. Powders and sprays may contain excipients and propellants.

[0082] Pharmaceutical compositions suitable for parenteral administrations comprise one or more compound in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain suitable antioxidants, buffers, solutes which render the formulation isotonic with the blood of the intended recipient, or suspending or thickening agents. Proper fluidity can be maintained, for example, by the use of coating materials, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. These compositions may also contain suitable adjuvants, such as wetting agents, emulsifying agents and dispersing agents. It may also be desirable to include isotonic agents. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption.

[0083] In some cases, in order to prolong the effect of a drug (e.g., pharmaceutical formulation or vitamin supplement or nutraceutical), it is desirable to slow its absorption from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility.

[0084] The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug may be accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms may be made by forming microencapsule matrices of the active ingredient in biodegradable polymers. Depending on the ratio of the active ingredient to polymer, and the nature of the particular polymer employed, the rate of active ingredient release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue. The

injectable materials can be sterilized for example, by filtration through a bacterial-retaining filter.

[0085] The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

[0086] The following examples are provided to further illustrate the methods of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

EXAMPLES

EXAMPLE 1

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E *in vitro*

[0087] C₂₀-D₃-retinal was prepared according to the literature procedure(47) and its *in vitro* ability to form A2E as compared to all-*trans*-retinal was measured by HPLC.

[0088] FIG. 3A plots the formation of all A2E for two reaction mixtures containing either all-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal (16 mg), ethanolamine (0.5 equivalents) and acetic acid (1.2 equivalents). A typical HPLC trace is shown in FIG. 3B for the all-*trans*-retinal and C₂₀-D₃-all-*trans*-retinal reaction mixtures. The area under the curve corresponds to the amount of A2E: the larger the area the more A2E. The concentrations of A2E in the two reactions mixtures were measured about every 8 hours for 50 hours. The concentrations at each time point was plotted and the data points fit to a line for each reaction mixture. A comparison of the slopes of the two lines for the two reaction revealed that A2E formation occurred 7-times faster for all-*trans*-retinal compared to C₂₀-D₃-all-*trans*-retinal. Hydrogen deuterium exchange was not observed during the reaction with the labeled retinal, as measured by mass spectrometry of the reaction mixture after 50 hours, which clearly showed the presence

of the tri-deuterated retinal, tri-deuterated retinal hydroxylamine Schiff base and tetra-deuterated A2E.

EXAMPLE 2

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of ATR-dimer *in vitro*

[0089] C₂₀-D₃-all-*trans*-retinal was prepared as described in Example 1 and its *in vitro* ability to form ATR-dimer as compared to all-*trans*-retinal was measured by HPLC. All-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal (10 mg) and proline (2 equivalents) in ethanol were mixed, and the reaction was followed by HPLC, the results of which are depicted in FIG. 4A. A typical HPLC trace is shown in FIG. 4B for the all-*trans*-retinal and C₂₀-D₃-all-*trans*-retinal reaction mixtures at the same time points. The concentrations of ATR-dimer in the two reaction mixtures were measured about every 15 min for 3 hours. The concentration at each time point was plotted and the data points fit to a line for each reaction mixture. A comparison of the slopes of the two lines showed that C₂₀-D₃-all-*trans*-retinal formed ATR-dimer 15 times slower than the unlabeled retinal as shown in FIG. 4C.

EXAMPLE 3

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E-lipofuscin in CD-1 (ICR) mice

[0090] C₂₀-D₃-all-*trans*-retinal was administered to mice in order to measure its ability to form A2E in the eye compared to all-*trans*-retinal. Nine, 8-week old, CD-1 (ICR) mice (from Charles River, Wilmington, MA) were divided up into two groups of five and administered 1.5 mg of ether all-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal by intraperitoneal injection (IP) injection in a 10% solution of Tween-20 in saline bi-weekly for 6 weeks. At the end of this six-week period, each mouse was given a total of 60,000 I.U. (18 mg) or about 28-times the original amount of vitamin A in the mouse's body. Massive dosing with C₂₀-D₃-all-*trans*-retinal quickly replaces normal vitamin A stores with the C₂₀-D₃-analog. And, the injected retinal rapidly accumulates in the eye

(rod outer segments), where at high enough concentrations it will react to form lipofuscin pigments. This is similar to the accumulation of *all-trans*-retinal in the ABCR^{-/-} mice and in patients with Stargardt's disease.

[0091] At the end of the six week period, the eyes were dissected, the retinas and eyecups pooled into groups of 4 or 5, and homogenated with 50 µL ethanol. The homogenate was centrifuged at 13,000 rpm for 5 minutes and 40 µL of the supernatant was drawn off and analyzed for A2E-lipofuscin by HPLC. Retinol and retinol esters were analyzed at 325 nm and A2E-lipofuscin was measured at 445 nm. Mice administered C₂₀-D₃-*all-trans*-retinal (n = 5) had 68% less A2E-lipofuscin as compared to mice administered *all-trans*-retinal (n = 4). Both groups of mice had roughly the same concentrations of retinol and retinol esters.

EXAMPLE 4

Replacing the C₂₀ hydrogens of *all-trans*-retinal with deuteriums reduces the formation of A2E in ABCR^{-/-} mice

[0092] C₂₀-D₃-*all-trans*-retinol acetate was prepared according to the literature procedure(47) and was administered to ABCR^{-/-} mice (48, 49) in order to measure its ability to lead to lipofuscin compared to that of *all-trans*-retinol acetate. Eight 2-month old, ABCR^{-/-} mice raised on a standard rodent diet were then fed a diet containing 20,000 I.U./kg of either C₂₀-D₃-*all-trans*-retinol acetate or *all-trans*-retinol acetate for 3 months. On this diet each mouse roughly received the daily-recommended amount of vitamin A or the same amount of the C₂₀-D₃-vitamin A drug, which was less than about 1mg/kg/day.

[0093] At the end of the 5 month period, the eyes were dissected, eyecups pooled into groups of six and homogenated with 80 µL ethanol. The homogenate was centrifuged at 13000 rpm for 5 min and 30 µL of the supernatant was drawn off and analyzed for A2E-lipofuscin by HPLC. A2E-lipofuscin was measured at 445 nm. Mice on the 3-month diet containing C₂₀-D₃-*all-trans*-retinol acetate had 44-58% less A2E-lipofuscin as compared to mice on a diet of *all-trans*-retinol acetate. This percentage of A2E reduction is on the same order of magnitude observed in similar studies in ABCR^{-/-} mice with the visual cycle antagonist TDH, TDT, Ret-NH₂, 13-*cis*-retinoic, acid and

fenretinide. However, in this example A2E reduction is achieved with doses of C₂₀-D₃-all-*trans*-retinol acetate that are 11- to 40-times less.

EXAMPLE 5

ABCR^{-/-} mice raised exclusively on a C₂₀-D₃-all-*trans*-retinol acetate diet show undetectable amounts of extractable lipofuscin pigments and reduced lipofuscin deposits.

[0094] As in Example 4, two groups of four ABCR^{-/-} mice were raised either on diets containing C₂₀-D₃-all-*trans*-retinol acetate or all-*trans*-retinol acetate. However, in this example the mice were offspring of mothers on the same diet, and thus were raised only on their respective vitamin A analogs. At 5.5-6 months of age the mice were sacrificed and the eyecups were analyzed for lipofuscin pigments as described in Example 4. The results are shown FIG 5. While both mice contained the same amount of eye retinol and retinol esters (FIG 5B) lipofuscin pigments were undetectable in mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet (FIG 5A) but were detectable in mice raised on the all-*trans*-retinol acetate diet (FIG 5A).

[0095] In order to measure the amount lipofuscin granules in the eyes of the above mice on a normal diet vs. the diet containing C₂₀D₃-all-*trans*-retinol acetate, eyecups from both groups of mice (2 from each group) were evaluated by electron microscopy. Mice on the C₂₀-D₃-all-*trans*-retinol acetate diet had less electron dense lipofuscin deposits compared to mice on a diet of all-*trans*-retinol acetate as shown in FIG. 6.

EXAMPLE 6

C₂₀-D₃-all-*trans*-retinal slows A2E-lipofuscin formation as well as Fenretinide and/or TDH in wild-type rats.

[0096] 45-50 day old, female, CD IGS rats (Charles River, Wilmington, MA) were divided up into four groups of three. Three of these groups were administered all-*trans*-retinal and the one group was given C₂₀-D₃-all-*trans*-retinal (IP injection in a 10%

solution of Tween-20 in saline) at 3 mg, bi- or tri-weekly for 8 weeks (20, 3 mg injections total). Thus, at the end of the 8-week period the animals received roughly 20 times their original stores of vitamin A, as retinal or C₂₀-D₃-all-*trans*-retinal. Massive dosing with C₂₀-D₃-all-*trans*-retinal quickly replaces normal vitamin A stores with the C₂₀-D₃-analog. Of the three groups administered all-*trans*-retinal, one group was given Fenretinide (50) and another TDH (23), at doses of roughly 1.5 mg/day/animal (both supplied in the drinking water emulsified with 1g/L of Nu-rice (RIBUS, Inc, St. Louis, MO)).

[0097] At the end of the 8 weeks, RPE, A2E-lipofuscin was evaluated in each of the four groups by HPLC as described in Example 3 and in FIG. 7. A2E-lipofuscin pigments were greatest in the animals receiving all-*trans*-retinal (the control group). While animals receiving C₂₀D₃-all-*trans*-retinal had 35% less A2E-lipofuscin than animals receiving all-*trans*-retinal. Likewise, animals receiving Fenretinide or TDH had 49% and 31% less A2E-lipofuscin compared to animals administered only all-*trans*-retinal.

CITED DOCUMENTS

[0098] The following documents, which have been cited above, are incorporated by reference as if recited in full herein:

1. Friedman, D.S.; O'Colmain, B.J.; Muñoz, B.; Tomany, S.C.; McCarty, C.; DeJong, P.T.V.M.; Nemesure, B.; Mitchell, P.; Kempen, J.; Congdon, N. Prevalence of age related macular degeneration in the United States. Arch. Ophthalmol. **2004**, 122, 564–572.
2. Rattner, A.; Nathans, J. Macular degeneration: recent advances and therapeutic opportunities. Nat. Rev. Neurosci. **2006**, 7, 860-872.
3. Jong, P.T.V.M.d. Age-related macular degeneration N. Engl J Med **2006**, 355, 478-485.
4. Fine, S.L.; Berger, J.W.; Maguire, M.G.; Ho, A.C. Age-related macular degeneration N Engl J Med **2007**, 342, 483-492.
5. Jarc-Vidmar, M.; Kraut, A.; Hawlina, M. Fundus autofluorescence imaging in Best's vitelliform dystrophy. Klinische Monatsblätter Fur Augenheilkunde **2003**, 220, 861-867.

6. Capon, M.; Marshall, J.; Krafft, J.; Alexander, R.; Hiscott, P.; Bird, A. Sorsby's fundus dystrophy: a light and electron microscopic study. *Ophthalmology* **1989**, *95*, 1969-1977.
7. Chong, N.; Alexander, R.; Gin, T.; Bird, A.; Luthert, P. TIMP-3 collagen, and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy *Invest Ophthalmol Vis Sci* **2000**, *41*, 898-902.
8. Alikmets, R.; Singh, N.; Sun, H.; Shroyer, N.F.; Hutchinson, A.; Chidambaram, A.; Gerrard, B.; Baird, L.; Stauffer, D.; Peiffer, A.; Rattner, A.; Smallwood, P.; Li, Y.; Anderson, K.L.; Lewis, R.A.; Nathans, J.; Leppert, M.; Dean, M.; R., L.J. A Photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat. Genet.* **1997**, *15*, 236-246.
9. Haralampus-Grynaviski, N.M.; Lamb, L.E.; Clancy, C.M.R.; Skumatz, C.; Burke, J.M.; Sarna, T.; Simon, J.D. Spectroscopic and morphological studies of human retinal lipofuscin granules. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*.
10. Marmorstein, A.D.; Marmorstein, L.Y.; Sakaguchi, H.; Hollyfield, J.G. Spectral Profiling of Autofluorescence Associated with Lipofuscin, Bruch's Membrane, and Sub-RPE Deposits in Normal and AMD Eyes. *Invest. Ophthalmol. Vis. Sci.* **2002**, *43*, 2435-2441.
11. Smith, R.T.; Chan, J.K.; Busuoic, M.; Sivagnanavel, V.; Bird, A.C.; Chong, N.V. Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration. *Invest Ophthalmol Vis Sci.* **2006**, *47*, 5495-5504.
12. Sakai, N.; Decatur, J.; Nakanishi, K.; Eldred, G.E. A2-E": An Unprecedented Pyridinium Bisretinoid. *J. Am. Chem. Soc.* **1996**, *118*, 1559-1560.
13. Fishkin, N.E.; Sparrow, J.R.; Allikements, R.; Nakanishi, K. Isolation and characterization of retinal pigment epithelial cell fluorophore: An all-*trans*-retinal dimer conjugate. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *100*, 7091-7096.
14. Sparrow, J.S.; Nakanishi, K.; Parish, C.A. The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells. *Invest. Ophthalmol. Vis. Sci.* **2000**, *41*, 1981-1989.

15. Suter, M.; Reme, C.E.; Christian Grimm; Wenzel, A.; Jaattela, M.; Esser, P.; Kociok, N.; Leist, M.; Richter, C. Age-related Macular Degeneration: The lipofuscin component n-retinyl-n-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells. *J. Bio. Chem.* **2000**, 275, 39625-39630.
16. Finnemann, S.; Leung, L.W.; Rodriguez-Boulan, E. The lipofuscin component A2E selectively inhibits phagolysosomal degradation of photoreceptor phospholipid by the retinal pigment epithelium. *Proc Natl Acad Sci U S A.* **2002**, 99, 3842-3847.
17. De, S.; Sakmar, T.P. Interaction of A2E with model membranes. Implications to the pathogenesis of age-related macular degeneration. *J Gen Physiol.* **2002**, 120, 147-157.
18. Bergmann, M.; Schütt, F.; Holz, F.G.; Kopitz, J. Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration. *FASEB J.* **2004**, 18, 562-564.
19. Radu, R.A.; Mata, N.L.; Bagla, A.; Travis, G.H. Light exposure stimulates formation of A2E oxiranes in a mouse model of Stargardt's macular degeneration. *Proc Natl Acad Sci U S A.* **2004**, 101, 5928–5933.
20. Ben-Shabat, S.; Parish, C.A.; Hashimoto, M.; Liu, J.; Nakanishi, K.; Sparrow, J.R. Fluorescent pigments of the retinal pigment epithelium and age-related macular degeneration. *Bioorg Med Chem Lett.* **2001**, 11, 1533-1540.
21. Schutt, F.; Bergmann, M.; Holz, F.G.; Dithmar, S.; Volcker, H.-E.; Kopitz, J. Accumulation of A2-E in mitochondrial membranes of cultured RPE cells. **2007**, 245, 391-398.
22. Schutt, F.; Davies, S.; Kopitz, J.; Holz, F.G.; Boulton, M.E. Photodamage to human RPE cells by A2-E, a retinoid component of lipofuscin. **41** **2000**, 2303-2308.
23. Maiti, P.; Kong, J.; Kim, S.A.; Sparrow, J.S.; Allikmets, R.; Rando, R.R. Small molecule RPE65 antagonists limit the visual cycle and prevent lipofuscin formation. *Biochemistry* **2006**, 45, 852-860.

24. Radu, R.A.; Mata, N.L.; Nusinowitz, S.; Liu, X.; Sieving, P.A.; Travis, G.H. Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargardt macular degeneration. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 4742-4747.
25. Golczak, M.; Maeda, A.; Bereta, G.; Maeda, T.; Kiser, P.D.; Hunzelmann, S.; Lintig, J.V.; Blaner, W.S.; Palczewski, K. Metabolic Basis of Visual Cycle Inhibition by Retinoid and Nonretinoid Compounds in the Vertebrate Retina. *J. Biol. Chem.* **2008**, *283*, 9543-9554.
26. Katz, M.L.; Drea, C.M.; Robison, W.G. Relationship between dietary retinol and lipofuscin in the retinal pigment epithelium. *Mech. Age. Dev.* **1986**, *35*, 291-305.
27. Radu, R.A.; Han, Y.; Bui, T.V.; Nusinowitz, S.; Bok, D.; Lichter, J.; Widder, K.; Travis, G.H.; Mata, N.L. Reductions in serum vitamin A arrest Accumulation of toxic retinal fluorophores: A potential therapy for treatment of lipofuscin based retinal diseases. *Invest Ophthalmol Vis Sci* **2005**, *46*, 4393-4401.
28. Wassell, J.; Boulton, M. A role for vitamin A in the formation of ocular lipofuscin. *Br J Ophthalmol* **1997**, *81*, 911-918.
29. Owsley, C.; Jackson, G.R. Aging and scotopic dysfunction. *Perception* **2000**, *29*, Abstract Supplement.
30. Owsley, C.; Jackson, G.R.; White, M.; Feist, R.; Edwards, D. Delays in rod-mediated dark adaptation in early age-related maculopathy. *Ophthalmology* **2001**, *108*, 1196-1202.
31. Baehr, W.; Wub, S.M.; Birdc, A.C.; Palczewski, K. The retinoid cycle and retina disease. *Vision Research* **2003**, *43*, 2957-2958.
32. Maeda, A.; Maeda, T.; Golczak, M.; Imanishi, Y.; Leahy, P.; Kubota, R.; Palczewski, K. Effects of potent inhibitors of the retinoid cycle on visual function and photoreceptor protection from light damage in mice. *Mol. Pharmacol.* **2006**, *70*, 1220-1229.
33. Hong, W.K.; Itri, L.M. *Retinoids and human cancer*, Second Edition Ed.; Raven Press Ltd: New York, 1994.
34. Gudas, L.J.; Sporn, M.B.; Roberts, A.B. *Cellular biology and biochemistry of retinoids*; Raven Press Ltd.: New York, 1994; 443-520 pp.

35. Nason-Burchenal, K.; Dmitrovsky, E. *The retinoids: cancer therapy and prevention mechanisms*: Berlin, 1999; 301-322 pp.
36. Dragnev, K.H.; Rigasa, J.R.; Dmitrovsky, E. The Retinoids and Cancer Prevention Mechanisms *Oncologist* **2003**, 5, 361-368.
37. Freemantle, S.J.; Spinella, M.J.; Dmitrovsky, E. Retinoids in cancer therapy and chemoprevention: promise meets resistance. *Oncogene* **2003**, 22, 7305–7315.
38. Soriatan, RXlist.com, <http://www.rxlist.com/cgi/generic/acitretin.htm#>, accessed Sept. 02, 2008. 2008.
39. Targretin, RXlist.com <http://www.rxlist.com/cgi/generic/bexarotene.htm>, accessed Sept. 02 2008.
40. Acutane, RXlist.com, <http://www.rxlist.com/cgi/generic/isotret.htm>, accessed Sept. 02 2008.
41. Camerini, T.; Mariani, L.; Palo, G.D.; Marubini, E.; Mauro, M.G.D.; Decens, A.; Costa, A.; Veronesi, U. Safety of the Synthetic Retinoid Fenretinide: Long-Term Results From a Controlled Clinical Trial for the Prevention of Contralateral Breast Cancer. *J. Clin. Oncol.* **2001**, 19, 1664-1670.
42. Puduvalli, V.K.; Yung, W.K.A.; Hess, K.R.; Kuhn, J.G.; Groves, M.D.; Levin, V.A.; Zwiebel, J.; Chang, S.M.; Cloughesy, T.F.; Junck, L.; Wen, P.; Lieberman, F.; Conrad, C.A.; Gilbert, M.R.; Meyers, C.A.; Liu, V.; Mehta, M.P.; Nicholas, M.K.; Prados, M. Phase II Study of Fenretinide (NSC 374551) in Adults With Recurrent Malignant Gliomas: A North American Brain Tumor Consortium Study. *J. Clin. Oncol.* **2004**, 22, 4282-4289.
43. Villablanca, J.G.; Khan, A.A.; Avramis, V.I.; Seeger, R.C.; Matthay, K.K.; Ramsay, N.K.; Reynolds, C.P. Phase I trial of 13-cis-retinoic acid in children with neuroblastoma following bone marrow transplantation. *J Clin Oncol.* **1995**, 13, 849-901.
44. Chemotherapy drugs, Isorettinoin, <http://www.chemocare.com/bio/isotretinoin.asp>, accessed September 8 2008.
45. Haskell, M.; Mazumder, R.M.; Peerson, J.M.; Jones, A.D.; Wahed, M.A.; Mahalanabis, D.; Brown, K.H. Use of deuterated-retinol-dilution technique to

- assess total body vitamin A stores of adult volunteers consuming different amounts of vitamin A1, 2, 3. *Amer. J. of Clinical Nutrition* **1999**, 70, 874-880.
46. Bausch, J.; Rietz, P. Method for the assessment of vitamin A liver stores. *Acta Vitaminol Enzymol* **1977**, 31, 99-112.
 47. Pardoen, J.A.; Mulder, P.P.J.; Van den Berg, E.M.M.; Lugtenburg, J. Synthesis of 8-, 9-, 12-, and 13-mono-¹³C-retinal. *Canadian Journal of Chemistry* **1985**, 63, 1431-1435.
 48. Weng, J.; Mata, N.L.; Azarian, S.M.; Tzekov, R.T.; Birch, D.G.; Travis, G.H. Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in abcr knockout mice. *Cell* **1999**, 9, 13-23.
 49. Kim, S.; Fishkin, N.; Kong, J.; Nakanishi, K.; Allikmets, R.; Sparrow, J.R. Rpe65 Leu450Met variant is associated with reduced levels of the retinal pigment epithelium lipofuscin fluorophores A2E and iso-A2E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 11668-11672.
 50. Soo-Jong; Kwon, Y.-J.; Han, H.-S.; Park, S.-H.; Park, M.-S.; Rho, Y.-S.; Sin, H.-S. Synthesis and Biological Activity of Novel Retinamide and Retinoate Derivatives. *Chemical & Pharmaceutical Bulletin* **2004**, 52, 501-506.

[0099] The scope of the present invention is not limited by the description, examples, and suggested uses herein and modifications can be made without departing from the spirit of the invention. Thus, it is intended that the present invention cover modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 20, 2015

Electronic Signature for Loretta E. Charles: /Loretta E. Charles/

Docket No.: 13533/541US2
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Ilyas Washington

Application No.: 14/510,975

Confirmation No.: 6583

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Art Unit: TBA

For: Compositions and Methods for Treating Macular
Degeneration

Examiner: TBA

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56 and in conformance with the procedures of 37 C.F.R. §§ 1.97 and 1.98 and M.P.E.P. § 609, attorney for Applicants hereby brings the documents listed on the attached PTO Form PTO/SB/08a to the attention of the Examiner. The documents are listed on the attached PTO Forms No. SB/08a. It is respectfully requested that the information be expressly considered during the prosecution of this application and that the documents be made of record therein and appear among the "References Cited" on any patent issue therefrom.

The filing of this Information Disclosure Statement and the enclosed PTO Forms No. SB/08a, shall not be construed as an admission that the information cited is prior art, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b).

Unless otherwise indicated, copies of each patent, publication or other information listed on the attached Forms, PTO/SB/08 are not attached as they were previously cited by or submitted to the U.S. Patent Office in prior U.S. Application Serial No. 12/733,631 which is relied upon for an earlier effective filing date under 35 U.S.C. § 120.

Applicant believes that no fees are due. However, if any fees are required, the Commissioner is authorized to charge any such fees and/or credit any overpayment to Kenyon & Kenyon LLP Deposit Account No.: 11-0600.

Dated: January 20, 2015

Respectfully submitted,

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	First Named Inventor	Ilyas Washington	
	Art Unit	TBA	
	Examiner Name	TBA	
	Attorney Docket Number	13533-541US2	

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**INFORMATION DISCLOSURE
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Application Number	14510975
Filing Date	2014-10-09
First Named Inventor	Ilyas Washington
Art Unit	TBA
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1	SAKAI, et al. "Ocular Age Pigment 'A2-E': An Unprecedented Pyridinium Bisretinoid," J. Am. Chem. Soc. (1996), Vol. 118, pp.1559-1560.	☐
2	SCHUTT, et al. "Accumulation of A2-E in mitochondrial membranes of cultured RPE cells," Graefe's Arch. Clin. Exp. Ophthalmol. (2007), Vol. 245, pp. 391-398.	☐
3	SCHUTT, et al. "Photodamage to human RPE cells by A2-E, a retinoid component of lipofuscin," Invest. Ophthalmol. Vis. Sci. (2000), Vol. 41, pp. 2303-2308.	☐
4	SHABAN, et al., "A2E and blue light in the retina: the paradigm of age-related macular degeneration," Bioi. Chem. (2002), Vol. 383, pp. 537-545.	☐
5	SHABAN, et al., "Phosphatidylglycerol potentially protects human retinal pigment epithelial cells against apoptosis induced by A2E, a compound suspected to cause age-related macula degeneration," Exp. Eye Res. (2002), Vol. 75, pp. 99-108.	☐
6	SMITH, "Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration," Invest Ophthalmol Vis Sci. (2006), Vol. 47, pp. 5495-5504.	☐
7	UM, et al. "Synthesis and Biological Activity of Novel Retinamide and Retinoate Derivatives," Chemical & Pharmaceutical Bulletin (2004), Vol. 52, pp. 501-506.	☐
8	SORIATANE, [online], [retrieved July 05, 2012] Retrieved from RXList: The Internet Drug Index using Internet <URL: http://www.rxlist.com/cgi/generic/acitretin.htm >.	☐
9	SPARROW, et al. "A2E, a Lipofuscin Fluorophore, in Human Retinal Pigmented Epithelial Cells in Culture, Invest. Ophthalmol Vis Sci (1999), Vol. 40, pp. 2988-2995.	☐
10	SPARROW, et al. "The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells," Invest. Ophthalmol. Vis. Sci. (2000), Vol. 41, pp. 1981-1989.	☐
11	SPARROW, et al., "A2E-epoxides damage DNA in retinal pigment epithelial cells. Vitamin E and other antioxidants inhibit A2E-epoxide formation," J. Bioi. Chem. (2003), Vol. 278, pp. 18207-18213.	☐

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Application Number	14510975
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12	SREEKUMAR et al. "Protection from oxidative stress by methionine sulfoxide reductases in RPE cells," Biochem Biophys Res Commun (2005), Vol. 334:1, pp. 245-253.	☐
13	SUTER, et al. "Age-related Macular Degeneration: The lipofuscin component n-retinyl-n-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells," J. Bio. Chem. (2000), Vol. 275, pp. 39625-39630.	☐
14	TARGRETIN, [online], [retrieved July 05, 2012] Retrieved from RXlist: The Internet Drug Index using Internet <URL: http://www.rxlist.com/cgi/generic/bexarotene.htm >.	☐
15	TOTH, "Functional changes of the aging rat retina in relation to the modifications of the ERG components," Aktuelle Gerontol (1976), Vol. 6, pp. 79-86.	☐
16	TRAVIS, G. H. et al., Diseases caused by defects in the visual cycle: retinoids as potential therapeutic agents," Annual Review of Pharmacology and Toxicology, Annual Review Inc., Palo Alto, CA (2007), Vol. 47, pp. 469-512 (NIH Public Access Author manuscript, pages 1-38).	☐
17	VILLABLANCA, et al. "Phase I trial of 13-cis-retinoic acid in children with neuroblastoma following bone marrow transplantation," J Clin Oncol. (1995), Vol. 13, pp. 894-901.	☐
18	WASELL, et al. "A role for vitamin A in the formation of ocular lipofuscin," Br J Ophthalmol (1997), Vol. 81, pp. 911-918.	☐
19	WATSON, et al. "Comparison of low-vision reading with spectacle-mounted magnifiers," J. Rehabil Res Dev. (2005), Vol. 42:4, pp. 459-470.	☐
20	WENG, et al. "Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in abcr knockout mice," Cell (1999), Vol. 98, pp. 13-23.	☐
21	WRIGHT, et al. "Hybrid eye tracking for computer-aided retinal surgery," Biomed Sci Instrum (1996), Vol. 32, pp. 225-235.	☐
22	WALKER, "New/Old Findings on Unique Vitamin E," [online], [retrieved on Sep 5 2012] retrieved from the Internet: < http://www.enerex.ca/en/articles/new-old-findings-on-unique-vitamin-e.htm >.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14510975
Filing Date	2014-10-09
First Named Inventor	Ilyas Washington
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	13533-541US2

23	Japanese Office Action with English translation from counterpart Japanese Application No.: 2012-260971 dated February 7, 2014.	☐
24	"What is Deuterium?" [retrieved on 2/11/2013], <URL: http://www.innovateus.net/printscience/what-deuterium >. 4 pages.	☐
25	FOSTER, Allan, "Deuterium Isotope Effects in Studies of Drug Metabolism," TIPS-- December 1984.	☐
26	HANDELMAN et al., "An Improved Protocol for Determining Ratios of Retinol-d4 to Retinol Isolated from Human Plasma", Anal. Chem. (1993), Vol. 65, pp. 2024-2028.	☐
27	HASKINS, N.J., "The Application of Stable Isotopes in Biomedical Research", Biomedical Mass Spectrometry (1982), Vol. 9:7, pp. 269-277.	☐
28	KUSHNER et al., "Pharmacological uses and perspectives of heavy water and deuterated compounds," Can. J. Physiol. Pharmacol. (1999), Vol. 77, pp. 79-88.	☐
29	PARK, et al. "Metabolism of Fluorine-Containing Drugs," Annu. Rev. Pharmacol. Toxicol. (2001), Vol. 41, pp. 443-470.	☐
30	TANG, G. et al., "Deuterium enrichment of retinol in humans determined by gas chromatography electron capture negative chemical ionization mass spectrometry", J. Nutr. Biochem (1998), Vol. 9, pp. 408-414.	☐
31	TUNG, Office Action for US Patent Application 12/874,783, Dated 08/16/2011.	☐
32	WOLEN, R., "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence", The Journal of Clinical Pharm. (1986), Vol. 26, pp. 419-424.	☐

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Art Unit	TBA
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

- ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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- ☐ See attached certification statement.
- ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Joseph A. Coppola/	Date (YYYY-MM-DD)	2015-01-20
Name/Print	Joseph A. Coppola	Registration Number	38,413

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Invention**

Compositions and Methods for Treating Macular Degeneration

As the below named inventor, I hereby declare that:

This declaration
is directed to:☐

The attached application, or

☒United States application or PCT international application number 14/510,975filed on October 9, 2014

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001
by fine or imprisonment of not more than five (5) years, or both.**WARNING:**

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LEGAL NAME OF INVENTOR

Inventor: Ilyas WashingtonDate (Optional): Dec. 16 2014Signature: 

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Electronic Patent Application Fee Transmittal

Application Number:	14510975			
Filing Date:	09-Oct-2014			
Title of Invention:	Compositions and Methods for Treating Macular Degeneration			
First Named Inventor/Applicant Name:	Ilyas Washington			
Filer:	Joseph A. Coppola/Loretta E. Charles			
Attorney Docket Number:	13533/541US2			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	2051	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Extension - 1 month with \$0 paid	2251	1	100	100
Miscellaneous:				
Total in USD (\$)				170

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EFS ID:	21253826
Application Number:	14510975
International Application Number:	
Confirmation Number:	6583
Title of Invention:	Compositions and Methods for Treating Macular Degeneration
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	26646
Filer:	Joseph A. Coppola/Loretta E. Charles
Filer Authorized By:	Joseph A. Coppola
Attorney Docket Number:	13533/541US2
Receipt Date:	20-JAN-2015
Filing Date:	09-OCT-2014
Time Stamp:	15:55:45
Application Type:	Utility under 35 USC 111(a)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		14510975
	Filing Date		2014-10-09
	First Named Inventor	Ilyas Washington	
	Art Unit	TBA	
	Examiner Name	TBA	
	Attorney Docket Number	13533-541US2	

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	2	6660297		2003-12-09	Bartels et al.	
	3	7566808		2009-07-28	Rando	
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Attorney Docket Number		13533-541US2

	2	20020169176	A1	2002-11-14	Elder et al.	
	3	20030032078		2003-02-13	Travis	
	4	20030149997		2003-08-07	Hageman	
	5	20040009907		2004-01-15	Alsobrook et al.	
	6	20040121407		2004-06-24	Distefano et al.	
	7	20040235113		2004-11-25	Shi et al.	
	8	20050059010		2005-03-17	Stone et al.	
	9	20050119536		2005-06-02	Hageman	
	10	20050176662		2005-08-11	Inana et al.	
	11	20050220768		2005-10-06	McVey et al.	
	12	20050256207		2005-11-17	McGrath	

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13	20060089411	A1	2006-04-27	Gierhart	
14	20060094063		2006-05-04	Mata et al.	
15	20060099714		2006-05-11	Mata et al.	
16	20060135460		2006-06-22	Widder et al.	
17	20060292099		2006-12-28	Milburn et al.	
18	20070014833		2007-01-18	Milburn et al.	
19	20070015827	A2	2007-01-18	Widder et al.	
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	1	1995004018	WO	B1	1995-02-09	Ligand Pharm Inc		☐

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Examiner Name	TBA
Attorney Docket Number	13533-541US2

2	1996024344	WO	A1	1996-08-15	Warner Lambert Co		☐
3	H10513197	JP	A	1998-12-15	Warner Lambert Co.		☐
4	2002072528	WO	B2	2002-09-19	Lilly Co Eli		☐
5	2002275095	JP	A	2002-09-25	Warner Lambert Co		☐
6	2004526725	JP	A	2004-09-02	Eli Lily & Co. et al		☐
7	2005000230	WO	A2	2005-01-06	Achkar, Charles et al.		☐
8	2005065669	WO	B3	2005-07-21	Alcon, Inc		☐
9	05087210	WO	A2	2005-09-22	Larsen, Lars		☐
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	1	Acutane [online], [retrieved on July 05, 2012] Retrieved from RXlist: The Internet Drug Index using Internet <URL: http://www.rxlist.com/cgi/generic/isotret.htm >.	☐
	2	Age-Related Eye Disease Study Research Group, "A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss," Arch. Ophthalmol. (2001) Vol. 119, 1417-1436.	☐
	3	ALIKMETS, et al. "A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy," Nat. Genet (1997), Vol. 15, pp. 236-246.	☐
	4	ASHMARIN, et al. "Thyroliberin: new physiological effects and prospects of clinical use," Vestn Ross Akad Med X Nauk (1992), VOL. 6, PP. 40-44. (with abstract translation)	☐
	5	BAEHR, et al. "The Retinoid Cycle and Retina Disease," Vision Research (2003) Vol. 43, pp. 2957-2958.	☐
	6	BAILLIE, T., "The Use of Stable Isotopes in Pharmacological Research", Pharmacological Reviews(1981), Vol. 33, No. 2, pp. 81-132.	☐
	7	BARRETT, et al. "Hybrid Tracking System for Retinal Photocoagulation Prototype II," Biomed Sci Instrum (1999) Vol. 35, pp. 259-64.	☐
	8	BAUSCH, et al. "Method for the Assessment of Vitamin A Liver Stores," Acta Vitaminol Enzymol31 (1977,) pp. 99-112.	☐
	9	BEN-SHABAT, et al. "Fluorescent pigments of the retinal pigment epithelium and age-related macular degeneration," Bioorg Med Chern Lett. 11(2001), pp. 1533-1540.	☐
	10	BERGEN, et al. "Synthesis of Tri-, Tetra-, and Penta-Deuterated Forms of Vitamin A," Journal of Labelled compounds and Radiopharmaceuticals (1998), vol. 25:1, pp. 11-21.	☐

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11	BERGMANN, et al. "Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration," FASEB J.18 (2004), pp. 562-564.	☐
12	CAMERINI, et al. "Safety of the Synthetic Retinoid Fenretinide: Long-Term Results From a Controlled Clinical Trial for the Prevention of Contralateral Breast Cancer," J. Clin. Oncol. (2001), Vol. 19, pp. 1664-1670.	☐
13	CAPON, et al. "Sorsby's fundus dystrophy: a light and electron microscopic study," Ophthalmology 96 (1989), pp.1769-1777.	☐
14	Isotretinoin, [online], [retrieved on July 05, 2012] Retrieved from Chemocare.com using Internet <URL: http://www.chemocare.com/bio/isotretinoin.asp >.	☐
15	CHONG, et al. "TIMP-3 collagen, and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy," Invest Ophthalmol Vis Sci (2000), Vol. 41, pp. 898-902.	☐
16	DE, et al. "Interaction of A2E with model membranes. Implications to the pathogenesis of age-related macular degeneration," J Gen Physiol. (2002), Vol. 120, pp. 147-157.	☐
17	DOWLING, "Neural and Photochemical Mechanisms of Visual Adaptation in the Rat," J. Gen. Physio. (1963), pp. 1287-1301	☐
18	DRAGNEV, et al. "The Retinoids and Cancer Prevention Mechanisms," Oncologist 5 (2000), pp. 361-368.	☐
19	FINE, et al. "Age-related macular degeneration," N Engl J Med. (2000), Vol. 342, pp. 483-492.	☐
20	FINNEMANN, et al. "The lipofuscin component A2E selectively inhibits phagolysosomal degradation of photoreceptor phospholipid by the retinal pigment epithelium," Proc Natl Acad Sci. (2002), Vol. 99, pp. 3842-3847.	☐
21	FISHKIN, et al. "Isolation and characterization of retinal pigment epithelial cell fluorophore: An all-trans-retinal dimer conjugate," Proc. Natl. Acad. Sci. (2005), Vol. 102, pp. 7091-7096.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14510975
Filing Date	2014-10-09
First Named Inventor	Ilyas Washington
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	13533-541US2

22	FREEMANTLE, et al. "Retinoids in cancer therapy and chemoprevention: promise meets resistance," Oncogene (2003), Vol. 22, pp. 7305-7315.	☐
23	FRIEDMAN, et al. "Prevalence of age related macular degeneration in the United States," Arch. Ophthalmol. (2004) Vol. 122, pp. 564-572.	☐
24	GOLCZAK, et al. "Metabolic Basis of Visual Cycle Inhibition by Retinoid and Non retinoid Compounds in the Vertebrate Retina," J. Biol. Chem. (2008), Vol. 283, pp. 9543-9554.	☐
25	GOLLAPALLI, et al. "The specific binding of retinoic acid to RPE65 and approaches to the treatment of macular degeneration," PNAS. (2004), Vol. 101:27, pp. 10030-10035.	☐
26	GUDAS, et al. "Cellular biology and biochemistry of retinoids"; The retinoids, Biology, Chemistry and Medicine (1994), Raven Press Ltd., New York, pp. 443-520.	☐
27	HARALAMPUS-GRYNAVSKI, et al. "Spectroscopic and morphological studies of human retinal lipofuscin granules," Proc. Natl. Acad. Sci. (2003), Vol. 100, pp. 3179-3184.	☐
28	HASKELL, et al. "Use of deuterated-retinol-dilution technique to assess total body vitamin A stores of adult volunteers consuming different amounts of vitamin A1-3", Amer. J. of Clinical Nutrition (1999), Vol. 70, pp. 874-880.	☐
29	JARC-VIDMAR, et al. "Fundus autofluorescence imaging in Best's vitelliform dystrophy," Klinische Monatsblätter Für Augenheilkunde (2003), Vol.220, pp. 861-867.	☐
30	JONG, "Age-related macular degeneration," N. Engl J Med 355 (2006), pp. 1474-1485.	☐
31	KATZ, et al. "Relationship between dietary retinol and lipofuscin in the retinal pigment epithelium," Mech Age. Dev. (1986), Vol. 35, pp. 291-305.	☐
32	KIM, et al. "Rpe65 Leu450Met variant is associated with reduced levels of the retinal pigment epithelium lipofuscin fluorophores A2E and iso-A2E," Proc. Nat. Acad. Sci. (2004), Vol. 101, pp. 11668-11672.	☐

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33	MAEDA, et al. "Effects of potent inhibitors of the retinoid cycle on visual function and photoreceptor protection from light damage in mice," Mol. Pharmacol. (2006), Vol. 70, pp. 1220-1229.	☐
34	MAITI, et al. "Small molecule RPE65 antagonists limit the visual cycle and prevent lipofuscin formation," Biochemistry (2006), Vol. 45, pp. 852-860.	☐
35	MARMORSTEIN, et al. "Spectral Profiling of Autofluorescence Associated with Lipofuscin, Bruch's Membrane, and Sub-RPE Deposits in Normal and AMD Eyes," Invest. Ophthalmol. Vis. Sci. (2002), Vol. 43, pp.2435-2441.	☐
36	MURATA, et al. "Suppression of laser-induced choroidal neovascularization by subconjunctival injection of 9alpha-fluoromedroxyprogesterone acetate (FMPA), an anti-angiogenic agent, in rats," Biol. Pharm Bull (2006), Vol. 29:12, pp. 2410-2414.	☐
37	NASON-BURCHENAL, et al. "The retinoids: cancer therapy and prevention mechanisms," Retinoids: The Biochemical and Molecular Basis of Vitamin A and Retinoid Action (1999), Berlin, pp. 301-322.	☐
38	OWSLEY, et al. "Aging and scotopic dysfunction," Perception 29 (2000), Abstract Supplement.	☐
39	OWSLEY, et al. "Delays in rod-mediated dark adaptation in early age-related maculopathy," Ophthalmology (2001), Vol.108, pp. 1196-1202.	☐
40	PAPADAKI et al. "Somatostatin for Uveitic Cystoid Macular Edema (CME)," Ocul ImmunolInflamm (2005), Vol. 13:6, pp. 469-470.	☐
41	PARDOEN, et al. "Synthesis of 8-, 9-, 12-, and 13-mono-13C-retinal," Canadian Journal of Chemistry (1985), Vol. 63, pp. 1431-1435.	☐
42	PARDOEN, et al. "Synthesis of retina is isotopically labeled at positions 11, 12, 14 and 20," Recueil des Travaux Chimiques des Pays-Bas (1986), Vol. 105, pp. 92-98.	☐
43	HALPERN, et al. "Cystoid macular edema in aphakia and pseudophakia after use of prostaglandin analogs," Semin Ophthalmol (2002), Vol. 17(3-4) pp. 181-186.	☐

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Attorney Docket Number	13533-541US2

44	PUDUVALLI, et al. "Phase II Study of Fenretinide (NSC 374551) in Adults With Recurrent Malignant Gliomas: A North American Brain Tumor Consortium Study," J. Clin. Oncol. (2004), Vol. 22, pp. 4282-4289.	☐
45	RADU, et al. "Reductions in serum vitamin A arrest Accumulation of toxic retinal fluorophores: A potential therapy for treatment of lipofuscin based retinal diseases," Invest Ophthalmol Vis Sci (2005), Vol. 46, pp. 4393-4401.	☐
46	RATTNER, et al. "Macular degeneration: recent advances and therapeutic opportunities," Nat. Rev. Neurosci. (2006), Vol. 7, pp. 860-872.	☐
47	RADU, et al. "Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargard'ts macular degeneration" Proc Natl Acad Sci (2003), Vol. 100, pp. 4742-4747.	☐
48	RADU, et al. "Light exposure stimulates formation of A2E oxiranes in a mouse model of Stargard'ts macular degeneration," Proc Natl Acad Sci (2004), Vol. 101, pp. 5928-5933.	☐
49	ROBISON, et al. "Deficiencies of vitamins E and A in the rat. Retinal damage and lipofuscin accumulation," Invest Ophthalmol Vis Sci (1980), Vol. 19, pp. 1030-1037.	☐
50	SAETTEL, et al. "Ab initio studies of [1 ,5]-H Shifts: pentadiene and beyond," J. Org. Chem. (2000), Vol. 65, pp. 2331-2336.	☐

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	14510975
Filing Date	2014-10-09
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Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	13533-541US2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

- ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

- ☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

- ☐ See attached certification statement.
- ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Joseph A. Coppola/	Date (YYYY-MM-DD)	2015-01-20
Name/Print	Joseph A. Coppola	Registration Number	38413

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 14/510,975				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A				
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	300		N/A				
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A				
TOTAL CLAIMS (37 CFR 1.16(j))	29 minus 20 =	*	x 40 =	360	OR					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00						
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00						
			TOTAL	1090		TOTAL				
* If the difference in column 1 is less than zero, enter "0" in column 2.										
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY		
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.										



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
14/510,975	10/09/2014	1629	1090	13533/541US2	29	1

CONFIRMATION NO. 6583

26646
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

FILING RECEIPT



Date Mailed: 10/20/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Ilyas Washington, New York, NY;

Applicant(s)

The Trustees of Columbia University in the City of New York, New York, NY

Power of Attorney: The patent practitioners associated with Customer Number 26646

Domestic Priority data as claimed by applicant

This application is a DIV of 12/733,631 10/14/2010 PAT 8877809
which is a 371 of PCT/US08/10676 09/12/2008
which claims benefit of 60/993,379 09/12/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 10/16/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/510,975**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

Compositions and Methods for Treating Macular Degeneration

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/510,975	10/09/2014	Ilyas Washington	13533/541US2

CONFIRMATION NO. 6583

FORMALITIES LETTER



26646
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

Date Mailed: 10/20/2014

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given **TWO MONTHS** from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
 - The line spacing on the specification, claims, and/or abstract is not 1½ or double spaced (see 37 CFR 1.52(b)).
 - The application contains drawings, but the specification does not contain a brief description of the several views of the drawings as required by 37 CFR 1.74 and 37 CFR 1.77(b)(9).

The following item(s) appear to have been **omitted** from the application:

- Figure(s) **3A-3C, 4C, 5A-5C, 6A-6D, 7A-7C** described in the specification.

Applicant must reply to this notice within the time period set forth in this notice to avoid abandonment of this application. Applicant must select one of the three following options and the reply must comply with the requirements set forth in the selected option and any other requirements set forth in this notice. The reply should also indicate which option applicant has selected.

I. Petition for date of deposit: Should applicant contend that the above-noted omitted item(s) was in fact deposited in the U.S. Patent and Trademark Office (USPTO) with the nonprovisional application papers, a copy of this Notice and a petition (and the petition fee set forth in 37 CFR 1.17(f) with evidence of such deposit **must** be filed within **TWO MONTHS** of the date of this Notice. The petition fee will be refunded if it is determined that the item(s) was received by the USPTO. **THIS TWO MONTH PERIOD IS EXTENDABLE UNDER 37 CFR 1.136(a) or (b).**

II. Petition for later filing date: Should applicant desire to supply the omitted item(s) and accept the date that such omitted item(s) was filed in the USPTO as the filing date of the above-identified application, a copy of this Notice, the omitted item(s), and a petition under 37 CFR 1.182 with the petition fee set forth in 37 CFR 1.17(f)

requesting the later filing date **must** be filed within **TWO MONTHS** of the date of this Notice. **THIS TWO MONTH PERIOD IS EXTENDABLE UNDER 37 CFR 1.136(a) or (b).**

Applicant is advised that generally the filing fee required for an application is the filing fee in effect on the filing date accorded the application and that payment of the requisite basic filing fee on a date later than the filing date of the application requires payment of a surcharge (37 CFR 1.16(f)). To avoid processing delays and payment of a surcharge, applicant should submit any balance due for the requisite filing fee based on the later filing date being requested when submitting the omitted item(s) and the petition (and petition fee) requesting the later filing date.

III. Acceptance of application as deposited: Applicant may accept the application as deposited in the USPTO by filing an appropriate amendment as set forth in either (A) or (B) below within **TWO MONTHS** of the date of this Notice. **THIS TWO MONTH PERIOD IS EXTENDABLE UNDER 37 CFR 1.136(a) or (b)**. The application will maintain a filing date as of the date of deposit of the application papers in the USPTO, and original application papers (i.e., the original disclosure of the invention) will include only those application papers present in the USPTO on the date of deposit. A petition is not required for this option.

(A) If applicant wants to accept the application as deposited without adding the subject matter that was in the omitted item (e.g., a missing page or figure), applicant is required to submit one or more of the following items without adding any new matter (see 35 U.S.C. 132(a)):

1. For a missing page of the specification,
 - a) a substitute specification including claims that amends the specification to renumber the pages consecutively and cancels any incomplete sentences, and
 - b) a statement that the substitute specification includes no new matter, in compliance with 37 CFR 1.121(b)(3) and 1.125;
2. For a missing figure of the drawings,
 - a) replacement drawing sheets in compliance with 37 CFR 1.121(d) to renumber the drawing figures consecutively (if necessary),
 - b) a substitute specification excluding claims that amends the specification to cancel any references to any omitted drawing(s) and corrects the references in the specification to the drawing figures to correspond with any relabeled drawing figures, and
 - c) a statement that the substitute specification includes no new matter, in compliance with 37 CFR 1.121(b)(3) and 1.125;
3. For a missing page of the claim listing only, a replacement claim listing with the claims renumbered consecutively or, if amendment to the claims is also necessary, then a complete claim listing in compliance with 37 CFR 1.121(c);
4. For a missing or unreadable compact disc,
 - a) a substitute specification (excluding the claims) deleting the reference to the compact disc and the files contained on the compact disc, and
 - b) a statement that the substitute specification includes no new matter, in compliance with 37 CFR 1.121(b)(3) and 1.125; and
5. For a missing or unreadable file submitted on a compact disc,
 - a) a substitute specification (excluding the claims) deleting the reference to the missing or unreadable file, and a statement that the substitute specification includes no new matter, in compliance with 37 CFR 1.121(b)(3) and 1.125; and
 - b) a replacement transmittal letter listing all of the files except the missing or unreadable file in compliance with 37 CFR 1.52(e)(3)(ii).

(B) Alternatively, if applicant wants to accept the application as deposited but wishes to add the subject matter in the omitted item (e.g., a missing page or figure) by relying on an incorporation by reference under 37 CFR 1.57 or other portions of the original disclosure, applicant is required to submit one or more of the following items without adding any new matter (see 35 U.S.C. 132(a)):

1. To add the subject matter in a missing page of specification,
 - a) a substitute specification excluding claims and

- b) a statement that the substitute specification includes no new matter, in compliance with 37 CFR 1.121(b)(3) and 1.125;
- 2. To add a missing figure of the drawings, new and replacement drawing sheets in compliance with 37 CFR 1.121(d);
- 3. To add the subject matter in a missing page of the claim listing, a complete claim listing in compliance with 37 CFR 1.121(c) (e.g., a claim in the missing page should be submitted as a new claim);
- 4. To add the subject matter in a missing or unreadable compact disc,
 - a) a replacement compact disc and a duplicate copy of the compact disc, in compliance with 37 CFR 1.52(e); and
 - b) a statement that the replacement compact disc contains no new matter in compliance with 37 CFR 1.52(e)(4); and,
- 5. To add the subject matter in a missing or unreadable file submitted on a compact disc,
 - a) a replacement compact disc that contains all of the files listed in the specification including the missing or unreadable file and a duplicate copy of the compact disc, in compliance with 37 CFR 1.52(e); and
 - b) a statement that the replacement compact disc contains no new matter in compliance with 37 CFR 1.52(e)(4).

If applicant is relying on an incorporation by reference under 37 CFR 1.57 to add the omitted subject matter, then applicant must also comply with the requirements of 37 CFR 1.57.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
The surcharge is due for any one of:
 - late submission of the basic filing fee, search fee, or examination fee,
 - late submission of inventor's oath or declaration,
 - filing an application that does not contain at least one claim on filing, or
 - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ **70** surcharge.
- \$ (0) previous unapplied payment amount.
- \$ **70** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Ilyas Washington

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice".
<https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html>

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at <http://www.uspto.gov/ebc>.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/emikru/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application Serial No. 14/510,975

Filed: October 9, 2014

Art Unit: To be determined

For: Compositions and Methods for Treating Macular
Degeneration

Examiner: To be determined

VIA EFS-Web
Commissioner for Patents
P.O. Box 1470
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being electronically
transmitted to the United States Patent and Trademark Office via the
Office Electronic Filing System on **October 16, 2014.**

Signature: /Loretta E. Charles/
Loretta E. Charles

SECOND PRELIMINARY AMENDMENT

Dear Sir/Madam:

Prior to examination on the merits, please consider the following amendments and
remarks.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CLAIMS

Listing of Claims:

1-49. (canceled)

50. (previously presented) A pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid and a pharmaceutically acceptable carrier, wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

51. (new) The pharmaceutical composition according to Claim 50, wherein the substituted C₂₀-D₁₋₃-retinoid is C₂₀-D₃-retinol, C₂₀-D₃-retinol ester, C₂₀-D₃-retinal or a C₂₀-D₃-pro-vitamin A carotenoid.

52. (new) The pharmaceutical composition according to Claim 51, wherein the C₂₀-D₁₋₃-retinoid is C₂₀-D₃-retinol acetate.

53. (new) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is in unit dosage form.

54. (new) The pharmaceutical composition according to Claim 50, wherein the C₂₀-D₃-retinoid, corresponding to the aldehyde of the C₂₀-D₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

55. (new) The pharmaceutical composition according to Claim 50, wherein the C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

56. (new) The pharmaceutical composition according to Claim 50 further comprising an effective amount of a supplement selected from the group consisting of a visual cycle antagonist, a molecule that inhibits influx of a retinoid into an eye, and combinations thereof.

57. (new) The pharmaceutical composition according to Claim 56, wherein the visual cycle antagonist is selected from the group consisting of TDH, TDT, 13-cis-retinoic acid, ret-NH₂, and combinations thereof.

58. (new) The pharmaceutical composition according to Claim 56, wherein the molecule that inhibits influx of a retinoid into an eye is fenretinide.

- 59.** (new) The pharmaceutical composition according to Claim 50 further comprising one or more additives.
- 60.** (new) The pharmaceutical composition according to Claim 59, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.
- 61.** (new) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 80 mg.
- 62.** (new) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 10 mg.
- 63.** (new) The pharmaceutical composition according to Claim 60, wherein the zinc is present in the pharmaceutical composition at between about 10 to about 80 mg.
- 64.** (new) The pharmaceutical composition according to Claim 60, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 3,000 mg.
- 65.** (new) The pharmaceutical composition according to Claim 60, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 15 mg.
- 66.** (new) The pharmaceutical composition according to Claim 60, wherein the vitamin E is present in the pharmaceutical composition at between about 15 to about 3,000 mg.
- 67.** (new) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.1 mg.
- 68.** (new) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.015 mg.
- 69.** (new) The pharmaceutical composition according to Claim 60, wherein the vitamin D is present in the pharmaceutical composition at between about 0.015 to about 0.1 mg.
- 70.** (new) The pharmaceutical composition according to Claim 50, wherein the substituted C₂₀-D₁₋₃-retinoid is present in the pharmaceutical composition at a level sufficient to deliver on average about 0.1 to about 90 mg/day to a patient.
- 71.** (new) The pharmaceutical composition of Claim 50, wherein the pharmaceutical composition comprises an additional active.

72. (new) The pharmaceutical composition according to Claim 71, wherein the additional

active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

73. (new) The pharmaceutical composition according to Claim 72, wherein the eye antioxidant is selected from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a trolox analogue (PNU-83836-E), bilberry extract, and combinations thereof.

74. (new) The pharmaceutical composition according to Claim 72, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

75. (new) The pharmaceutical composition according to Claim 72, wherein the negatively charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

76. (new) The pharmaceutical composition according to Claim 50, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

77. (new) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is suitable for administration directly to the eye.

78. (new) The pharmaceutical composition according to Claim 50, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

Remarks

Before this Amendment, claim 50 was pending. By this Amendment, new claims 51-78 have been added. Each new claim presented herein corresponds to a claim presented in the parent application, where an explanation of the support for each claim was provided. The following paragraph identifies the corresponding claim in the parent application for each new claim.

Claim 51 corresponds to Claim 62 in the parent application; Claim 52 corresponds to Claim 57 in the parent application; Claim 53 corresponds to Claim 52 in the parent application; Claim 54 corresponds to Claim 58 in the parent application; Claim 55 corresponds to Claim 59 in the parent application; Claim 56 corresponds to Claim 84 in the parent application; Claim 57 corresponds to Claim 85 in the parent application; Claim 58 corresponds to Claim 86 in the parent application; Claim 59 corresponds to Claim 87 in the parent application; Claim 60 corresponds to Claim 88 in the parent application; Claims 61-69 correspond to Claim 89-97 in the parent application; Claim 70 corresponds to Claim 98 in the parent application; Claim 71 corresponds to 99 in the parent application; Claim 72 corresponds to Claim 100 in the parent application; Claim 73 corresponds to Claim 101 in the parent application; Claim 74 corresponds to Claim 102 in the parent application; Claim 75 corresponds to Claim 103 in the parent application; Claim 76 corresponds to Claim 104 in the parent application; Claim 77 corresponds to Claim 107 in the parent application; and Claim 78 corresponds to Claim 111 in the parent application.

Respectfully submitted,

Date: October 16, 2014

BY: /Joseph A. Coppola/
Joseph A. Coppola
Reg. No. 38,413

KENYON & KENYON LLP
One Broadway
New York, NY 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)
Customer No. 26646

Electronic Patent Application Fee Transmittal

Application Number:	14510975			
Filing Date:				
Title of Invention:	Compositions and Methods for Treating Macular Degeneration			
First Named Inventor/Applicant Name:	Ilyas Washington			
Filer:	Joseph A. Coppola/Loretta E. Charles			
Attorney Docket Number:	13533/541US2			
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	9	40	360
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Total in USD (\$)				360

Electronic Acknowledgement Receipt

EFS ID:	20432923
Application Number:	14510975
International Application Number:	
Confirmation Number:	6583
Title of Invention:	Compositions and Methods for Treating Macular Degeneration
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	26646
Filer:	Joseph A. Coppola/Loretta E. Charles
Filer Authorized By:	Joseph A. Coppola
Attorney Docket Number:	13533/541US2
Receipt Date:	16-OCT-2014
Filing Date:	
Time Stamp:	13:22:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$ 360
RAM confirmation Number	11505
Deposit Account	110600
Authorized User	KENYON & KENYON LLP

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13533-541US2_2nd-Preliminary-Amendment-9-16-2014.pdf	175451 921a24b6214c148cab05dcab26380cdb0af5f662	yes	7
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Preliminary Amendment		3	7	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	29743 703d5aa074a0aff5bd11f59678c2c0989b8cb886	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			205194		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s) : Ilyas Washington
 Serial No. : 14/510,975
 Filed : October 9, 2014
 For : Compositions and Methods for Treating Macular Degeneration
 Art Unit : TBD
 Examiner : TBD
 Confirmation No. : 6583

Commissioner for Patents
 P.O. Box 1450
 Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Sir/Madam:

Transmitted herewith is a Second Preliminary Amendment for entry into the above-identified application.

The additional claims fee is calculated below.

	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT NUMBER EXTRA	RATE (\$) PER CLAIM	FEE (\$)
BASIC FEE						
TOTAL CLAIMS	29	9	20	9	x 80.00	720.00
INDEPENDENT CLAIMS						
MULTIPLE DEPENDENT CLAIM						
If Small Entity, divide total by 2					TOTAL	720.00
Small Entity					Total Due	360.00

The additional claims fee of \$360.00 is being submitted herewith.

Applicant believes that no additional fees are due. However, if any additional fees are required, the Director is authorized to charge said fees and/or credit any overpayments to Kenyon & Kenyon LLP Deposit Account No. 11-0600.

Respectfully Submitted,

Dated: October 16, 2014

By: /Joseph A. Coppola/

Joseph A. Coppola

Reg. No. 38,413

KENYON & KENYON LLP

One Broadway

New York, New York 10004

(212) 425-7200

CUSTOMER NO.: 26646

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Divisional of U.S. Patent Application Serial No.
12/733,631

Filed: Herewith

Art Unit: To be determined

For: Compositions and Methods for Treating Macular
Degeneration

Examiner: To be determined

VIA EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being electronically
transmitted to the United States Patent and Trademark Office via the
Office Electronic Filing System on **October 9, 2014.**

Signature: /Loretta E. Charles/
Loretta E. Charles

PRELIMINARY AMENDMENT

Dear Sir/Madam:

Prior to application on the merits, please consider the following amendments and
remarks.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks begin on page 4 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph 2 on page 1 as follows:

This application is a divisional of U.S. Patent Application Serial No. 12/733,631,
which is a U.S. National Stage Application of International Application No.
PCT/2008/010676, which was filed on September 12, 2008, and which claims
priority to U.S. Provisional Application No. 60/993,379, which was filed on
September 12, 2007, all of which are incorporated by reference as if recited in full
herein.

CLAIMS

Listing of Claims:

1-49. (canceled)

50. (new) A pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid and a pharmaceutically acceptable carrier, wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

Remarks

Before this Amendment, claims 1-49 were pending. By this Amendment, claims 1-49 have been canceled and new claim 50 added. Accordingly, claim 50 is now pending. Support for claim 50 is found in the application as filed at page 10, paragraph [0031]; original claim 22; and pages 18-19, paragraph [0057].

Respectfully submitted,

Date: October 9, 2014

BY: /Joseph A. Coppola/
Joseph A. Coppola
Reg. No. 38,413

KENYON & KENYON LLP
One Broadway
New York, NY 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)
Customer No. 26646

Electronic Patent Application Fee Transmittal				
Application Number:				
Filing Date:				
Title of Invention:		Compositions and Methods for Treating Macular Degeneration		
First Named Inventor/Applicant Name:		Ilyas Washington		
Filer:		Joseph A. Coppola/Loretta E. Charles		
Attorney Docket Number:		13533/541US2		
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				730

Electronic Acknowledgement Receipt

EFS ID:	20379576
Application Number:	14510975
International Application Number:	
Confirmation Number:	6583
Title of Invention:	Compositions and Methods for Treating Macular Degeneration
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	26646
Filer:	Joseph A. Coppola/Loretta E. Charles
Filer Authorized By:	Joseph A. Coppola
Attorney Docket Number:	13533/541US2
Receipt Date:	09-OCT-2014
Filing Date:	
Time Stamp:	18:08:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$730
RAM confirmation Number	4537
Deposit Account	110600
Authorized User	KENYON & KENYON LLP

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	13533-541US2-ADS.pdf	1571930	no	7
			acbe63fd81ccf37debfd1505cf1473d48da54b8b		
Warnings:					
Information:					
2		13533-541US2_Application.pdf	386156	yes	49
			370eb52f5334b81889903bc94014872c06b4c614		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	41	
	Claims		42	48	
	Abstract		49	49	
Warnings:					
Information:					
3	Drawings-only black and white line drawings	13533-541US2_Figures.pdf	554015	no	7
			64b4c6e80a6f6a32f80c4cd4ab90e055ef20d5f3		
Warnings:					
Information:					
4	Preliminary Amendment	13533-541US2_Preliminary-Amendment.pdf	133191	no	4
			f9e9febeaf03cef58746ebd883a740830e6a3857		
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	32490	no	2
			008c37c895327fd7ea1c07a06f4a563c7c856b79		
Warnings:					
Information:					
Total Files Size (in bytes):			2677782		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	13533/541US2
		Application Number	
Title of Invention	Compositions and Methods for Treating Macular Degeneration		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2

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Application Information:

Title of the Invention	Compositions and Methods for Treating Macular Degeneration		
Attorney Docket Number	13533/541US2	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	7	Suggested Figure for Publication (if any)	

Filing By Reference :

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	13533/541US2
		Application Number	
Title of Invention	Compositions and Methods for Treating Macular Degeneration		

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For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

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Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	12733631	2010-10-14
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12733631	a 371 of international	PCT/US08/10676	2008-09-12
Prior Application Status	Expired	Remove	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	13533/541US2
		Application Number	
Title of Invention	Compositions and Methods for Treating Macular Degeneration		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US08/10676	Claims benefit of provisional	60993379	2007-09-12
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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

☐ 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	13533/541US2
		Application Number	
Title of Invention	Compositions and Methods for Treating Macular Degeneration		

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		Application Number	
Title of Invention	Compositions and Methods for Treating Macular Degeneration		
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First Name	Joseph A.	Last Name	Coppola	Registration Number
				38413
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	13533/541US2
		Application Number	
Title of Invention	Compositions and Methods for Treating Macular Degeneration		

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COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

GOVERNMENT FUNDING

[0001] This invention was made with government support under Grant EY T32 013933 awarded by the National Eye Institute of the National Institutes of Health. The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] The present application claims the benefit of U.S. provisional patent application no. 60/993,379, filed 12 September 2007, which is incorporated by reference as if recited in full herein.

FIELD OF THE INVENTION

[0003] The present invention relates, inter alia, to compounds, compositions, and methods to slow lipofuscin formation/accumulation in order to treat or ameliorate an ophthalmologic disorder, such as, e.g., macular degeneration, without, or with reduced, adverse visual effects. More particularly, the present invention relates to compounds and compositions that may be used to treat or ameliorate an ophthalmologic disorder, such as, e.g., macular degeneration, by slowing or limiting the accumulation of age pigments or lipofuscin in the retinal pigment epithelium ("RPE") cells of the retina. The present invention also relates to methods of treating or ameliorating an ophthalmologic disorder, such as, e.g., macular degeneration, in a mammal by administering to a mammal in need of such treatment an effective amount of the compounds and/or compositions disclosed herein.

BACKGROUND OF THE INVENTION

[0004] The macula is located at the back of the eye in the center of the retina. When the millions of cells in this light-sensitive, multilayer tissue deteriorate, central vision is lost along with the ability to perform tasks such as reading, writing, driving, and seeing color. This “macular degeneration” principally affects the elderly and has a prevalence of about 3% in populations between 75-79 years of age and about 12% for populations over 80 years of age.(1) In younger populations, macular degeneration is found in individuals with genetic disorders, such as Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy and Malattia Leventinese (Dojne Honeycomb or Dominant Radial Drusen). Stargardt Disease is the most common form of inherited juvenile macular degeneration, affecting about 1 in 10,000 children.

[0005] There are no therapies currently available for genetic or dry (non-neovascular) age related macular degeneration. Vitamin supplements such as antioxidants, and diet changes, such as low fat diets, have been shown to slow disease progression in some clinical studies. However, for the majority of patients, diagnosis is followed by the progressive loss of central vision.(2-4)

[0006] The above listed macular dystrophies are all marked by the accumulation of lipofuscin, fluorescent deposits, in the retinal pigment epithelium (RPE) cell layer (5-11). The only compounds that have been characterized to date from RPE lipofuscin, A2E (N-retinylidene-N-retinylethanolamine) and ATR-dimer (all-*trans*-retinal dimer), are derived from reactions of all-*trans*-retinal, an isomer of 11-*cis*-retinal, the chromophore of the visual pigments (12, 13). These toxic retinal dimers have been shown to cause RPE cell death, which is thought to lead to photoreceptor cell degeneration and vision loss (2, 14-22). Slowing the visual cycle

using RPE 65 antagonists (23-25) or retarding the delivery of vitamin A (retinol) to the RPE by, *e.g.*, limiting dietary intake of vitamin A (26) or blocking serum retinol binding proteins (27) have been shown to impede or abolish RPE lipofuscin formation in animal models. Conversely, increasing the amount of all-*trans*-retinal in outer segments, such as occurs with the mutations in *abcr*^{-/-} (responsible for recessive Stargardt disease), leads to the rapid accumulation of lipofuscin pigments (8).

[0007] The above cited evidence leads to the conclusion that lipofuscin and/or A2E and ATR-dimer in RPE cells may reach levels that contribute to a decline in cell function followed by vision loss and that vitamin A plays an important role in ocular lipofuscin formation. (28)

[0008] Several vitamin A analogs have been shown to limit lipofuscin formation in a mouse model by slowing down the visual cycle. The ABCR^{-/-} mouse model has been used to test approaches to limit RPE lipofuscin formation. Mice lacking the ABCR (also known as ABCA4) gene encoding a photoreceptor-specific adenosine triphosphate (ATP)-binding cassette transporter, lack the ability to properly shuttle vitamin A (in the form of retinal) in the eye. ABCR^{-/-} mice were developed as an animal model of human recessive Stargardt's Disease (8). As in humans with recessive Stargardt's disease, ABCR^{-/-} mice accumulate large lipofuscin deposits in RPE cells of their eyes, as shown in FIG. 1, and eventually experience delayed dark adaptation. Lipofuscin accumulation and vision loss observed in this mouse model is also thought to be relevant to age-related macular degeneration (AMD) and other macular dystrophies.

[0009] In attempts to slow down the visual cycle, visual cycle enzymes have been targeted. In such approaches, small molecules have been proposed as

antagonists to visual cycle enzymes. In this methodology, the drug (often a vitamin A derivative) binds to visual cycle proteins, which blocks participation by the proteins in the visual cycle, and slows the visual cycle. Another approach to slowing the visual cycle includes impeding the delivery of vitamin A from the blood to the eye.

[0010] Drug candidates for inhibiting lipofuscin formation by slowing down the visual cycle have been evaluated by their ability to cause delayed dark adaptation (a side effect of an impaired visual cycle) and their ability to impede the age related accumulation of eye lipofuscin as measured by the concentration of A2E and other byproducts of the visual cycle, e.g., ATR-dimer. Examples of such drug candidates and their corresponding mechanisms of action to slow the visual cycle are summarized below:

[0011] 13 *cis*-retinoic acid (Acutane or isotretinoin) is thought to inhibit the enzymes 11-*cis*-retinol dehydrogenase and RPE65 involved in the visual cycle.(19, 24) When administered, 13 *cis*-retinoic acid has been shown to cause delayed dark adaptation. When 3-month-old ABCR knockout mice (n=3) were administered 13-*cis*-retinoic acid at 40 mg/kg/day for one month, the mice showed a decrease in A2E formation by about 40-50% compared to control ABCR knockout mice (n=3).(24) Furthermore, when 2-month-old ABCR knockout mice were administered 13-*cis*-retinoic acid at 20 mg/kg/day for two months, the mice also showed a decrease in lipofuscin formation in the RPE cell layer as judged by electron microscopy.

[0012] (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one (TDT) is thought to inhibit RPE65.(23) When TDT is administered to mice, delayed dark adaptation is observed. When 2-month-old ABCR knockout mice (n=2) were administered TDT at 50 mg/kg bi-weekly for two months, they showed a decrease in

A2E formation by about 50-85% compared to control ABCR knockout mice (n=2).(23)

[0013] (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine (TDH) is also thought to inhibit RPE65 and when given to mice, causes delayed dark adaptation.(23) When 2-month-old ABCR knockout mice (n=2) were administered TDH at 50 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50% compared to control ABCR knockout mice (n=2).(23)

[0014] All-*trans*-retinylamine (Ret-NH₂) is thought to inhibit RPE65 and when administered to mice results in severe delayed dark adaptation. When 1-month-old ABCA4 knockout mice were given Ret-NH₂ at 40 mg/kg bi-weekly for two months, they showed a decrease in A2E formation by about 50% compared to control ABCA4 knockout mice.(25)

[0015] N-(4-hydroxyphenyl) retinamide (Fenretinide) slows the influx of retinol into the eyes by reducing levels of vitamin A bound to serum retinol-binding protein. Thus, treatment with Fenretinide lowers the levels of vitamin A in the eye which leads to delayed dark adaptation. When 2-month-old ABCA4 knockout mice (n=3) were administered Fenretinide at 20 mg/kg/day for one month, they showed a decrease in A2E formation by about 40-50% compared to control ABCA4 knockout mice (n=3).(27)

[0016] Thus, recently proposed therapeutic approaches to limit lipofuscin formation are based upon slowing the visual cycle (1, 10, 11, 12). There are, however, disadvantages to slowing the visual cycle as a means to impede lipofuscin formation in order to prevent, e.g., macular degeneration. Four of these disadvantages are detailed below.

[0017] 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. Poor night vision (Scotopic dysfunction) is already a functional marker of early age-related maculopathy (ARM), and has been linked to the occurrence of falls and vehicle collisions.(29, 30) A further slowing down of the visual cycle is expected to make night vision worse in patients who already suffer from poor night vision.

[0018] Second, in order to sufficiently impede lipofuscin formation, one would have to slow down the visual cycle for a prolonged period of time. But, long-term slowing of the visual cycle leads to photoreceptor cell death and loss of vision.(31, 32) In fact, impairment of the visual cycle is the cause of various retinal diseases such as Stargardt's disease, retinitis pigmentosa, Lebers Congenital Amaurosis, Fundus Albipunctatus, age-related macular degeneration and Congenital Stationary Night Blindness.

[0019] Third, the above methodology often uses vitamin A analogs to impede proteins involved in vitamin A processing in the eye. However, vitamin A analogs of diverse structures, pharmacological profiles, receptor affinities, and biologic activities have been shown to be toxic. Indeed, numerous vitamin A analogs have been shown in experimental animal models, cellular models, epidemiological data and clinical trials to inhibit or retard various biological functions such as, for example, bone growth, reproduction, cell division, cell differentiation and regulation of the immune system.(33-37). Thus, inhibiting vitamin A processing in the eye is also expected to retard some of these basic bodily functions, which may lead to significant adverse side effects.

[0020] For example, vitamin A analogs that are currently used to treat certain cancers and/or psoriasis such as, e.g., Bexarotene (Targretin), Etretinate (Tegison)

Acitretin (Soriatane), Fenretinide (*N*-(4-hydroxyphenyl) retinamide or 4-HPR) and 13 *cis*-retinoic acid (Accutane or isotretinoin) have side effects, which include, e.g., dry nose, nosebleeds, chapped lips, mouth sores, increased thirst, sore tongue, bleeding gums, dry mouth, cold sores, dry or irritated eyes, dry skin, peeling or scaly skin, hair loss, easy bruising, muscle aches, nausea, stomach upset, cough or swelling of the hands or feet, vision problems, chest pain, tightness in the chest, abnormal pulse, dizziness, vomiting, severe headache, and yellowing of the eyes/skin (jaundice).(38-40)

[0021] Fourth, in animal models, candidate drugs for limiting lipofuscin formation have been shown to be effective only in relatively large doses. For example, studies in mouse models typically use doses around 11-40 mg/kg/day. But, current vitamin A analogs are typically used in the clinic at doses of 1-3 mg/kg/day to minimize side effects. Larger dosing regimes will lead to increased side effects.

[0022] For example, Fenretinide (*N*-(4-hydroxyphenyl) retinamide or 4-HPR) is currently used to treat cancer and clinical trials are in progress for AMD. The most common adverse effects reported among 1,432 patients who underwent treatment with this drug at a dosage of 200 mg/day for a five year period were: diminished dark adaptation, cumulative incidence (16%) and dermatologic disorders (16%). Less common effects were gastrointestinal symptoms (8%) and disorders of the ocular surface (8%).(41) At this relatively low dose a delay in dark adaptation, an assessment of the effectiveness of a drug to impede lipofuscin formation, was only observed in 16% of patients. In another study when patients were administered larger oral doses of 600 or 900 mg/m² bid in 6-week cycles, mild to moderate adverse effects were reported in 43 (95%) of the 45 patients that were possibly

linked to Fenretinide. These side effects included: fatigue, headache, skin changes (dry skin, pruritus, and rash) and digestive tract symptoms (abdominal pain, cramping, diarrhea, stomatitis, and xerostomia). Grade 2 toxicities reported as possibly linked to Fenretinide treatment included seizures and confusion.(42)

[0023] A patient with an anaplastic astrocytoma who had been receiving treatment with Fenretinide at the 600 mg/m² bid dose for one cycle presented with headaches, nausea, and vomiting, and was found to have a small intracranial bleed in the region of the basal ganglia. He recovered without deficits and continued treatment without further events. Another patient, who was also undergoing treatment at the 600 mg/m² bid dosage and was receiving oral anticoagulation with warfarin for deep venous thrombosis, died after developing an uncontrollable nasal bleed (international normalized ratio > 6.0). Of the four patients treated at the 900 mg/m² bid dose, one had grade 3 vomiting, grade 2 speech impairment, and grade 1 memory impairment, which improved without residual symptoms.(42)

[0024] A typical dose of 13 *cis*-retinoic acid (Accutane or isotretinoin) for treatment of acne is 0.5 to 1 mg/kg/day for children and 2.0 mg/kg/day for adults for fourteen days in a row, followed by a 14-day break. This twenty-eight day course is usually repeated five more times.(40) These doses are about 10 to 80 times less than what was used in mice to impede A2E formation.(24) For larger doses of 13 *cis*-retinoic acid used to treat cancer, side effects occurring in more than 30% of users included headache, fever, dry skin, dry mucous membranes (mouth, nose), bone pain, nausea and vomiting, rash, mouth sores, itching, sweating, and eyesight changes.(43, 44)

[0025] Side effects occurring in 10-29% of users of 13 *cis*-retinoic acid include back pain, muscle and joint pain, allergic reaction, abdominal pain, poor appetite,

dizziness, drowsiness, insomnia, anxiety, numbness and tingling of hands and feet, weakness, depression, hair loss (thinning), dry eyes, sensitivity to light (see eye problems), decreased night vision, which may persist after treatment is stopped, feet or ankle swelling, and low blood counts.(44) In addition, it has been observed that white and red blood cells and platelets may temporarily decrease, which may put a patient at increased risk for infection, anemia and/or bleeding. Side effects also include abnormal blood tests: increased triglyceride, cholesterol and/or blood sugar levels.

[0026] The above disadvantages make slowing of the visual cycle a difficult methodology to adapt alone for the clinical treatment of ophthalmologic disorders, e.g., macular degeneration.

SUMMARY OF THE INVENTION

[0027] Accordingly, it would be advantageous to provide treatments for ophthalmologic disorders, e.g., macular degeneration, that do not have, or limit one or more of, the side effects summarized above. In particular, it would be advantageous to provide compounds, compositions, and methods for impeding or halting the accumulation of lipofuscin or age pigments in the RPE cells of the retina without slowing, or slowing minimally, the visual cycle.

[0028] In this regard, one embodiment of the present invention is a method of retarding formation of a lipofuscin pigment in the retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

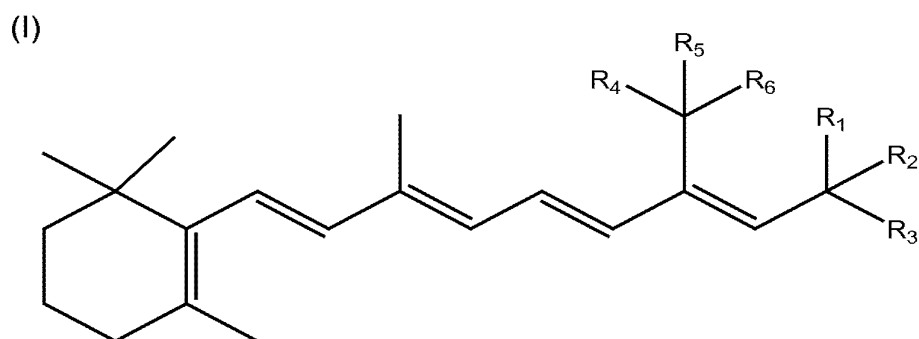
[0029] Another embodiment of the present invention is method of treating or ameliorating the effects of a disease characterized by an accumulation of a

lipofuscin pigment in a retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

[0030] A further embodiment of the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate in a patient under conditions sufficient to impede the formation of A2E.

[0031] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina containing a substituted C₂₀-retinoid and pharmaceutically acceptable carrier.

[0032] A further embodiment of the invention is a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I:



wherein:

R₁ is oxo or H;

R₂ is H or nothing;

R₃ is hydroxy or oxo or CHR₇ where R₇ forms a carotenoid and

R₄, R₅, and R₆ are independently selected from the group consisting of ¹H, ²H, ³H, halogen, and C₁₋₈alkyl.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1 shows HPLC and UV-vis profiles of lipofuscin pigments extracted from the eyecups (six of them minus the retina) of 5.5-6 month old, ABCR^{-/-} mice. Lipofuscin pigments such A2E and ATR dimer, represented by peaks 2, 3 and 4 have been characterized and are derived from all-*trans*-retinal. Other lipofuscin pigments such as peaks 1 and 5 are also derived from all-*trans*-retinal, however, they have not been fully characterized. The above pigments are also found in humans and are thought to contribute to the macular degeneration.

[0034] FIG. 2 is a reaction scheme showing the biosynthesis of A2E and ATR-dimer from all-*trans*-retinal and a biological amine.

[0035] FIG. 3A shows HPLC profiles of reaction mixtures of C₂₀-D₃-all-*trans*-retinal and all-*trans*-retinal with ethanolamine for the formation of A2E. FIG. 3B is an expanded view of FIG. 3A. A2E formation was monitored over time by measuring the appearance of peaks starting at around 15 min. Both HPLC traces were measured about 30 hours into the reactions. For all-*trans*-retinal, a considerable amount of A2E has formed as well as an unidentified compound with a retention time at around 14.5 min as seen in the expanded view. On the other hand, for C₂₀-D₃-all-*trans*-retinal A2E formation is much slower and the peak at 14.5 min is almost absent. FIG. 3C is a plot of A2E formation over time for the above reactions. C₂₀-D₃-all-*trans*-retinal forms A2E about 7-times slower than all-*trans*-retinal.

[0036] FIG. 4 shows HPLC profiles of reaction mixtures of C₂₀-D₃-all-*trans*-retinal (A) and all-*trans*-retinal (B) with proline for the formation of ATR-dimer. ATR-dimer formation was monitored over time by measuring the appearance of peaks starting at around 8 min. Both HPLC traces were measured about 1 hour into the

reactions. For all-*trans*-retinal, a considerable amount of ATR-dimer has formed. On the other hand, for C₂₀-D₃-all-*trans*-retinal ATR-dimer formation is much slower. FIG. 4C is a plot of ATR-dimer formation over time for the above reactions. C₂₀-D₃-all-*trans*-retinal forms A2E about 14-times slower than all-*trans*-retinal.

[0037] FIG. 5 shows HPLC profiles of lipofuscin pigments extracted from the eyecups (six of them minus the retina) of 5.5-6 month old, ABCR^{-/-} mice raised on a diet of either retinol acetate (trace A (FIG. 5A)) or C₂₀-D₃-all-*trans*-retinol acetate (trace B (FIG. 5B)). Mice raised on retinol acetate show considerable accumulation of lipofuscin pigments as shown by the HPLC peaks. On the other hand, lipofuscin pigments were undetectable in mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet. FIG. 5C shows plots of total retinol and retinol ester or D₃-retinol and D₃-retinol ester concentrations in the above mice raised on either the retinol acetate or C₂₀-D₃-all-*trans*-retinol acetate diets, respectively. Both groups had roughly the same amount of retinol in the eye, despite having different concentrations of lipofuscin pigments.

[0038] FIG. 6 shows electron micrographs of RPE layers from 5.5-6 month old, ABCR^{-/-} mice raised on a diet of either retinol acetate (FIGs. 6A and 6B) or C₂₀-D₃-all-*trans*-retinol acetate (FIGs. 6C and 6D). Due to the uncertainty in distinguishing lipofuscin from melanin bodies. Comparisons were made between the numbers of all dark, electron dense bodies found in the RPE between mice on the retinol acetate diet vs. those on the C₂₀-D₃-all-*trans*-retinol acetate diet. In addition to the electron dense lipofuscin and melanin bodies, RPE phagosomes, mitochondria, and lipid droplets are also present but were ultrastructurally distinct. Mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet have considerably less electron dense bodies (i.e. lipofuscin bodies) compared to mice raised on the retinol acetate diet.

[0039] FIG. 7A shows total A2E, as measured by HPLC peak area at 445 nm, for rats (three females per group) treated/raised on either retinal, C₂₀-D₃-retinal, retinal plus Fenretinide (FEN) or retinal plus TDH. Animals treated with retinal had the greatest amount of A2E-lipofuscin (normalized to 100%). Whereas, animals treated with C₂₀-D₃-retinal or retinal plus Fenretinide or the RPE65 antagonist, TDH, showed less A2E-lipofuscin. FIG. 7B shows that all four groups of animals had roughly the same amount of eye retinol. FIG. 7C shows that levels of eye all-trans-retinal were increased in the C₂₀-D₃-retinal group.

DETAILED DESCRIPTION OF THE INVENTION

[0040] In the present invention, methods are provided to slow lipofuscin formation that do not rely on slowing the visual cycle or small molecules that inhibit the visual cycle (i.e., visual cycle antagonists). Thus, many of the disadvantages, such as, delayed dark adaptation, unformed visual pigment, which can leading to vision impairment and loss, high drug doses, and the potentially adverse side effects of prior methods are avoided.

[0041] More particularly, in the present invention provides methods for selectively replacing atoms on vitamin A in order to hamper its intrinsic reactivity to form vitamin A derived lipofuscin pigments, such as, A2E and ATR dimer, while at the same time preserving the chemical structure of vitamin A such that participation in the visual cycle (binding to visual cycle proteins) is minimally disturbed. Because such changes to the structure of vitamin A do not interfere with normal vitamin A metabolism or function, one of the utilities of the present invention is that many potential side effects are avoided. Furthermore, because the compounds of the present invention (disclosed in more detail below) do not compete with natural

retinoids for protein binding (because, e.g., they can perform the job of natural retinoids), smaller doses are needed for treatment of e.g., macular degeneration, compared to previous treatments using, e.g., visual cycle antagonists.

[0042] In the present invention, when the C₂₀ hydrogens of all-*trans*-retinoids are replaced by fluorine atoms (F₃), the formation of A2E is eliminated, as measured by monitoring the disappearance of C₂₀-F₃-all-*trans*-retinal and the absence of the corresponding fluorinated A2E by HPLC. A2E and the ATR-dimer are believed to be formed *in vivo* by a multi-step reaction sequence involving two molecules of all-*trans*-retinal, as shown in FIG. 2. In the first step, all-*trans*-retinal condenses with a biological amine to form the imine. This imine is then thought to undergo a [1,5] hydrogen shift involving a hydrogen atom at carbon C₂₀ (step 2). Subsequent reaction (step 3) with another molecule of retinal either by 1,2- or 1,4-addition followed by cyclizations (step 4) yields A2E or ATR-dimer precursors, respectively. A2E is subsequently formed after spontaneous oxidation in air, and ATR dimer, after elimination (step 4).

[0043] It has been shown that replacing certain C-H bonds with C-F bonds in retinal (*i.e.*, C₂₀-F₁₋₃-retinal) hampers the reactivity of all-*trans*-retinal, and, thus slows or eliminates the formation of A2E *in vitro*. By replacing hydrogen atoms at C₂₀ with fluorine, the [1,5] hydrogen shift step is blocked. Accordingly, C₂₀-F₁₋₃-retinal is expected to appreciably slow A2E and ATR-dimer biosynthesis.

[0044] A small change in the reaction rate of all-*trans*-retinal to form its toxic dimers is expected to translate into a large decrease in RPE lipofuscin formation over a lifetime. The methods of the present invention will slow the formation of the toxic pigments and will not slow (or will not slow significantly) visual cycle kinetics, because the regeneration of 11-*cis*-retinal does not involve the breaking of the C₂₀

hydrogen bond. Therefore, treatment with a C₂₀-F₁₋₃-retinoid (which may be transformed into C₂₀-F₁₋₃-retinal in the body) will be particularly useful in impeding lipofuscin formation in humans who suffer from Stargardt Disease or other diseases or conditions associated with lipofuscin formation and/or macular degenerations.

[0045] C₂₀-D₁₋₃-retinoid according to the present invention will also be useful as a therapy to treat or ameliorate macular degeneration without adverse (or significantly adverse) visual effects. When C₂₀ hydrogens are replaced by deuteriums, A2E formation is about seven times slower (FIG. 3) and ATR-dimer formation is about 15 times slower (FIG. 4). This kinetic isotope effect will slow A2E and ATR-dimer formation *in vivo*. Deuterated vitamin A is widely used in humans and shows no toxicity (45, 46). Thus, a treatment using a C₂₀-D₁₋₃-retinoid should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects.

[0046] In view of the foregoing, one embodiment of the present invention is a method of retarding formation of a lipofuscin pigment in the retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of a C₂₀-D₁₋₃-retinoid and a C₂₀-F₁₋₃-retinoid. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, all-*trans*-retinoid (ATR)-dimer, and combinations thereof.

[0047] Preferably, the substituted C₂₀-retinoid is administered to the patient as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C₂₀-retinoid is administered as a unit dosage form.

[0048] In the present invention, the patient may be a mammal, preferably a human. In this embodiment, the substituted C₂₀-retinoid is a compound or combination of compounds disclosed herein, preferably compounds of Formula I, including Formulae Ic-Ie and Formula II, which are defined below.

[0049] In this embodiment, an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina will vary by patient and the particular substituted C₂₀-retinoid used. Typically, such amount will be about 0.05 to about 300 mg/day, including, e.g., 0.5-50, 1-25, and 3-10 mg/day.

[0050] Another embodiment of the present invention is method of treating or ameliorating the effects of an ophthalmologic disorder, such as, e.g. a disease characterized by an accumulation of a lipofuscin pigment in a retina. This method includes the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinoids and C₂₀-F₁₋₃-retinoids. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

[0051] Preferably, the substituted C₂₀-retinoid is administered as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C₂₀-retinoid is administered as a unit dosage form.

[0052] In this embodiment, the disease maybe selected from the group consisting of Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy, age related macular degeneration, and Malattia Leventinese. Preferably, the disease is macular degeneration.

[0053] In this embodiment, the administration step includes replacing a component of the patient's diet that contains retinoid(s) or Vitamin A with a

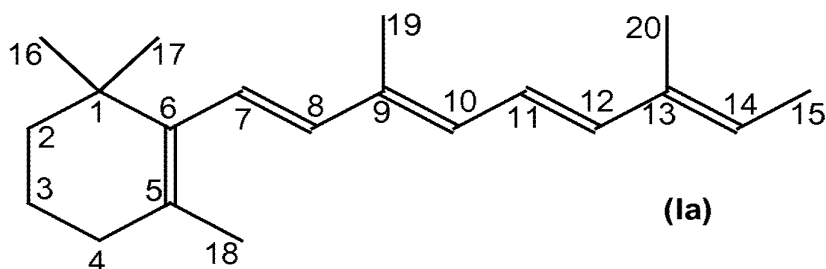
component that contains a substituted C₂₀-retinoid. By “replacing a component of a patient’s diet” it is meant that a part of the diet that contains vitamin A or its precursors (including, but not limited to carotenoids) is replaced with a component that contains a substituted C₂₀-retinoid. Preferably, from about 1% to about 95%, including, e.g., from about 5-75%, 10-50%, or 20-30%, of the retinoid(s) in the patient’s diet is replaced with a substituted C₂₀-retinoid. The replacement may be through, e.g., administering substituted C₂₀-retinoid containing foods or through treatment with compositions of the present invention, including pharmaceuticals or nutraceuticals, in lieu of consuming retinoid- or Vitamin A-containing foods that would have otherwise been consumed.

[0054] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina, which composition contains a substituted C₂₀-retinoid and a pharmaceutically acceptable carrier. Preferably, the substituted C₂₀-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinoid and C₂₀-F₁₋₃-retinoid. Preferably, the composition is in a unit dosage form. Preferably, the composition is a vitamin supplement or a pharmaceutical formulation.

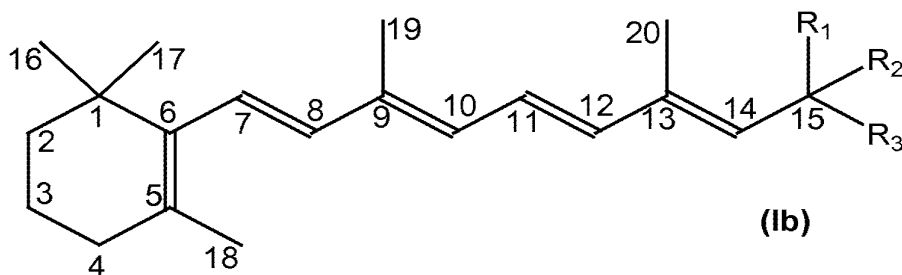
[0055] A further embodiment of the present invention is a method of retarding formation of a lipofuscin pigment selected from the group consisting of an A2E, an ATR dimer, and combinations thereof. This method comprises replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate under conditions sufficient to impede the formation of A2E, ATR dimer, or both, or an A2E and/or an ATR-dimer derivative. As used in the present invention, “conditions sufficient to impede the formation of A2E, ATR dimer, or both are well known in the art or may be determined empirically, if desired. The replacing step in this embodiment is described in more detail below.

[0056] A further embodiment of the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate under conditions sufficient to impede the formation of A2E. The replacing step in the last two embodiments may be accomplished using known method, including the methods disclosed above. For example, the substrate replacement may take place in the eye of the patient, e.g., the substrate may be administered directly to the eye via eye drops, ointment, or injection. Alternatively, the substrate may be administered systemically via, e.g., ingestion of a pill or capsule or absorption through a patch or by injection.

[0057] In the present invention, the “substituted C₂₀-retinoid” includes all retinols, retinol acetates, retinol esters, and retinoic acids as defined below as well as pharmaceutical salts thereof and metabolites thereof. For purposes of the present invention, the number scheme set forth in formula 1a for retinoids shall be used:



Thus, retinol, retinol acetate, retinol palmitate, retinoic acid, and beta-carotene have the following structures:



wherein

R_1 and R_2 are both H and R_3 is OH (retinol); or

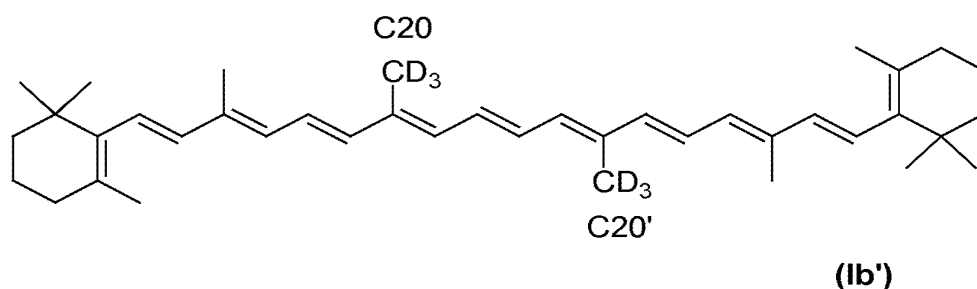
R_1 and R_2 are both H and R_3 is OCOCH_3 (retinol acetate); or

R_1 and R_2 are both H and R_3 is OCOR (retinol ester such as, e.g., retinol palmitate)

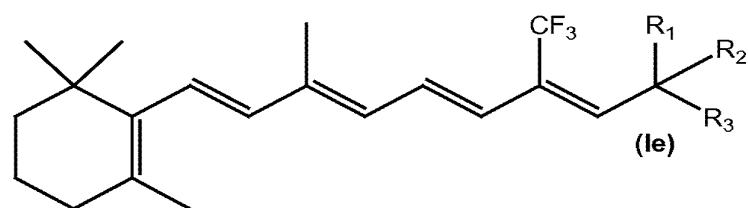
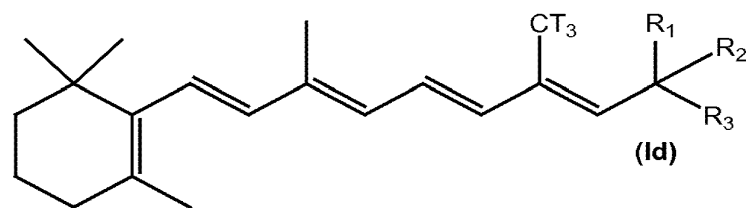
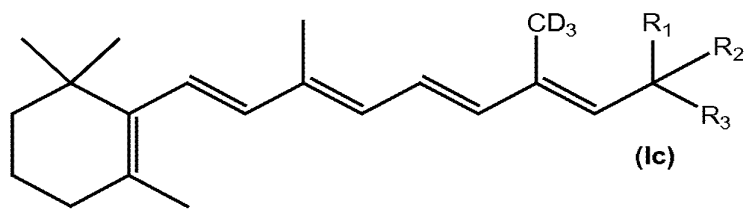
or

R_1 is $=\text{O}$, R_2 is nothing and R_3 is OH (retinoic acid) or

R_1 is H, R_3 is nothing, and R_2 is $=\text{CH-R}_7$, where R_7 forms a carotenoid. In this embodiment, R_7 together with the rest of the compound forms, e.g., a beta-carotene or another pro-vitamin A carotenoid such as the deuterated beta-carotene shown in formulae Ib' below:

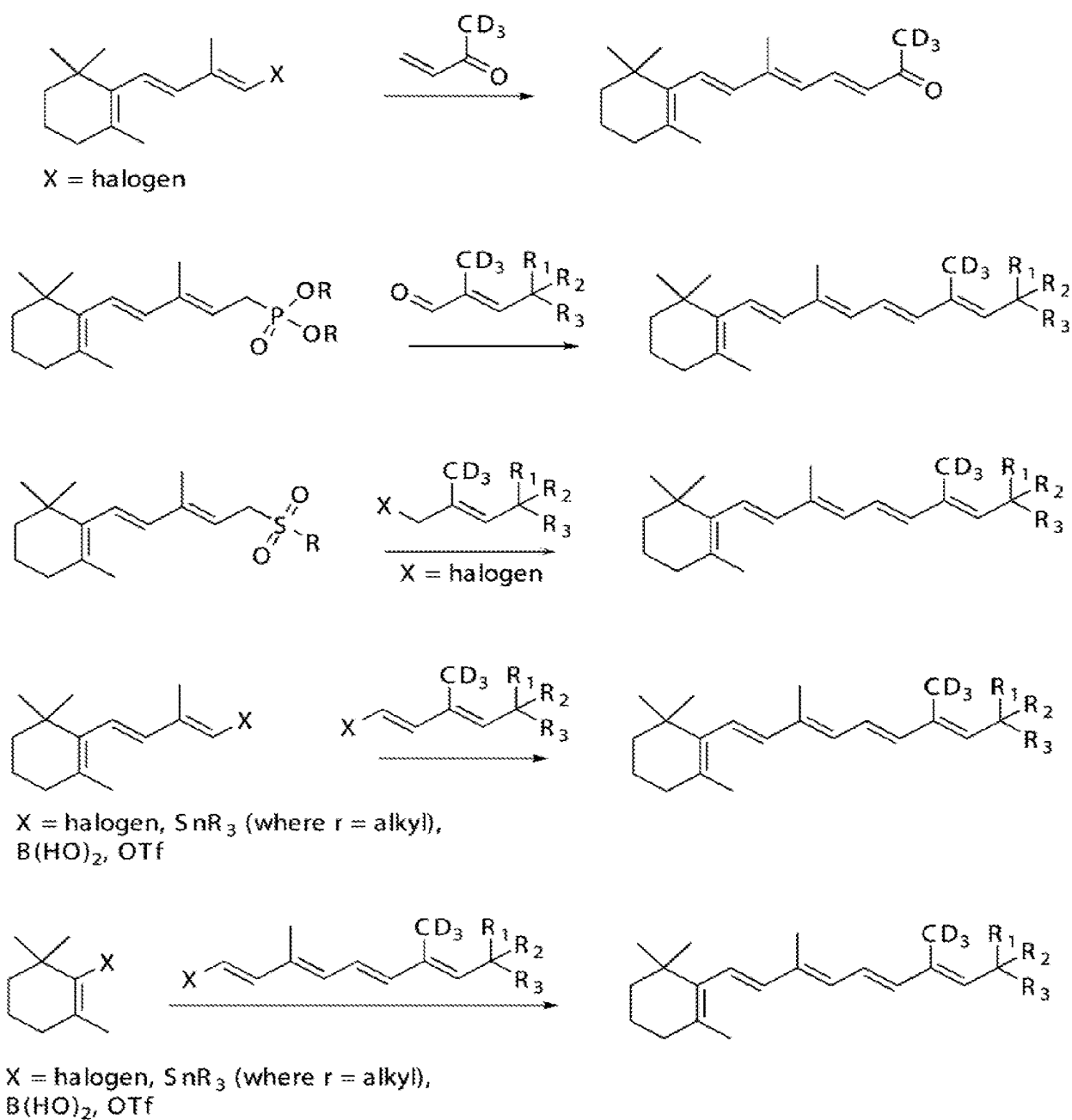


[0058] Exemplary substituted C_{20} -retinoid compounds that may be used in the compositions of the present invention include the following (compounds Ic-le):

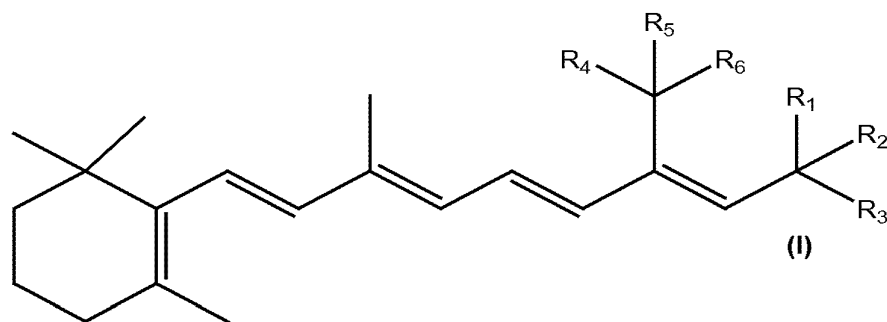


wherein R_1 , R_2 , and R_3 are as defined in Formula Ib.

[0059] Exemplary methods and reaction schemes for making substituted C20-retinoid compounds according to the present invention are set forth below:



[0060] In another embodiment, the invention is a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I:



wherein:

R_1 is oxo or H;

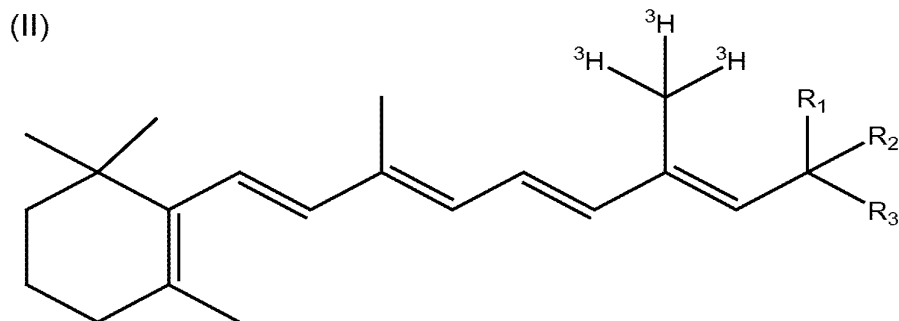
R_2 is H or nothing;

R_3 is hydroxy or oxo or $=CH-R_7$, where R_7 forms a carotenoid; and

R_4 , R_5 , and R_6 are independently selected from the group consisting of ^2H (D), ^3H (T), halogen, and C_{1-8} alkyl. Preferably, the halogen is fluorine (F).

[0061] In this embodiment, R_4 , R_5 , and R_6 may also be independently selected from H or a substituent that slows lipofuscin formation, a substituent that slows the formation of at least one of A2E or ATR dimer formation, or a substituent that slows hydrogen abstraction or migration at the C_{20} position compared to a retinoid that is not substituted at the C_{20} position, e.g. a $C_{20}-H_3$ retinoid. The present invention further contemplates any combination of the foregoing substituents at R_4 , R_5 , and R_6 .

[0062] Preferably, in the composition of the present invention the compound has the structure of formula II:



wherein:

R_1 is oxo or H;

R_2 is H or nothing; and

R_3 is hydroxy or oxo or $=\text{CH}-\text{R}_7$, where R_7 forms a carotenoid.

[0063] In the present invention, the compositions may further contain a supplement. Representative, non-limiting examples of a supplement according to the present invention are visual cycle antagonists, molecules that inhibit influx of a retinoid into an eye, or combinations thereof.

[0064] Exemplary, non-limiting visual cycle antagonists according to the present invention include TDH, TDT, 13-*cis*-retinoic acid, ret- NH_2 , and combinations thereof. An exemplary, non-limiting visual cycle antagonist according to the present invention is fenretinide. Other visual cycle antagonists within the scope of the present invention include those disclosed in R. Rando, U.S. Application Serial No. 11/199,594 filed August 8, 2005, which application is incorporated by reference as if recited in full herein.

[0065] In the present invention, one or more additives may be included in the compositions. Exemplary, non-limiting additives that may be included in the

compositions of the present invention include zinc, vitamin E, vitamin D, and combinations thereof.

[0066] The zinc, vitamin E, and vitamin D additives may be present in the compositions of the present invention in amounts that are effective to, e.g., enhance the bioavailability of the substituted C₂₀-retinoid compounds of the present invention, including Formula I, Formulae Ic-e, and Formula II. Thus, in the present invention, zinc may be present in the composition at between about 3 to about 80 mg, preferably between about 3 to about 10 mg or between about 10 to about 80 mg. Vitamin E may be present in the composition at between about 3 to about 3,000 mg, preferably between about 3 to about 15 mg or between about 15 to about 3,000 mg. Vitamin D may be present in the composition at between about 0.005 to about 0.1 mg, preferably between about 0.005 to about 0.015 mg or between about 0.015 to about 0.1 mg.

[0067] The compositions of the present invention may also include one or more additional additives, including, for example, eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof. The use of anti-oxidants has been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Arch. Ophthalmol., 119: 1417-36 (2001); Sparrow, et al., J. Biol. Chem., 278:18207-13 (2003). Examples of suitable anti-oxidants that could be used in a composition of the present invention in combination with a compound of formulae I, including formulae Ic-le and II, include vitamin C, vitamin E, beta-carotene and other carotenoids, coenzyme Q, OT-551 (Othera Pharmaceuticals Inc.), 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (also known as Tempol), butylated hydroxytoluene, resveratrol, a trolox analogue (PNU-83836-E), bilberry extract, and combinations thereof.

[0068] The use of certain minerals has also been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Arch. Ophthalmol., 119: 1417-36 (2001). Thus, the present invention contemplates the optional inclusion of one or more of such minerals. Examples of suitable minerals that could be used in a composition of the present invention include copper-containing minerals, such as cupric oxide (by way of example only); zinc-containing minerals, such as zinc oxide (by way of example only); and selenium-containing compounds, and combinations thereof.

[0069] The use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies. See, e.g., Shaban & Richter, Biol. Chem., 383:537-45 (2002); Shaban, et al., Exp. Eye Res., 75:99-108 (2002). Examples of suitable negatively charged phospholipids that could optionally be used in a composition of the present invention include cardiolipin, phosphatidylglycerol, and combinations thereof. Positively-charged and/or neutral phospholipids may also provide benefit for patients with macular degenerations and dystrophies when used in combination with a composition of the present invention.

[0070] The use of certain carotenoids has been correlated with the maintenance of photoprotection necessary in photoreceptor cells. Carotenoids are naturally-occurring yellow to red pigments of the terpenoid group that can be found in plants, algae, bacteria, and certain animals, such as birds and shellfish. Carotenoids are a large class of molecules in which more than 600 naturally occurring carotenoids have been identified. Carotenoids include hydrocarbons (carotenes) and their oxygenated, alcoholic derivatives (xanthophylls). They include actinioerythrol, astaxanthin, canthaxanthin, capsanthin, capsorubin, beta-8'-apo-carotenal (apo-carotenal), beta-12'-apo-carotenal, alpha-carotene, beta-carotene,

"carotene" (a mixture of alpha- and beta-carotenes), gamma-carotenes, beta-cyrtloxanthin, lutein, lycopene, violerythrin, zeaxanthin, and esters of hydroxyl- or carboxyl-containing members thereof. Many of the carotenoids occur in nature as cis- and trans-isomeric forms, while synthetic compounds are frequently racemic mixtures.

[0071] In humans, the retina selectively accumulates mainly two carotenoids: zeaxanthin and lutein. These two carotenoids are thought to aid in protecting the retina because they are powerful antioxidants and absorb blue light. Examples of suitable carotenoids for optional use in a composition of the present invention include lutein and zeaxanthin, as well as any of the aforementioned carotenoids and combinations thereof.

[0072] Effective dosage forms, modes of administration, and dosage amounts, in addition to those disclosed above, may be determined empirically, and making such determinations is within the skill of the art. It is understood by those skilled in the art that the dosage amount will vary with the route of administration, the rate of excretion, the duration of the treatment, the identity of any other drugs being administered, the age, size, and species of mammal, e.g., human patient, and like factors well known in the arts of medicine and veterinary medicine. In general, a suitable dose of a compound according to the invention will be that amount of the compound, which is the lowest dose effective to produce the desired effect. For example, a compound of the invention is present in the composition at a level sufficient to deliver about 0.1 to about 90 mg/day to a patient. The effective dose of a compound maybe administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

[0073] A compound of the present invention may be administered in any desired and effective manner: as pharmaceutical compositions for oral ingestion, or as an ointment or drop for local administration to the eyes, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous, topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. Further, a compound of the present invention may be administered in conjunction with other treatments. A compound or composition of the present invention may be encapsulated or otherwise protected against gastric or other secretions, if desired.

[0074] While it is possible for a compound of the invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition) or a vitamin supplement or a nutraceutical. The pharmaceutically acceptable compositions of the invention comprise one or more compounds as an active ingredient in admixture with one or more pharmaceutically-acceptable carriers and, optionally, one or more other compounds, drugs, ingredients and/or materials. Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art. See, *e.g.*, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.).

[0075] Pharmaceutically acceptable carriers are well known in the art (see, *e.g.*, Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (*e.g.*, lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (*e.g.*, dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, water, aqueous

solutions (e.g., saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (e.g., ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and tryglycerides), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, oils (e.g., corn, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, etc. Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Carriers suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

[0076] The pharmaceutical compositions or vitamin supplements or nutraceuticals of the invention may, optionally, contain additional ingredients and/or materials commonly used in such pharmaceutical compositions or vitamin supplements or nutraceuticals. These ingredients and materials are well known in the art and include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, sucrose and acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption

accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate; (10) suspending agents, such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth; (11) buffering agents; (12) excipients, such as lactose, milk sugars, polyethylene glycols, animal and vegetable fats, oils, waxes, paraffins, cocoa butter, starches, tragacanth, cellulose derivatives, polyethylene glycol, silicones, bentonites, silicic acid, talc, salicylate, zinc oxide, aluminum hydroxide, calcium silicates, and polyamide powder; (13) inert diluents, such as water or other solvents; (14) preservatives; (15) surface-active agents; (16) dispersing agents; (17) control-release or absorption-delaying agents, such as hydroxypropylmethyl cellulose, other polymer matrices, biodegradable polymers, liposomes, microspheres, aluminum monostearate, gelatin, and waxes; (18) opacifying agents; (19) adjuvants; (20) wetting agents; (21) emulsifying and suspending agents; (22), solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; (23) propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane; (24) antioxidants; (25) agents which render the formulation isotonic with the blood of the intended recipient, such as sugars and sodium chloride; (26) thickening agents; (27) coating materials, such as lecithin; and (28) sweetening, flavoring, coloring, perfuming and

preservative agents. Each such ingredient or material must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Ingredients and materials suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable ingredients and materials for a chosen dosage form and method of administration may be determined using ordinary skill in the art.

[0077] Pharmaceutical compositions or vitamin supplements or nutraceuticals suitable for oral administration may be in the form of capsules, cachets, pills, tablets, powders, granules, a solution or a suspension in an aqueous or non-aqueous liquid, an oil-in-water or water-in-oil liquid emulsion, an elixir or syrup, a pastille, a bolus, an electuary or a paste. These formulations may be prepared by methods known in the art, *e.g.*, by means of conventional pan-coating, mixing, granulation or lyophilization processes.

[0078] Solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like) may be prepared by mixing the active ingredient(s) with one or more pharmaceutically-acceptable carriers and, optionally, one or more fillers, extenders, binders, humectants, disintegrating agents, solution retarding agents, absorption accelerators, wetting agents, absorbents, lubricants, and/or coloring agents. Solid compositions of a similar type maybe employed as fillers in soft and hard-filled gelatin capsules using a suitable excipient. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using a suitable binder, lubricant, inert diluent, preservative, disintegrant, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine. The tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be

scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein. They may be sterilized by, for example, filtration through a bacteria-retaining filter. These compositions may also optionally contain opacifying agents and may be of a composition such that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. The active ingredient can also be in microencapsulated form.

[0079] Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. The liquid dosage forms may contain suitable inert diluents commonly used in the art. Besides inert diluents, the oral compositions may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents. Suspensions may contain suspending agents.

[0080] Pharmaceutical compositions for rectal or vaginal administration may be presented as a suppository, which maybe prepared by mixing one or more active ingredient(s) with one or more suitable nonirritating carriers which are solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound. Pharmaceutical compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such pharmaceutically-acceptable carriers as are known in the art to be appropriate.

[0081] Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, drops

and inhalants. The active compound may be mixed under sterile conditions with a suitable pharmaceutically-acceptable carrier. The ointments, pastes, creams and gels may contain excipients. Powders and sprays may contain excipients and propellants.

[0082] Pharmaceutical compositions suitable for parenteral administrations comprise one or more compound in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain suitable antioxidants, buffers, solutes which render the formulation isotonic with the blood of the intended recipient, or suspending or thickening agents. Proper fluidity can be maintained, for example, by the use of coating materials, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. These compositions may also contain suitable adjuvants, such as wetting agents, emulsifying agents and dispersing agents. It may also be desirable to include isotonic agents. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption.

[0083] In some cases, in order to prolong the effect of a drug (e.g., pharmaceutical formulation or vitamin supplement or nutraceutical), it is desirable to slow its absorption from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility.

[0084] The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug may be

accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms may be made by forming microencapsule matrices of the active ingredient in biodegradable polymers. Depending on the ratio of the active ingredient to polymer, and the nature of the particular polymer employed, the rate of active ingredient release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue. The injectable materials can be sterilized for example, by filtration through a bacterial-retaining filter.

[0085] The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

[0086] The following examples are provided to further illustrate the methods of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

EXAMPLES

EXAMPLE 1

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E *in vitro*

[0087] C₂₀-D₃-retinal was prepared according to the literature procedure(47) and its *in vitro* ability to form A2E as compared to all-*trans*-retinal was measured by HPLC.

[0088] FIG. 3A plots the formation of all A2E for two reaction mixtures containing either all-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal (16 mg), ethanolamine (0.5 equivalents) and acetic acid (1.2 equivalents). A typical HPLC trace is shown in FIG. 3B for the all-*trans*-retinal and C₂₀-D₃-all-*trans*-retinal reaction mixtures. The area under the curve corresponds to the amount of A2E: the larger the area the more A2E. The concentrations of A2E in the two reactions mixtures were measured about every 8 hours for 50 hours. The concentrations at each time point was plotted and the data points fit to a line for each reaction mixture. A comparison of the slopes of the two lines for the two reaction revealed that A2E formation occurred 7-times faster for all-*trans*-retinal compared to C₂₀-D₃-all-*trans*-retinal. Hydrogen deuterium exchange was not observed during the reaction with the labeled retinal, as measured by mass spectrometry of the reaction mixture after 50 hours, which clearly showed the presence of the tri-deuterated retinal, tri-deuterated retinal hydroxylamine Schiff base and tetra-deuterated A2E.

EXAMPLE 2

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of ATR-dimer *in vitro*

[0089] C₂₀-D₃-all-*trans*-retinal was prepared as described in Example 1 and its *in vitro* ability to form ATR-dimer as compared to all-*trans*-retinal was measured by HPLC. All-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal (10 mg) and proline (2 equivalents) in ethanol were mixed, and the reaction was followed by HPLC, the results of which are depicted in FIG. 4A. A typical HPLC trace is shown in FIG. 4B for the all-*trans*-retinal and C₂₀-D₃-all-*trans*-retinal reaction mixtures at the same time points. The concentrations of ATR-dimer in the two reaction mixtures were measured about every 15 min for 3 hours. The concentration at each time point was plotted and the data points fit to a line for each reaction mixture. A comparison of the slopes of the

two lines showed that C₂₀-D₃-all-*trans*-retinal formed ATR-dimer 15 times slower than the unlabeled retinal as shown in FIG. 4C.

EXAMPLE 3

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E-lipofuscin in CD-1 (ICR) mice

[0090] C₂₀-D₃-all-*trans*-retinal was administered to mice in order to measure its ability to form A2E in the eye compared to all-*trans*-retinal. Nine, 8-week old, CD-1 (ICR) mice (from Charles River, Wilmington, MA) were divided up into two groups of five and administered 1.5 mg of either all-*trans*-retinal or C₂₀-D₃-all-*trans*-retinal by intraperitoneal injection (IP) injection in a 10% solution of Tween-20 in saline bi-weekly for 6 weeks. At the end of this six-week period, each mouse was given a total of 60,000 I.U. (18 mg) or about 28-times the original amount of vitamin A in the mouse's body. Massive dosing with C₂₀-D₃-all-*trans*-retinal quickly replaces normal vitamin A stores with the C₂₀-D₃-analog. And, the injected retinal rapidly accumulates in the eye (rod outer segments), where at high enough concentrations it will react to form lipofuscin pigments. This is similar to the accumulation of all-*trans*-retinal in the ABCR^{-/-} mice and in patients with Stargardt's disease.

[0091] At the end of the six week period, the eyes were dissected, the retinas and eyecups pooled into groups of 4 or 5, and homogenated with 50 µL ethanol. The homogenate was centrifuged at 13,000 rpm for 5 minutes and 40 µL of the supernatant was drawn off and analyzed for A2E-lipofuscin by HPLC. Retinol and retinol esters were analyzed at 325 nm and A2E-lipofuscin was measured at 445 nm. Mice administered C₂₀-D₃-all-*trans*-retinal (n = 5) had 68% less A2E-lipofuscin as compared to mice administered all-*trans*-retinal (n = 4). Both groups of mice had roughly the same concentrations of retinol and retinol esters.

EXAMPLE 4

Replacing the C₂₀ hydrogens of all-*trans*-retinal with deuteriums reduces the formation of A2E in ABCR^{-/-} mice

[0092] C₂₀-D₃-all-*trans*-retinol acetate was prepared according to the literature procedure(47) and was administered to ABCR^{-/-} mice (48, 49) in order to measure its ability to lead to lipofuscin compared to that of all-*trans*-retinol acetate. Eight 2-month old, ABCR^{-/-} mice raised on a standard rodent diet were then fed a diet containing 20,000 I.U./kg of either C₂₀-D₃-all-*trans*-retinol acetate or all-*trans*-retinol acetate for 3 months. On this diet each mouse roughly received the daily-recommended amount of vitamin A or the same amount of the C₂₀-D₃-vitamin A drug, which was less than about 1mg/kg/day.

[0093] At the end of the 5 month period, the eyes were dissected, eyecups pooled into groups of six and homogenated with 80 µL ethanol. The homogenate was centrifuged at 13000 rpm for 5 min and 30 µL of the supernatant was drawn off and analyzed for A2E-lipofuscin by HPLC. A2E-lipofuscin was measured at 445 nm. Mice on the 3-month diet containing C₂₀-D₃-all-*trans*-retinol acetate had 44-58% less A2E-lipofuscin as compared to mice on a diet of all-*trans*-retinol acetate. This percentage of A2E reduction is on the same order of magnitude observed in similar studies in ABCR^{-/-} mice with the visual cycle antagonist TDH, TDT, Ret-NH₂, 13-*cis*-retinoic, acid and fenretinide. However, in this example A2E reduction is achieved with doses of C₂₀-D₃-all-*trans*-retinol acetate that are 11- to 40-times less.

EXAMPLE 5

ABCR^{-/-} mice raised exclusively on a C₂₀-D₃-all-*trans*-retinol acetate diet show undetectable amounts of extractable lipofuscin pigments and reduced lipofuscin deposits.

[0094] As in Example 4, two groups of four ABCR^{-/-} mice were raised either on diets containing C₂₀-D₃-all-*trans*-retinol acetate or all-*trans*-retinol acetate. However, in this example the mice were offspring of mothers on the same diet, and thus were raised only on their respective vitamin A analogs. At 5.5-6 months of age the mice were sacrificed and the eyecups were analyzed for lipofuscin pigments as described in Example 4. The results are shown FIG 5. While both mice contained the same amount of eye retinol and retinol esters (FIG 5C) lipofuscin pigments were undetectable in mice raised on the C₂₀-D₃-all-*trans*-retinol acetate diet (FIG 5B) but were detectable in mice raised on the all-*trans*-retinol acetate diet (FIG 5A).

[0095] In order to measure the amount lipofuscin granules in the eyes of the above mice on a normal diet vs. the diet containing C₂₀D₃-all-*trans*-retinol acetate, eyecups from both groups of mice (2 from each group) were evaluated by electron microscopy. Mice on the C₂₀-D₃-all-*trans*-retinol acetate diet had less electron dense lipofuscin deposits compared to mice on a diet of all-*trans*-retinol acetate as shown in FIG. 6.

EXAMPLE 6

C₂₀-D₃-all-*trans*-retinal slows A2E-lipofuscin formation as well as Fenretinide and/or TDH in wild-type rats.

[0096] 45-50 day old, female, CD IGS rats (Charles River, Wilmington, MA) were divided up into four groups of three. Three of these groups were administered all-*trans*-retinal and the one group was given C₂₀-D₃-all-*trans*-retinal (IP injection in a 10% solution of Tween-20 in saline) at 3 mg, bi- or tri-weekly for 8 weeks (20, 3 mg injections total). Thus, at the end of the 8-week period the animals received roughly 20 times their original stores of vitamin A, as retinal or C₂₀-D₃-all-*trans*-retinal. Massive dosing with C₂₀-D₃-all-*trans*-retinal quickly replaces normal vitamin A stores

with the C₂₀-D₃-analog. Of the three groups administered all-*trans*-retinal, one group was given Fenretinide (50) and another TDH (23), at doses of roughly 1.5 mg/day/animal (both supplied in the drinking water emulsified with 1g/L of Nu-rice (RIBUS, Inc, St. Louis, MO)).

[0097] At the end of the 8 weeks, RPE, A2E-lipofuscin was evaluated in each of the four groups by HPLC as described in Example 3 and in FIG. 7. A2E-lipofuscin pigments were greatest in the animals receiving all-*trans*-retinal (the control group). While animals receiving C₂₀D₃-all-*trans*-retinal had 35% less A2E-lipofuscin than animals receiving all-*trans*-retinal. Likewise, animals receiving Fenretinide or TDH had 49% and 31% less A2E-lipofuscin compared to animals administered only all-*trans*-retinal.

CITED DOCUMENTS

[0098] The following documents, which have been cited above, are incorporated by reference as if recited in full herein:

1. Friedman, D.S.; O'Colmain, B.J.; Muñoz, B.; Tomany, S.C.; McCarty, C.; DeJong, P.T.V.M.; Nemesure, B.; Mitchell, P.; Kempen, J.; Congdon, N. Prevalence of age related macular degeneration in the United States. Arch. Ophthalmol. **2004**, 122, 564–572.
2. Rattner, A.; Nathans, J. Macular degeneration: recent advances and therapeutic opportunities. Nat. Rev. Neurosci. **2006**, 7, 860-872.
3. Jong, P.T.V.M.d. Age-related macular degeneration N. Engl J Med **2006**, 355, 478-485.
4. Fine, S.L.; Berger, J.W.; Maguire, M.G.; Ho, A.C. Age-related macular degeneration N Engl J Med **2007**, 342, 483-492.
5. Jarc-Vidmar, M.; Kraut, A.; Hawlina, M. Fundus autofluorescence imaging in Best's vitelliform dystrophy. Klinische Monatsblätter Fur Augenheilkunde **2003**, 220, 861-867.
6. Capon, M.; Marshall, J.; Krafft, J.; Alexander, R.; Hiscott, P.; Bird, A. Sorsby's fundus dystrophy: a light and electron microscopic study. Ophthalmology **1989**, 95, 1969-1977.
7. Chong, N.; Alexander, R.; Gin, T.; Bird, A.; Luthert, P. TIMP-3 collagen, and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy Invest Ophthalmol Vis Sci **2000**, 41, 898-902.
8. Alikmets, R.; Singh, N.; Sun, H.; Shroyer, N.F.; Hutchinson, A.; Chidambaram, A.; Gerrard, B.; Baird, L.; Stauffer, D.; Peiffer, A.; Rattner, A.; Smallwood, P.; Li, Y.; Anderson, K.L.; Lewis, R.A.; Nathans, J.; Leppert, M.; Dean, M.; R.,

- L.J. A Photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat. Genet.* **1997**, *15*, 236-246.
9. Haralampus-Grynaviski, N.M.; Lamb, L.E.; Clancy, C.M.R.; Skumatz, C.; Burke, J.M.; Sarna, T.; Simon, J.D. Spectroscopic and morphological studies of human retinal lipofuscin granules. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*.
 10. Marmorstein, A.D.; Marmorstein, L.Y.; Sakaguchi, H.; Hollyfield, J.G. Spectral Profiling of Autofluorescence Associated with Lipofuscin, Bruch's Membrane, and Sub-RPE Deposits in Normal and AMD Eyes. *Invest. Ophthalmol. Vis. Sci.* **2002**, *43*, 2435-2441.
 11. Smith, R.T.; Chan, J.K.; Busuoic, M.; Sivagnanavel, V.; Bird, A.C.; Chong, N.V. Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration. *Invest Ophthalmol Vis Sci.* **2006**, *47*, 5495-5504.
 12. Sakai, N.; Decatur, J.; Nakanishi, K.; Eldred, G.E. A2-E": An Unprecedented Pyridinium Bisretinoid. *J. Am. Chem. Soc.* **1996**, *118*, 1559-1560.
 13. Fishkin, N.E.; Sparrow, J.R.; Allikements, R.; Nakanishi, K. Isolation and characterization of retinal pigment epithelial cell fluorophore: An all-*trans*-retinal dimer conjugate. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *100*, 7091-7096.
 14. Sparrow, J.S.; Nakanishi, K.; Parish, C.A. The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells. *Invest. Ophthalmol. Vis. Sci.* **2000**, *41*, 1981-1989.
 15. Suter, M.; Reme, C.E.; Christian Grimm; Wenzel, A.; Jaattela, M.; Esser, P.; Kociok, N.; Leist, M.; Richter, C. Age-related Macular Degeneration: The lipofuscin component n-retinyl-n-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells. *J. Bio. Chem.* **2000**, *275*, 39625-39630.
 16. Finnemann, S.; Leung, L.W.; Rodriguez-Boulan, E. The lipofuscin component A2E selectively inhibits phagolysosomal degradation of photoreceptor phospholipid by the retinal pigment epithelium. *Proc Natl Acad Sci U S A.* **2002**, *99*, 3842-3847.
 17. De, S.; Sakmar, T.P. Interaction of A2E with model membranes. Implications to the pathogenesis of age-related macular degeneration. *J Gen Physiol.* **2002**, *120*, 147-157.
 18. Bergmann, M.; Schütt, F.; Holz, F.G.; Kopitz, J. Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration. *FASEB J.* **2004**, *18*, 562-564.
 19. Radu, R.A.; Mata, N.L.; Bagla, A.; Travis, G.H. Light exposure stimulates formation of A2E oxiranes in a mouse model of Stargardt's macular degeneration. *Proc Natl Acad Sci U S A.* **2004**, *101*, 5928-5933.
 20. Ben-Shabat, S.; Parish, C.A.; Hashimoto, M.; Liu, J.; Nakanishi, K.; Sparrow, J.R. Fluorescent pigments of the retinal pigment epithelium and age-related macular degeneration. *Bioorg Med Chem Lett.* **2001**, *11*, 1533-1540.
 21. Schutt, F.; Bergmann, M.; Holz, F.G.; Dithmar, S.; Volcker, H.-E.; Kopitz, J. Accumulation of A2-E in mitochondrial membranes of cultured RPE cells. **2007**, *245*, 391-398.
 22. Schutt, F.; Davies, S.; Kopitz, J.; Holz, F.G.; Boulton, M.E. Photodamage to human RPE cells by A2-E, a retinoid component of lipofuscin. *41* **2000**, 2303-2308.

23. Maiti, P.; Kong, J.; Kim, S.A.; Sparrow, J.S.; Allikmets, R.; Rando, R.R. Small molecule RPE65 antagonists limit the visual cycle and prevent lipofuscin formation. *Biochemistry* **2006**, *45*, 852-860.
24. Radu, R.A.; Mata, N.L.; Nusinowitz, S.; Liu, X.; Sieving, P.A.; Travis, G.H. Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargardt macular degeneration. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 4742-4747.
25. Golczak, M.; Maeda, A.; Bereta, G.; Maeda, T.; Kiser, P.D.; Hunzelmann, S.; Lintig, J.V.; Blanner, W.S.; Palczewski, K. Metabolic Basis of Visual Cycle Inhibition by Retinoid and Nonretinoid Compounds in the Vertebrate Retina. *J. Biol. Chem.* **2008**, *283*, 9543-9554.
26. Katz, M.L.; Drea, C.M.; Robison, W.G. Relationship between dietary retinol and lipofuscin in the retinal pigment epithelium. *Mech. Age. Dev.* **1986**, *35*, 291-305.
27. Radu, R.A.; Han, Y.; Bui, T.V.; Nusinowitz, S.; Bok, D.; Lichter, J.; Widder, K.; Travis, G.H.; Mata, N.L. Reductions in serum vitamin A arrest Accumulation of toxic retinal fluorophores: A potential therapy for treatment of lipofuscin based retinal diseases. *Invest Ophthalmol Vis Sci* **2005**, *46*, 4393-4401.
28. Wassell, J.; Boulton, M. A role for vitamin A in the formation of ocular lipofuscin. *Br J Ophthalmol* **1997**, *81*, 911-918.
29. Owsley, C.; Jackson, G.R. Aging and scotopic dysfunction. *Perception* **2000**, *29*, Abstract Supplement.
30. Owsley, C.; Jackson, G.R.; White, M.; Feist, R.; Edwards, D. Delays in rod-mediated dark adaptation in early age-related maculopathy. *Ophthalmology* **2001**, *108*, 1196-1202.
31. Baehr, W.; Wub, S.M.; Birdc, A.C.; Palczewski, K. The retinoid cycle and retina disease. *Vision Research* **2003**, *43*, 2957-2958.
32. Maeda, A.; Maeda, T.; Golczak, M.; Imanishi, Y.; Leahy, P.; Kubota, R.; Palczewski, K. Effects of potent inhibitors of the retinoid cycle on visual function and photoreceptor protection from light damage in mice. *Mol. Pharmacol.* **2006**, *70*, 1220-1229.
33. Hong, W.K.; Itri, L.M. *Retinoids and human cancer*, Second Edition Ed.; Raven Press Ltd: New York, 1994.
34. Gudas, L.J.; Sporn, M.B.; Roberts, A.B. *Cellular biology and biochemistry of retinoids*; Raven Press Ltd.: New York, 1994; 443-520 pp.
35. Nason-Burchenal, K.; Dmitrovsky, E. *The retinoids: cancer therapy and prevention mechanisms*; Berlin, 1999; 301-322 pp.
36. Dragnev, K.H.; Rigasa, J.R.; Dmitrovsky, E. The Retinoids and Cancer Prevention Mechanisms *Oncologist* **2003**, *5*, 361-368.
37. Freemantle, S.J.; Spinella, M.J.; Dmitrovsky, E. Retinoids in cancer therapy and chemoprevention: promise meets resistance. *Oncogene* **2003**, *22*, 7305-7315.
38. Soriatan, RXlist.com, <http://www.rxlist.com/cgi/generic/acitretin.htm#>, accessed Sept. 02, 2008. 2008.
39. Targretin, RXlist.com <http://www.rxlist.com/cgi/generic/bexarotene.htm>, accessed Sept. 02 2008.
40. Acutane, RXlist.com, <http://www.rxlist.com/cgi/generic/isotret.htm>, accessed Sept. 02 2008.
41. Camerini, T.; Mariani, L.; Palo, G.D.; Marubini, E.; Mauro, M.G.D.; Decens, A.; Costa, A.; Veronesi, U. Safety of the Synthetic Retinoid Fenretinide: Long-

- Term Results From a Controlled Clinical Trial for the Prevention of Contralateral Breast Cancer. *J. Clin. Oncol.* **2001**, 19, 1664-1670.
42. Puduvalli, V.K.; Yung, W.K.A.; Hess, K.R.; Kuhn, J.G.; Groves, M.D.; Levin, V.A.; Zwiebel, J.; Chang, S.M.; Cloughesy, T.F.; Junck, L.; Wen, P.; Lieberman, F.; Conrad, C.A.; Gilbert, M.R.; Meyers, C.A.; Liu, V.; Mehta, M.P.; Nicholas, M.K.; Prados, M. Phase II Study of Fenretinide (NSC 374551) in Adults With Recurrent Malignant Gliomas: A North American Brain Tumor Consortium Study. *J. Clin. Oncol.* **2004**, 22, 4282-4289.
 43. Villablanca, J.G.; Khan, A.A.; Avramis, V.I.; Seeger, R.C.; Matthay, K.K.; Ramsay, N.K.; Reynolds, C.P. Phase I trial of 13-cis-retinoic acid in children with neuroblastoma following bone marrow transplantation. *J Clin Oncol.* **1995**, 13, 849-901.
 44. Chemotherapy drugs, Isorettinoin, <http://www.chemocare.com/bio/isotretinoin.asp>, accessed September 8 2008.
 45. Haskell, M.; Mazumder, R.M.; Peerson, J.M.; Jones, A.D.; Wahed, M.A.; Mahalanabis, D.; Brown, K.H. Use of deuterated-retinol-dilution technique to assess total body vitamin A stores of adult volunteers consuming different amounts of vitamin A1, 2, 3. *Amer. J. of Clinical Nutrition* **1999**, 70, 874-880.
 46. Bausch, J.; Rietz, P. Method for the assessment of vitamin A liver stores. *Acta Vitaminol Enzymol* **1977**, 31, 99-112.
 47. Pardoen, J.A.; Mulder, P.P.J.; Van den Berg, E.M.M.; Lugtenburg, J. Synthesis of 8-, 9-, 12-, and 13-mono-¹³C-retinal. *Canadian Journal of Chemistry* **1985**, 63, 1431-1435.
 48. Weng, J.; Mata, N.L.; Azarian, S.M.; Tzekov, R.T.; Birch, D.G.; Travis, G.H. Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in abcr knockout mice. *Cell* **1999**, 9, 13-23.
 49. Kim, S.; Fishkin, N.; Kong, J.; Nakanishi, K.; Allikmets, R.; Sparrow, J.R. Rpe65 Leu450Met variant is associated with reduced levels of the retinal pigment epithelium lipofuscin fluorophores A2E and iso-A2E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 11668-11672.
 50. Soo-Jong; Kwon, Y.-J.; Han, H.-S.; Park, S.-H.; Park, M.-S.; Rho, Y.-S.; Sin, H.-S. Synthesis and Biological Activity of Novel Retinamide and Retinoate Derivatives. *Chemical & Pharmaceutical Bulletin* **2004**, 52, 501-506.

[0099] The scope of the present invention is not limited by the description, examples, and suggested uses herein and modifications can be made without departing from the spirit of the invention. Thus, it is intended that the present invention cover modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method of retarding formation of a lipofuscin pigment in the retina comprising administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.
2. The method according to claim 1, wherein the substituted C₂₀-retinoid is selected from the group consisting of a C₂₀-D₃-retinoid, a C₂₀-T₃-retinoid, and a C₂₀-F₃-retinoid.
3. The method according to claim 1, wherein the lipofuscin pigment is selected from the group consisting of A2E, all-*trans*-retinal (ATR)-dimer, and combinations thereof.
4. The method according to claim 1, wherein the substituted C₂₀-retinoid is administered as part of a pharmaceutical or a nutraceutical composition.
5. The method according to claim 1, wherein the substituted C₂₀-retinoid is administered as a unit dosage form.
6. A method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina comprising administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.
7. The method according to claim 6, wherein the substituted C₂₀-retinoid is selected from the group consisting of a C₂₀-D₃-retinoid, a C₂₀-T₃-retinoid, and a C₂₀-F₃-retinoid.
8. The method according to claim 6, wherein the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

9. The method according to claim 6, wherein the substituted C₂₀-retinoid is administered as part of a pharmaceutical nutraceutical composition

10. The method according to claim 6, wherein the substituted C₂₀-retinoid is administered as a unit dosage form.

11. The method according to claim 6, wherein the disease is macular degeneration.

12. The method according to claim 6, wherein the disease is selected from the group consisting of Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy, age related macular degeneration, and Malattia Leventinese.

13. The method according to claim 6, wherein the administration step comprises replacing a component of the patient's diet that contains an all-*trans*-retinoid with a component that contains a substituted C₂₀-retinoid.

14. A composition for retarding formation of a lipofuscin pigment in the retina comprising a substituted C₂₀-retinoid and pharmaceutically acceptable carrier.

15. A composition according to claim 14, wherein the substituted C₂₀-retinoid is selected from the group consisting of a C₂₀-D₃-retinoid, a C₂₀-T₃-retinoid, and a C₂₀-F₃-retinoid.

16. A unit dosage form comprising the composition of claim 15.

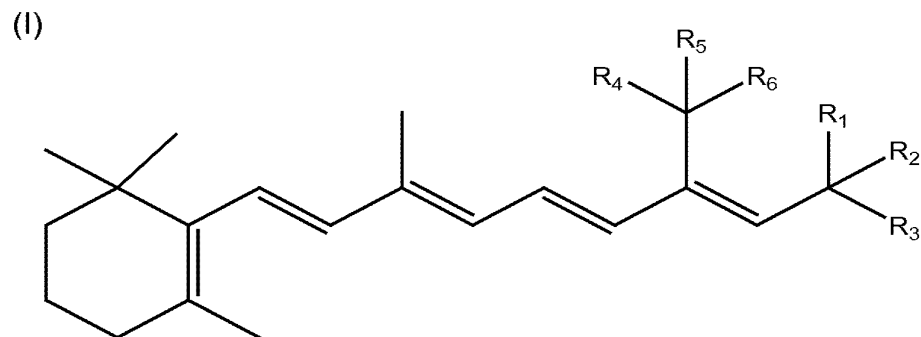
17. A composition according to claim 15, which is a vitamin supplement.

18. A composition according to claim 15, which is a pharmaceutical formulation.

19. A method of retarding formation of a lipofuscin pigment selected from the group consisting of an A2E, an ATR dimer, and combinations thereof, the

method comprising replacing an all-*trans*-retinal (ATR) substrate with a C₂₀-D₃-retinoid substrate under conditions sufficient to impede formation of A2E, ATR dimer, or both A2E and ATR dimer.

20. A composition comprising a pharmaceutically acceptable carrier and a compound according to formula I:



wherein:

R₁ is oxo or H;

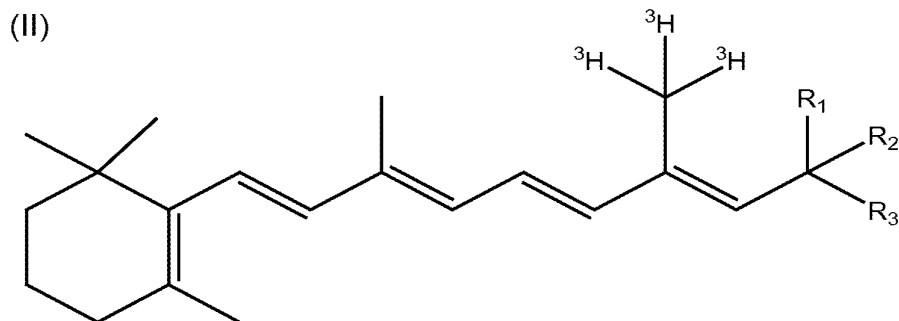
R₂ is H or nothing;

R₃ is hydroxy or oxo or =CH-R₇, where R₇ forms a carotenoid; and

R₄, R₅, and R₆ are independently selected from the group consisting of ¹H, ²H, ³H, halogen, and C₁₋₈alkyl.

21. The composition according to claim 20, wherein the halogen is F.

22. The composition according to claim 21, wherein the compound is formula II:



wherein:

R₁ is oxo or H;

R₂ is H or nothing; and

R₃ is hydroxy or oxo or =CH-R₇, where R₇ forms a carotenoid.

23. The composition of claim 20, wherein R₄, R₅, and R₆ are independently selected from H or a substituent that slows lipofuscin formation.

24. The composition of claim 20, wherein R₄, R₅, and R₆ are independently selected from H or a substituent that slows the formation of at least one of A2E or ATR dimer.

25. The composition of claim 20, wherein R₄, R₅, and R₆ are independently selected from H or a substituent that slows hydrogen abstraction or migration at the C₂₀ position.

26. A composition according to claim 20 further comprising a supplement selected from the group consisting of a visual cycle antagonist, a molecule that inhibits influx of a retinoid into an eye, and combinations thereof.

27. A composition according to claim 26, wherein the visual cycle antagonist is selected from the group consisting of TDH, TDT, 13-*cis*-retinoic acid, ret-NH₂, and combinations thereof.

28. A composition according to claim 26, wherein the molecule that inhibits influx of a retinoid into an eye is fenretinide.

29. The composition according to claim 26 further comprising one or more additives.

30. The composition according to claim 29, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.

31. The composition according to claim 30, wherein the zinc is present in the composition at between about 3 to about 80 mg.

32. The composition according to claim 30, wherein the zinc is present in the composition at between about 3 to about 10 mg.

33. The composition according to claim 30, wherein the zinc is present in the composition at between about 10 to about 80 mg.

34. The composition according to claim 30, wherein the vitamin E is present in the composition at between about 3 to about 3,000 mg.

35. The composition according to claim 30, wherein the vitamin E is present in the composition at between about 3 to about 15 mg.

36. The composition according to claim 30, wherein the vitamin E is present in the composition at between about 15 to about 3,000 mg.

37. The composition according to claim 30, wherein the vitamin D is present in the composition at between about 0.005 to about 0.1 mg.

38. The composition according to claim 30, wherein the vitamin D is present in the composition at between about 0.005 to about 0.015 mg.

39. The composition according to claim 30, wherein the vitamin D is present in the composition at between about 0.015 to about 0.1 mg.

40. The composition according to claim 20, wherein the compound is present in the composition at a level sufficient to deliver about 0.1 to about 90 mg/day to a patient.

41. The composition according to claim 20 further comprising an additional active.

42. The composition according to claim 41, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

43. The composition according to claim 42, wherein the eye antioxidant is selected from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a trolox analogue (PNU-83836-E), bilberry extract, and combinations thereof.

44. The composition according to claim 42, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

45. The composition according to claim 42, wherein the negatively charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

46. The composition according to claim 42, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

47. A method of retarding formation of A2E in a patient comprising replacing an all-*trans*-retinal (ATR) substrate with a substituted C₂₀-D₃-retinoid substrate in a patient under conditions sufficient to impede the formation of A2E.

48. The method according to claim 47, wherein the replacing step comprises administering to the patient a substituted C₂₀-D₃-retinoid substrate.

49. The method according to claim 48, wherein the substituted C₂₀-D₃-retinoid substrate is administered directly to the eye.

ABSTRACT

Methods of retarding formation of a lipofuscin pigment in the retina and of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina are provided. These methods include the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Further provided are methods of retarding formation of A2E and/or ATR-dimer by replacing an *all-trans*-retinal (ATR) substrate with a C₂₀-D₃-retinal substrate under conditions sufficient to impede the formation of A2E. Compositions for retarding formation of a lipofuscin pigment in the retina containing a substituted C₂₀-retinoid and a pharmaceutically acceptable carrier are also provided.

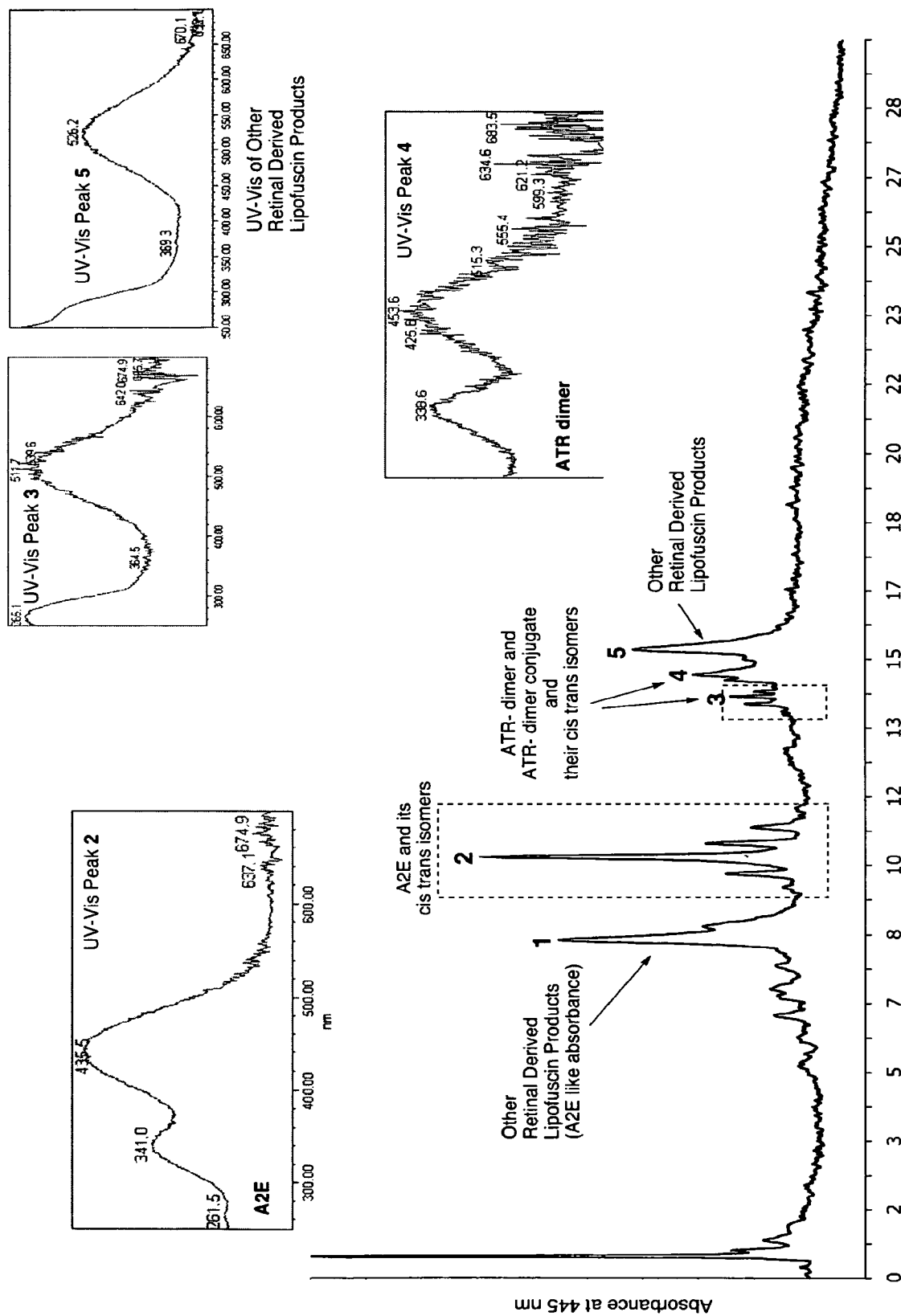


FIG 1.

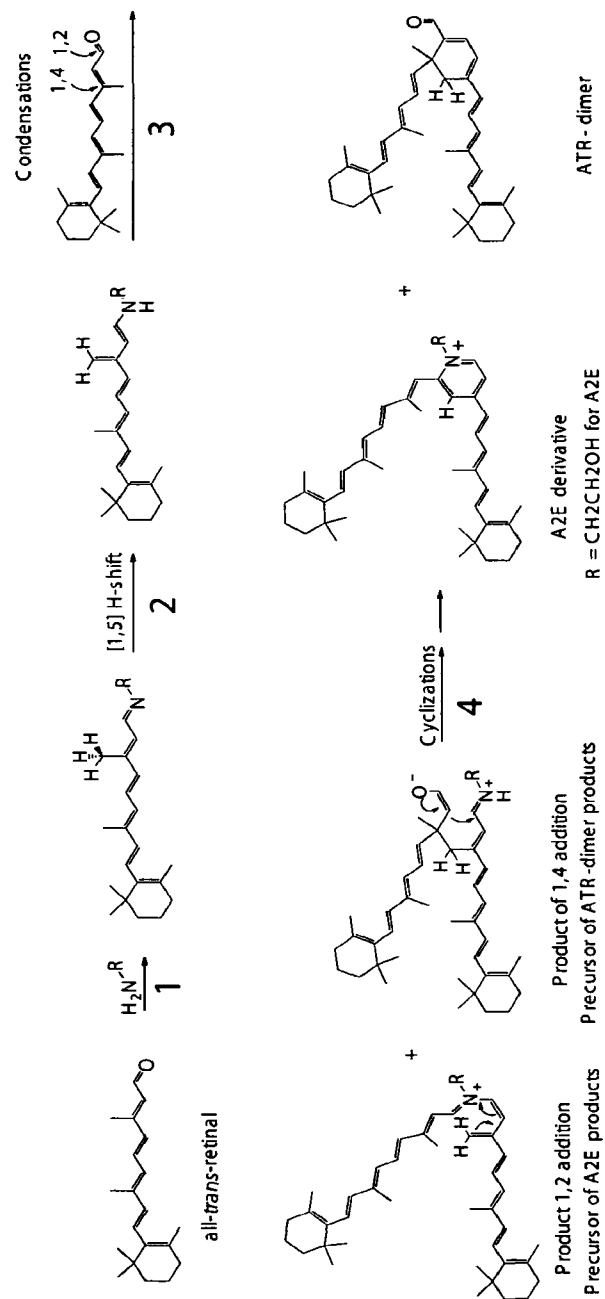


FIG 2.

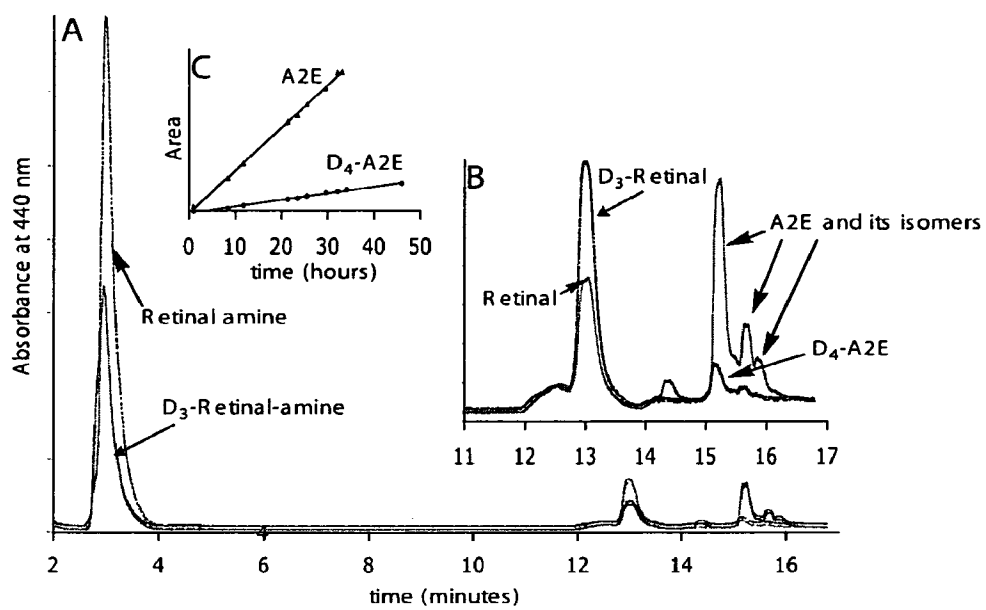


FIG 3.

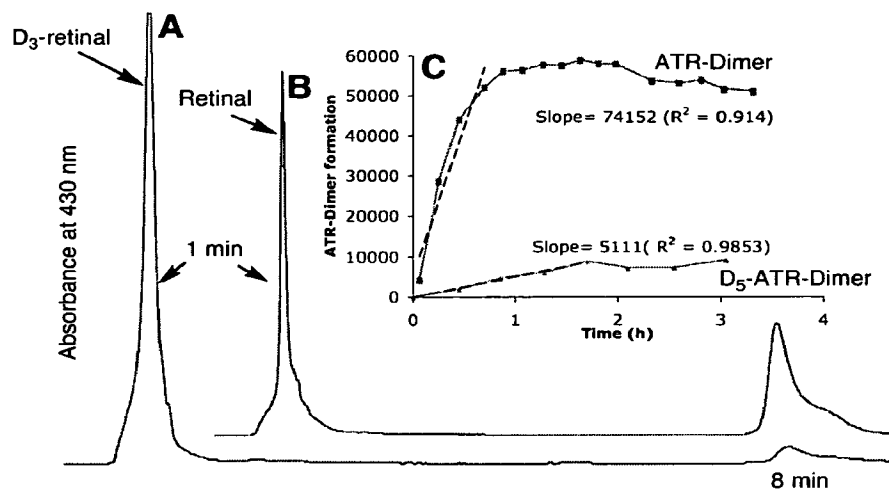


FIG 4.

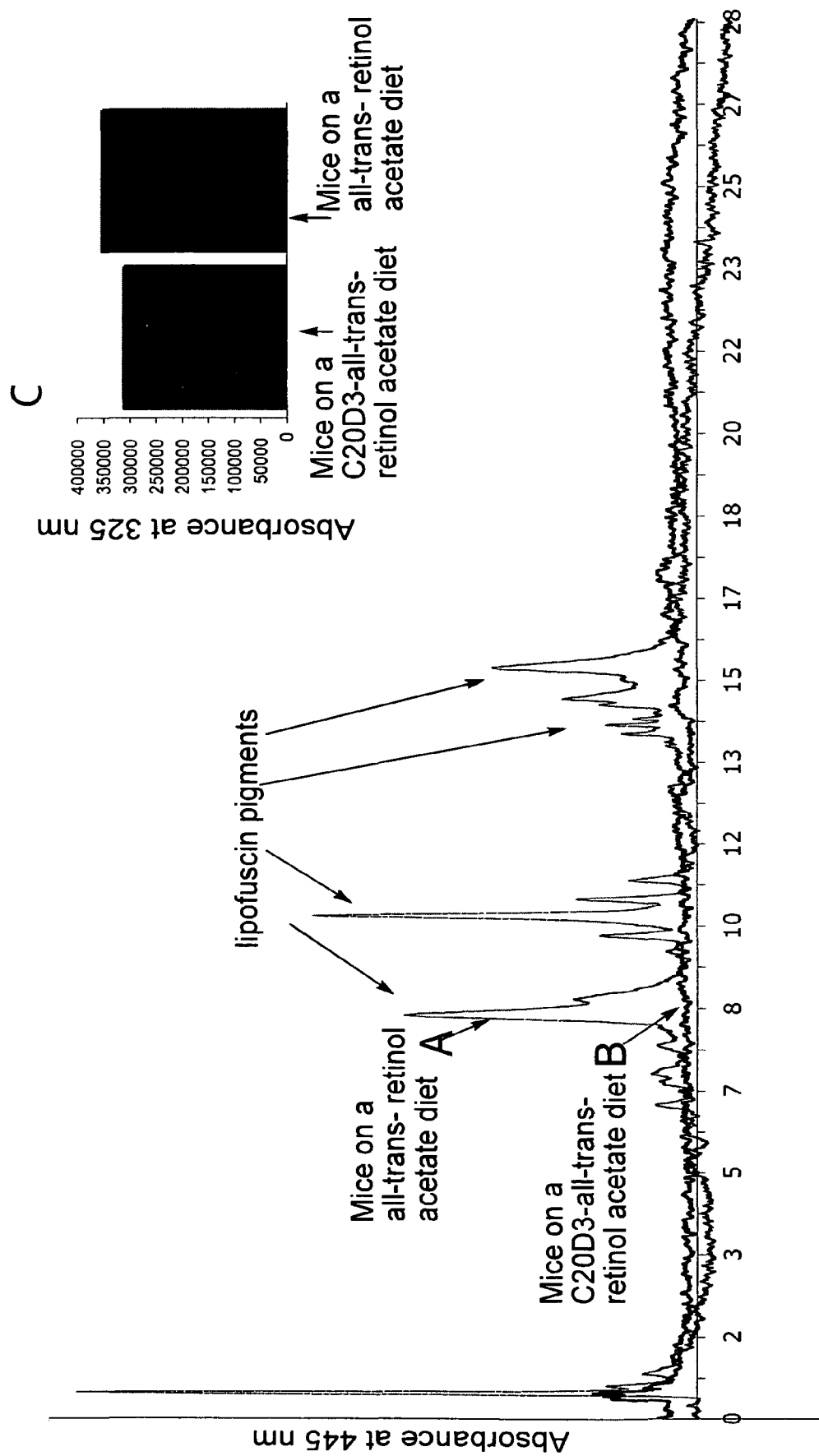
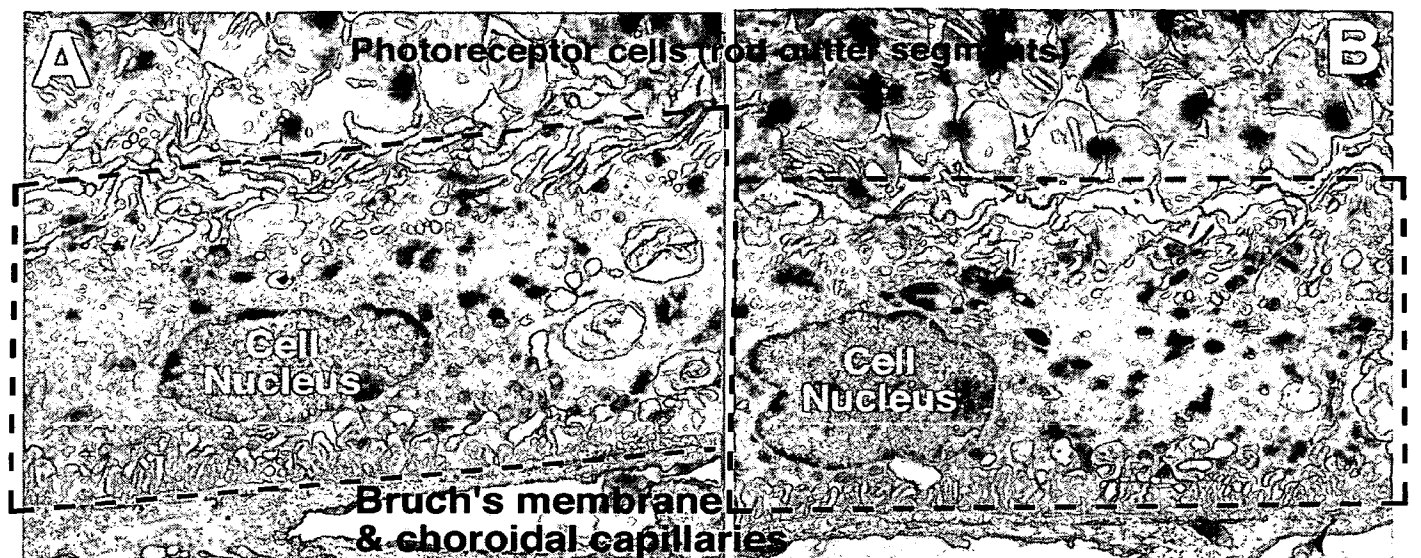
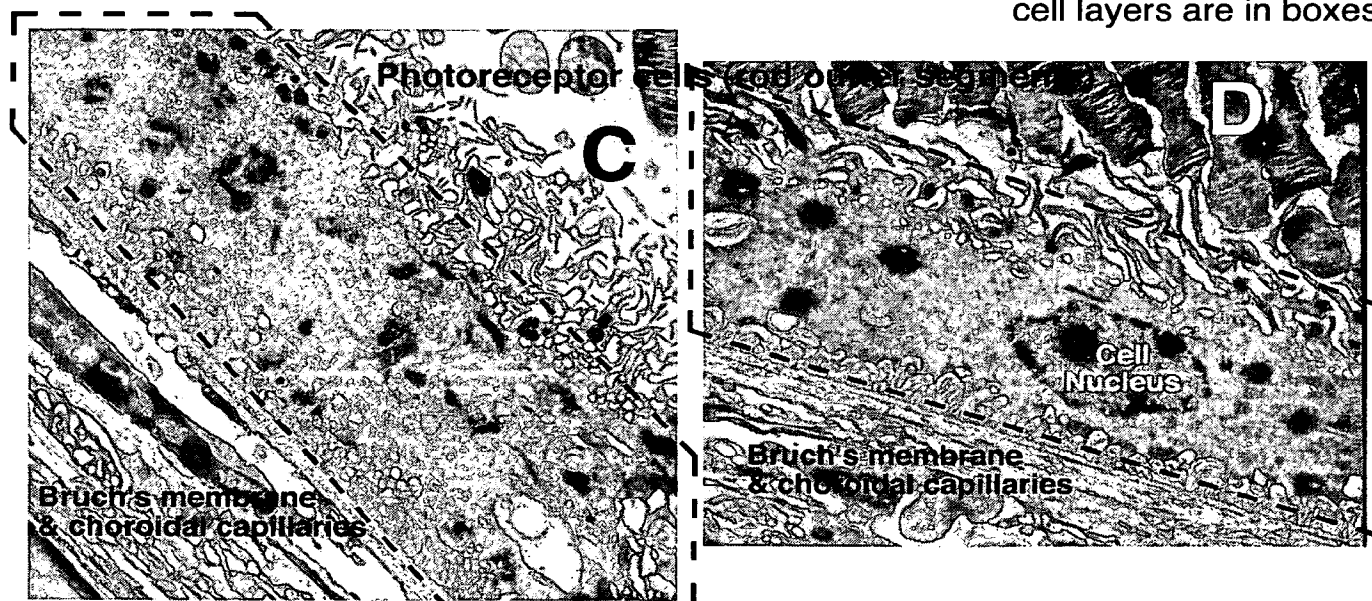


FIG 5.



Vitamin A diet (6 mg/kg diet)

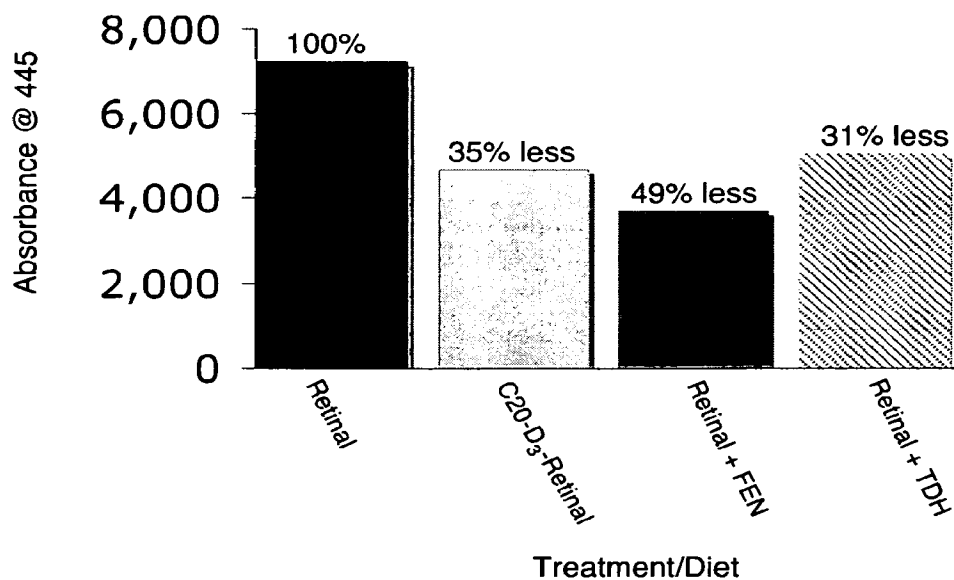
Retinal Pigment Epithelium
cell layers are in boxes



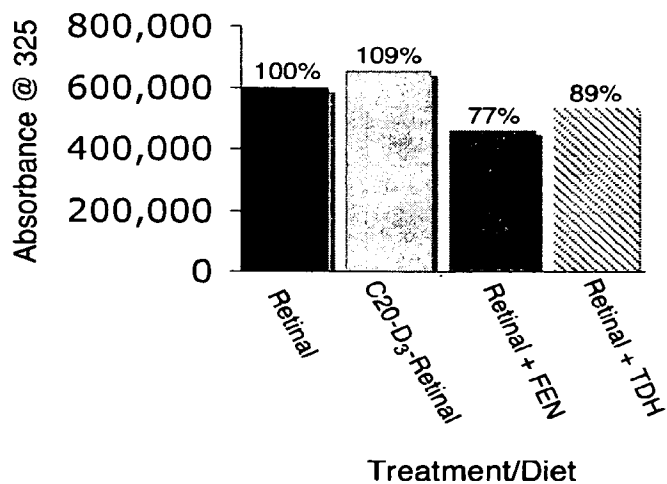
D3-Vitamin A diet (6 mg/kg diet)

FIG 6.

A Total A2E



B Total Retinol



C Total all-trans-retinal

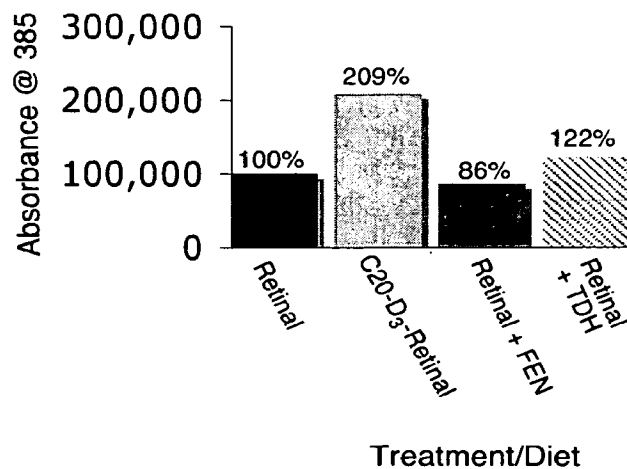


FIG. 7.