UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,877,809 B2
APPLICATION NO.	: 12/733631
DATED	: November 4, 2014
INVENTOR(S)	: Ilyas Washington

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 1 of the specification, please delete the second paragraph on lines 14-19 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."

Signed and Sealed this
Eighteenth Day of October, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

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 12, 2016 Signature: /Mei Bai/
(Mei Bai, Ph.D.)

Docket No.: 126277-00102
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Ilyas Washington

Patent No.: 8,877,809

Issued: November 4, 2014

For: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.323

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified patent, Patentee notes an error which should be corrected. Specifically, Patentee notes that the specification inadvertently states that the invention is made with government support. This statement is incorrect, because this invention was not funded by any government grant. Therefore, please amend the specification as follows.

At column 1, delete the second paragraph on lines 14-19 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.~~

This error was present in the application as filed by Patentee.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Please charge our Deposit Account No. 50-4876 in the amount of $100.00 covering the fee set forth in 37 C.F.R. § 1.20(a). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-4876, under Order No. 126277-00102.

Dated: September 12, 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 Patentee

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,877,809

APPLICATION NO. : 12/733,631

ISSUE DATE : November 4, 2014

INVENTOR(S) : Ilyas Washington

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 1 of the specification, please delete the second paragraph on lines 14-19 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.~~

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 12, 2016 Signature: /Mei Bai/ (Mei Bai, Ph.D.)

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Mei Bai, Ph.D.
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110

1

Electronic Patent Application Fee Transmittal

Application Number:	12733631
Filing Date:	14-Oct-2010
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Filer:	Mei Bai
Attorney Docket Number:	126277-00102

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

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:				
Certificate of Correction	2811	1	100	100

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	26895549
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	126277-00102
Receipt Date:	12-SEP-2016
Filing Date:	14-OCT-2010
Time Stamp:	14:54:17
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$100
RAM confirmation Number	1442
Deposit Account	504876
Authorized User	BAI, MEI
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	Request for Certificate of Correction	Request_for_Certificate_of_Correction_Fee_Required.pdf	23572 02efadaba3bc5cd020a5c04eaff6f80a58fdc00f	no	2
Warnings:					
Information:					
2	Request for Certificate of Correction	Certificate_of_Correction.pdf	18221 53312d38518fffd20f78fba2a31e2d582892eb78	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30226 2b80c5b6180bed198d4bced30218ddd129cd481a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	72019		

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.

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/733,631	10/14/2010	Ilyas Washington	13533/541US

CONFIRMATION NO. 4180

POWER OF ATTORNEY NOTICE

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

OC00000079200512

Date Mailed: 12/09/2015

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

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

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(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**.

/hachristian/

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/733,631	10/14/2010	Ilyas Washington	13533/541US

CONFIRMATION NO. 4180

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

POA ACCEPTANCE LETTER

OC000000079200544

Date Mailed: 12/09/2015

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**.

/hachristian/

2207

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.
CU Ref.: CU2207; Our Ref.: 126277-00102

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

[X] Practitioners associated with the Customer Number: 86738

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

[X] The address associated with Customer Number: 86738

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

Assignee Name and Address:

The Trustees of Columbia University in the City of New York
535 West 116th Street, Mail Code 4308
Office of the General Counsel, 412 Low Library
New York, New York 10027

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	11/24/2015
Name		Telephone	
Title			

Thomas H. Burrows Jr., J.D.
Associate General Counsel
Columbia University
New York, N.Y. U.S.A.
(212) 854-0681

ME1 21440706v.1

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.
CU Ref.: CU2207; Our Ref.: 126277-00102

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: _____

Application No./Patent No.: 8,877,809 Filed/Issue Date: November 4, 2014

Titled: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

The Trustees of Columbia University in the City of New York (Name of Assignee), a University (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [x] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above, by virtue of either:

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 025141, Frame 0787, or for which a copy therefore is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[x] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature _____ Date 11/24/2015

Printed or Typed Name _____ Title _____

Thomas H. Burrows Jr., J.D.
Associate General Counsel
Columbia University
New York, N.Y. U.S.A.
(212) 854-0681

Electronic Acknowledgement Receipt

EFS ID:	24213654
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	13533/541US
Receipt Date:	01-DEC-2015
Filing Date:	14-OCT-2010
Time Stamp:	09:18:38
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	Power_to_Prosecute_executed.PDF	68694 0765cf831bc3f2955c4104381eb212991064c7c5	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73	373_b_executed.PDF	69440 21cad25127a59741e7827f611825dc662cad7a63	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	138134

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.

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

26646 7590 07/16/2015

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER
FAY, ZOHREH A

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
07/16/2015	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

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Patent No. 8,877,809	: ON REDETERMINATION OF
Issued: November 4, 2014	: PATENT TERM ADJUSTMENT
Application No. 12/733,631	:
Filing or 371(c) Date: October 14, 2010	:
Dkt. No.: 13533/541US	:

This decision is in response to the "REQUEST FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT UNDER 37 C.F.R. § 1.705(b)," filed January 5, 2015, requesting that the patent term adjustment be increased from 1064 days to 1107 days.

The Office has re-determined the PTA to be 964 days.

This redetermination of patent term adjustment is NOT the Director's decision on the applicant's request for reconsideration for purposes of seeking judicial review under 35 U.S.C. § 154(b)(4).

Relevant Procedural History

The above-identified application matured into U.S. Patent No. 8,877,809 on November 4, 2014. The patent issued with a patent term adjustment of 1064 days. Patentee asserts that the patent is entitled to 1107 days.

Decision

Patentee and the Office are not in agreement with respect to the "A" delay under 35 U.S.C. § 154(b)(1)(A) and 37 C.F.R. 1.702(a). The date of commencement herein is March 12, 2010, the date that is 36 months from the priority date of September 12, 2007. Accordingly, the adjustment under 37 CFR 1.702(a)(1) was properly accorded as 545 days. The adjustment commenced May 13, 2011, the day after the date that is 14 months from the date of commencement, and ended November 7, 2012, the date that the restriction requirement was mailed. Accordingly, the "A" delay totals 545 days.

Patentee and the Office are not in agreement as to the amount of applicant delay under 37 CFR 1.704(b). The patent term adjustment is subject to an additional reduction of 100 days pursuant to 37 CFR 1.704(b) in connection with the reply filed October 14, 2010. The reduction commenced July 7, 2010 and ended October 14, 2010. Be advised that the instant application is not subject to the provisions of the Smith-Leahy America Invents Act, 77 FR 157, 1382 OG 105, with respect to delayed submission of an oath or declaration as the international filing date of the instant application is September 12, 2008, which is prior to the effective date of the AIA.

Patentee contest the reduction of 64 days with respect to the reply filed May 30, 2014 and argue that the "Supplemental Response" was expressly requested by the examiner. A review of the record reveals that the reply filed May 30, 2014 was not a supplemental reply and was in fact a reply within the meaning of 35 USC 132. Accordingly, the applicant delay was properly calculated pursuant to 37 CFR 1.704(b), the delay having commenced March 29, 2014, the day after the date that is three months after the date that the final rejection was mailed, and ended May 30, 2014, the date that the reply was filed.

As the information disclosure statement (IDS) filed April 21, 2014 was filed prior to the submission of a proper reply the final Office action, the submission of the IDS does not subject the patent term to further reduction.

Accordingly, the applicant delay totals 183 days (100 days + 13 days + 6 days + 64 days).

Patentee and the Office are not in agreement with respect to the "B" delay under 35 U.S.C. § 154(b)(1)(B)(i) and 37 C.F.R. 1.702(b). Herein the "B" delay was properly calculated as 602 days. The adjustment pursuant to 37 CFR 1.702(b) commenced March 13, 2013, the day after the date that is three years from the date of commencement, and ended November 4, 2014, the date that the patent issued. Accordingly, the "B" delay totals 602 days.

In Wyeth v. Kappos, 591 F.3d 1364 (Fed. Cir. 2010), the United States Court of Appeals for the Federal Circuit determined that overlap occurs when the calendar days overlap between the "A" and "B" delays. Under this interpretation, the Office finds that there are zero overlapping days of Office delay.

Overall PTA Calculation

Formula:

"A" delay + "B" delay + "C" delay - Overlap - applicant delay = X

USPTO's Calculation:

545 + 602 + 0 - 0 - 183 = 964

Patentee's Calculation:

547 + 604 – 44 = 1107

Conclusion

Patentee is entitled to PTA of 964 days. Using the formula "A" delay + "B" delay + "C" delay - overlap - applicant delay = X, the amount of PTA is calculated as following: 545 + 602 + 0 – 0 – 183 = 964 days.

Patentee has two (2) months from the date of the Office's redetermination of patent term adjustment to request reconsideration of the patent term adjustment if patentee continues to disagree with this determination (no petition fee). This two month period is extendible under 37 CFR 1.136(a). The new/renewed request for reconsideration may be filed without any additional fee. However, patentee who responds more than two months after the mail date of the redetermination is required to pay the extension of time fee. After the period of time to respond has expired, the Office will sua sponte issue a certificate of correction adjusting the PTA to 964 days.

Telephone inquiries specific to this matter should be directed to the undersigned at (571) 272-3205.

/ALESIA M. BROWN/

Alesia M. Brown
Attorney Adviser
Office of Petitions

Enclosure: Copy of DRAFT Certificate of Correction
Copy of PTA Screen

DRAFT COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT : 8,877,809

DATED : November 4, 2014

INVENTOR(S) : Washington

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 USC 154(b) by 1064 days

Delete the phrase "by 1064 days" and insert – by 964 days--

Patent Term Adjustments

Patent Term Adjustment (PTA) for Application Number: 12/733,631

Filing or 371(c) Date:	10-14-2010	Overlapping Days Between { A and B} or { A and C} :	0
Issue Date of Patent:	11-04-2014	Non-Overlapping USPTO Delays:	1147
A Delays:	545	PTO Manual Adjustments:	-100
B Delays:	602	Applicant Delays:	83
C Delays:	0	Total PTA Adjustments:	964

Patent Term Adjustment History | Explanation of Calculations

Number	Date	Contents Description	PTO(Days)	APPL(Days)	Start
96	07-11-2015	Adjustment of PTA Calculation by PTO		100	0
96	07-11-2015	Adjustment of PTA Calculation by PTO		100	0
91.5	11-04-2014	PTA 36 Months	602		91.4
91.4	03-12-2010	Commencement Date			0
91	11-04-2014	Patent Issue Date Used in PTA Calculation			0
90	10-01-2014	Export to Final Data Capture			0
89	09-30-2014	Dispatch to FDC			0
88	09-30-2014	Application Is Considered Ready for Issue			0
87	09-29-2014	Issue Fee Payment Verified			0
86	09-29-2014	Issue Fee Payment Received			0
85	08-19-2014	Finished Initial Data Capture			0
84	07-01-2014	Export to Initial Data Capture			0
83	06-27-2014	Electronic Review			0
82	06-27-2014	Email Notification			0
81	06-27-2014	Mail Notice of Allowance			0
80	06-25-2014	Office Action Review			0
79	06-25-2014	Office Action Review			0
78	06-25-2014	Issue Revision Completed			0
77	06-24-2014	Office Action Review			0
76	06-24-2014	Office Action Review			0
75	06-24-2014	Notice of Allowance Data Verification Completed			0

74	06-19-2014	Allowed Case Returned to the Examiner for Clerical Processing		0
73	06-19-2014	Document Verification		0
72	06-19-2014	Office Action Review		0
71	06-19-2014	Office Action Review		0
70	06-13-2014	Examiner's Amendment Communication		0
69	06-13-2014	Allowability Notice		0
65	06-02-2014	Date Forwarded to Examiner		0
64	05-30-2014	Response after Final Action	64	44
63	05-30-2014	Request for Extension of Time - Granted		0
62	05-30-2014	Email Notification		0
61	05-30-2014	Mail Advisory Action (PTOL - 303)		0
58	05-27-2014	Office Action Review		0
57	05-27-2014	Advisory Action (PTOL-303)		0
56	05-01-2014	Email Notification		0
55	05-01-2014	Mail Advisory Action (PTOL - 303)		0
54	04-29-2014	Office Action Review		0
53	04-28-2014	Advisory Action (PTOL-303)		0
52	04-28-2014	Information Disclosure Statement considered		0
51	04-21-2014	Electronic Information Disclosure Statement		0
50	04-21-2014	Information Disclosure Statement (IDS) Filed		0
49	04-01-2014	Date Forwarded to Examiner		0
48	03-27-2014	Response after Final Action		0
47	03-27-2014	PILOT- Request for After Final Consideration Program		0
46	12-27-2013	Electronic Review		0
45	12-27-2013	Email Notification		0
44	12-27-2013	Mail Final Rejection (PTOL - 326)		0
43	12-23-2013	Office Action Review		0
42	12-20-2013	Final Rejection		0

41	09-19-2013	Date Forwarded to Examiner			0
40	09-16-2013	Response after Non-Final Action			0
39	06-14-2013	Mail Non-Final Rejection			0
38	06-13-2013	Office Action Review			0
37	06-12-2013	Non-Final Rejection			0
36	09-05-2012	Information Disclosure Statement considered			0
34	02-26-2013	Information Disclosure Statement considered			0
33	04-05-2013	Change in Power of Attorney (May Include Associate POA)			0
32	03-27-2013	Correspondence Address Change			0
31	02-26-2013	Electronic Information Disclosure Statement		6	28
30	02-26-2013	Information Disclosure Statement (IDS) Filed			0
29	02-25-2013	Date Forwarded to Examiner			0
28	02-20-2013	Response to Election / Restriction Filed		13	26
27	02-20-2012	Request for Extension of Time - Granted			0
26	11-07-2012	Mail Restriction Requirement	545		91.4
25	11-05-2012	Office Action Review			0
24	11-04-2012	Restriction/Election Requirement			0
23	09-05-2012	Reference capture on IDS			0
22	09-05-2012	Information Disclosure Statement (IDS) Filed			0
21	09-05-2012	Information Disclosure Statement (IDS) Filed			0
20	02-10-2011	PG-Pub Issue Notification			0
19	02-07-2011	Case Docketed to Examiner in GAU			0
13	11-16-2010	Application Dispatched from OIPE			0
12	10-14-2010	371 Completion Date			0
11	11-01-2010	Sent to Classification Contractor			0
10	11-02-2010	Filing Receipt			0
9	11-02-2010	Notice of DO/EO Acceptance Mailed			0
8	10-14-	Additional Application Filing Fees			0

	2010		
7	10-14-2010	Applicants have given acceptable permission for participating foreign	0
5	10-14-2010	A statement by one or more inventors satisfying the requirement under 35 USC 115, Oath of the Applic	0
4	04-05-2010	Notice of DO/EO Missing Requirements Mailed	0
2	03-17-2010	Cleared by OIPE CSR	0
0.5	09-12-2008	International Filing date	0

Close Window

Office of Petitions: Routing Sheet



Application No. 12733631

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [ ] **GRANTED**
- [x] **DISMISSED**
- [ ] **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month: 1

Application No.: 12733631

12733631

For US serial numbers: enter nun
For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: BROWN, ALESIA M.

Count (1) - Palm Credit 12/733,631

Decision: DISMISSED

FINANCE WORK NEEDED ☐ Select Check Box for YES

DISMISSED

Decision Type: 551 - 37 CFR 1.705(d) - PATENT TERM ADJUSTMENT AF

551

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED ☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED ☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: *7/11/2015*

Office of Petitions Internal Document - Ver. 5.0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Ilyas Washington

Application No.: 12/733,631 Confirmation No.: 4180
Patent No. 8,877,809

Filing Date: March 10, 2010 Art Unit: 1621

For: Compositions and Methods for Treating Macular Degeneration Examiner: Fay, Zohreh A.

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

REQUEST FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT UNDER 37 C.F.R. § 1.705(b)

Dear Madam:

This is a request for reconsideration of the patent term adjustment of 1064 days listed on the Issue Notification mailed from the U.S. Patent and Trademark Office on October 15, 2014 in the above-identified patent. This request for reconsideration of the patent term adjustment is timely as it is being filed within two months from the date the patent was granted (November 4, 2014). In accordance with 37 C.F.R. § 1.705(b), Applicant hereby applies for patent term adjustment under 35 U.S.C. § 154(b) of **1107** days.

I. Fee

The fee required by 37 C.F.R. § 1.705(b)(1) and 37 C.F.R. § 1.18(e) is being paid by EFS Web. Please charge any deficiencies or any additional fees due in response to this request to Deposit Account No. 11-0600.

II. Statement of the Facts Involved

In view of the following, it is respectfully requested that Patentee be granted a patent term adjustment of **1107 days**. The patent term adjustment pursuant to 35 U.S.C. § 154(b) as shown on the face of the above-identified patent is incorrectly noted as 1064 days.

The factual bases for the above-adjustment are set forth as follows:

A. Examination Delays Pursuant to 37 C.F.R. § 1.702 and § 1.703

Pursuant to 37 C.F.R. § 1.703(f), the period of adjustment of the term of the patent under 37 C.F.R. § 1.702 is the sum of the periods of examination delay calculated under subparagraphs (a)-(e), to the extent that such periods are not overlapping, less the sum of the periods calculated under § 1.704 (the Applicant Delay). In the above-identified patent, Patentee is entitled to a period of examination delay equal to the sum of the periods of delay under § 1.703(a)(1), § 1.703(b)(1), § 1.704(b) and § 1.704(c) for the reasons set forth below.

(i) "14 Month Delay" Pursuant to 37 C.F.R. § 1.703(a)(1)

In accordance with 37 C.F.R. § 1.703(a)(1), as amended by the final rule published May 15, 2014 in the Federal Register, Vol. 79, No. 94, p. 27755, Patentee is entitled to a period of patent term adjustment due to the failure by the Office to mail an action under 35 U.S.C. § 132 or a notice of allowance under 35 U.S.C. § 151, whichever occurs first; not later than 14 months after the date on which the application was filed under 35 U.S.C. 111(a) or the date the national stage commenced under 35 U.S.C. 371(b) or (f) in an international application and ending on the date of mailing of either an action under 35 U.S.C. 132 (hereinafter "the 14 Month Delay"). As the "date the national stage commenced under 35 U.S.C. 371(b) or (f) in an international application" is the actual filing date of the application in the United States, the 14 Month Delay began on May 11, 2011 (14 months plus one day from March 10, 2010), and ended on November 7, 2012 (the mailing date of the Restriction Requirement). Accordingly, the period of patent term adjustment due to the 14 Month Delay by the Office is 547 days, which is not in agreement

with the period (545 days) calculated by the Office on the Patent Term Adjustment History.

(ii) "Three Year Delay" Pursuant to 37 C.F.R. § 1.703(b)

Pursuant to 37 CFR §1.702(b), Patentees are entitled to a period of delay due to the failure of the Office to issue a patent within three years after the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) in an international application (hereinafter "the Three Year Delay"). As set forth in 37 CFR §1.703(b), the Three Year Delay Period begins on the day after the date that is three years after the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) in an international application. Thus, the Three Year Delay began on March 11, 2013 (three years plus one day from March 10, 2010), and ended on November 4, 2014 (the issue date of the patent). Accordingly, the period of patent term adjustment due to the 14 Month Delay by the Office is 604 days, which is not in agreement with the period (602 days) calculated by the Office on the Patent Term Adjustment History.

(iii) Total Examination Delay Pursuant to 37 C.F.R. § 1.703(f)

As set forth in 37 C.F.R. § 1.703(f), the period of examination delay based on the grounds set forth in 37 C.F.R. § 1.702 is the sum of the period of the 14 Month Delay (547 days), the period of the Three Years Delay (604 days), to the extent that these periods are not overlapping. Accordingly, Patentee calculates that the total period of the examination delay is **1151**, which is not in agreement with the period (1147 days) calculated by the Office on the Patent Term Adjustment History.

B. "Applicant Delay" Pursuant to 37 C.F.R. § 1.704(a)

In accordance with 37 C.F.R. § 1.704(a), the period of adjustment of the term of a patent under §§ 1.703(a)-(e) shall be reduced by a period equal to the period of time during which the applicant failed to engage in reasonable efforts to conclude prosecution (processing or examination) of the application (the Applicant Delay).

(i) Total Examination Delay Pursuant to 37 C.F.R. § 1.704(b) ("Three Month Delay")

In accordance with 37 C.F.R. § 1.704(b), the periods of time in excess of three months that are taken to reply to any notice or action by the Office making any rejection, objection,

argument, or other request, measuring such three-month period from the date the notice or action was mailed or given to the applicant, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date that is three months after the date of mailing or transmission of the Office communication notifying the applicant of the rejection, objection, argument, or other request and ending on the date the reply was filed.

A Notice to File Missing Parts of Non-provisional Application was mailed on April 5, 2010 requesting filing of the oath or declaration and payment of the surcharge. Request for payment of the surcharge was in error as Applicant had provided a general authorization to charge any fees upon filing of the application (see page of 3 of the transmittal filed on March 10, 2010) and the submission of an inventor's oath or declaration may be postponed until the application is otherwise in condition for allowance. Accordingly, the filing of the Declaration and payment of the surcharge on October 14, 2014 does not constitute Applicant Delay, which is in agreement with the period (0 days) calculated by the Office on the Patent Term Adjustment History.

A Restriction Requirement was mailed on November 7, 2012. A Response by Patentee was filed February 20, 2013, outside the 3 months provided by 35 U.S.C. §154(b). Accordingly, the period of patent term adjustment due to the 3- Month Delay by the Applicant is 13 days, which is in agreement with the period calculated by the Office on the Patent Term Adjustment History.

(ii) Total Examination Delay Pursuant to 37 C.F.R. § 1.704(c) ("Supplemental Response Delay")

In accordance with 37 C.F.R. § 1.704(c), submission of a supplemental reply or other paper, other than a supplemental reply or other paper expressly requested by the examiner, after a reply has been filed, in which case the period of adjustment set forth in §1.703 shall be reduced by the number of days, if any, beginning on the day after the date the initial reply was filed and ending on the date that the supplemental reply or other such paper was filed.

An Information Disclosure Statement was filed on February 26, 2013, six days after the response to the Restriction Requirement was filed on February 20, 2013. Accordingly, the period of patent term adjustment due to the Supplemental Response Delay by the Applicant is 6

days, which is in agreement with the period calculated by the Office on the Patent Term Adjustment History.

An Information Disclosure Statement was filed on April 21, 2014, 25 days after the response to the Office Action was filed on March 27, 2014. Accordingly, the period of patent term adjustment due to the Supplemental Response Delay by the Applicant is 25 days, which is not in agreement with the period (0 days) calculated by the Office on the Patent Term Adjustment History.

A Supplemental Response expressly requested by the Examiner was filed May 30, 2014. In accordance with 37 C.F.R. § 1.704(c), a supplemental reply expressly requested by the examiner does not constitute Applicant Delay. In particular, the Supplemental Response was filed following Examiner Interviews held on May 15, 22, and 27, 2014 (see Amendment after Final filed May 30, 2014, page 7, under "Interview Summary"). During the interviews, the rejections raised by the Examiner in the Final Office Action mailed December 27, 2013 and possible claim language to overcome those rejections were discussed and it was agreed that the Applicant would file the claims presented in the May 30, 2014 Supplemental Response. Subsequently, the Examiner indicated in the Notice of Allowance mailed on June 27, 2014 that the claims resulting from the Examiner Interviews and presented in the May 30, 2014 Supplemental Response were allowable.[1] The Examiner also stated that the Advisory Action mailed on May 30, 2014 was mailed in error, so it should not have any bearing on the Patent Term Adjustment calculation (see Notice of Allowance, continuation sheet). Accordingly, as the response filed on May 30, 2014 was a result of discussions with the Examiner in which the claims presented therein were expressly requested by the Examiner, no Applicant Delay should accrue (i.e., 0 days of Applicant delay), which is not in agreement with the period calculated by the Office (64 days) on the Patent Term Adjustment History.

Patentee calculates that the total reduction in the period of adjustment due to Applicant Delay is **44 days**, which is not in agreement with the period (83 days) calculated by the Office on the Patent Term Adjustment History.

C. Calculation of Correct Patent Term Adjustment Pursuant to 37 C.F.R. § 1.702(f)

As set forth in 37 C.F.R. § 1.703(f), Patentee is entitled to a period of patent term

[1] The Examiner made one minor typographical correction to claim 61 in an Examiner's Amendment.

adjustment equal to the period of examination delays (*i.e.,* 1151 days) reduced by the period of Applicant Delay (*i.e.,* 44 days). Therefore, Patentee submits that the correct patent term adjustment for the above-identified patent is **1107 days**, which is the difference between the total period of examination delay (1151 days) and Applicant Delay (44 days).

In accordance with 37 C.F.R. §1.702(b)(2)(iii), Patentee submits that this patent is not subject to a terminal disclaimer.

Any applicant delays under 37 C.F.R. § 1.704 are set forth above. There were no other circumstances constituting a failure to engage in reasonable efforts to conclude processing of examination of the above-identified application, as set forth in 37 C.F.R. § 1.704.

Patentee respectfully requests grant of this Application for Patent Term Adjustment.

In accordance with 37 C.F.R. § 1.705(b)(1), Applicant submits herewith the fee of $200 set forth in 37 C.F.R. § 1.18(e). Should any additional fees be necessary, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 11-0600.

Respectfully Submitted,

Dated: January 5, 2015

/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 NUMBER 26646

Electronic Patent Application Fee Transmittal

Application Number:	12733631
Filing Date:	14-Oct-2010
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:	13533/541US

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Application for patent term adjustment	1455	1	200	200
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**200**

Electronic Acknowledgement Receipt

EFS ID:	21116212
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	13533/541US
Receipt Date:	05-JAN-2015
Filing Date:	14-OCT-2010
Time Stamp:	13:44:43
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$200
RAM confirmation Number	24
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 1.20 (Post Issuance fees)

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	Patent Term Adjustment Petition	13533-541US_PTA_Recalculation-Request-1-5-2015.pdf	167058 f68be7a0e2cfc469b6a7ce4dd071bf48788d2c6f	no	6
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30521 2041cf6759e41b773a312b3117474def2332abc7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	197579		

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.

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	11/04/2014	8877809	13533/541US	4180

26646 7590 10/15/2014

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

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 1064 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 United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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)

26646 7590 06/27/2014
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

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.

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.

Via EFS-Web Loretta E. Charles	(Depositor's name)
/Loretta E. Charles/	(Signature)
September 29, 2014	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

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	09/29/2014

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,
(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 KENYON & KENYON LLP
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: The Trustees of Columbia University in the City of New York

(B) RESIDENCE: (CITY and STATE OR COUNTRY): New York, NY

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 11-0600 (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 /Joseph A. Coppola/ Date September 29, 2014

Typed or printed name Joseph A. Coppola Registration No. 38,413

Electronic Patent Application Fee Transmittal

Application Number:	12733631
Filing Date:	14-Oct-2010
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:	13533/541US

Filed as Small Entity

U.S. National Stage under 35 USC 371 Filing Fees

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
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	20268989
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	13533/541US
Receipt Date:	29-SEP-2014
Filing Date:	14-OCT-2010
Time Stamp:	13:46:41
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$480
RAM confirmation Number	44
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	Issue Fee Payment (PTO-85B)	13533-541US_Issue-Fee-Transmittal_9-29-2014.pdf	134442 bbb661bdff64c3655158df83f24511f016fd714c	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30395 9f2cee11ed63ba0fda17326cfc2adfdd32a75fa2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	164837		

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

26646 7590 06/27/2014

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER
FAY, ZOHREH A

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/27/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

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	09/29/2014

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)

26646 7590 06/27/2014
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

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.

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.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

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	09/29/2014

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,
(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 _____
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 — 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.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — 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.
- ❑ Applicant changing to regular undiscounted fee 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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

26646 7590 06/27/2014
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/27/2014

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. 12/733,631	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 *See Continuation Sheet*.
   ☐ 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 *61, 115-140*. 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)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date See Continuation Sheet
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Continuation of Item 1. This communication is responsive to : the amendments and remarks filed on May 30, 2014. The advisory action of May 30, 2014 does not belong to the instant application.

Continuation of Attachment(s) 2. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 3/10/2010, 9/5/2012, 2/26/2013, 4/21/2014.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Joseph Coppola on June 12, 2014.

The application has been amended as follows:

In claim 61, line 6 "," has been canceled.

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
/ZOHREH FAY/
Primary Examiner, Art Unit 1621

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12/733,631
Filing Date	March 10, 2010
First Named Inventor	Ilyas WASHINGTON
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	C035795/0307366

U.S.PATENTS

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.	5,310,764		5/10/1994	Baranowitz, et al.	
	2.	6,660,297		12/9/2003	Bartels, et al.	
	3.	7,566,808		7/28/2009	Rando	

If you wish to add additional U.S. Published Application citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

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
	4.	2002/0012966		1/31/2002	Shi, et al.	
	5.	2003/0032078		2/13/2003	Travis	
	6.	2003/0149997		8/7/2003	Hageman	
	7.	2004/0009907		1/15/2004	Alsobrook, et al.	
	8.	2004/0121407		6/24/2004	Distefano et al.	
	9.	2004/0235113		11/25/2004	Shi, et al.	
	10.	2005/0059010		3/17/2005	Stone, et al.	
	11.	2005/0119536		6/2/2005	Hageman	
	12.	2005/0176662		8/11/2005	Inana, et al.	
	13.	2005/0220768		10/6/2005	McVey, et al.	
	14.	2005/0256207		11/17/2005	McGrath	
	15.	2006/0094063		5/4/2006	Mata, et al.	
	16.	2006/0099714		5/11/2006	Mata, et al.	
	17.	2006/0135460		6/22/2006	Widder, et al.	
	18.	2006/0292099		12/28/2006	Milburn, et al.	
	19.	2007/0135481		6/14/2007	Jordan, et al.	
	20.	2007/0014833		1/18/2007	Milburn, et al.	
	21.	2007/0015827		1/18/2007	Widder, et al.	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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Filing Date	March 10, 2010
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Examiner Name	Not yet assigned
Attorney Docket Number	C035795/0307366

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1.	JP 2004-526725			9/2/2004	Eli Lilly & Co. et al.		Abstract
	2.	WO 05/087210			9/22/2005	Lars Michael Larsen		
	3.	WO 07/19503			2/15/2007	President and Fellows of Harvard College		

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	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.*, 119: 1417-36 (2001).	
	3.	Alikmets, et al. "A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy," *Nat. Genet* 15, 236-246 (1997).	
	4.	Ashmarin, et al. "Thyroliberin: new physiological effects and prospects of clinical use," *Vestn Ross Akad Med Nauk* 6, 40-4 (1992). (with abstract translation)	X
	5.	Baehr, et al. "The retinoid cycle and retina disease," *Vision Research* 43, 2957-2958 (2003).	
	6.	Barrett, et al. "Hybrid tracking system for retinal photocoagulation prototype II," *Biomed Sci Instrum* (1999) 35: 259-64.	
	7.	Bausch, et al. "Method for the assessment of vitamin A liver stores," *Acta Vitaminol Enzymol* 31, 99-112 (1977).	
	8.	Ben-Shabat, et al. "Fluorescent pigments of the retinal pigment epithelium and age-related macular degeneration," *Bioorg Med Chem Lett.* 11, 1533-1540 (2001).	
	9.	Bergen, et al. "Synthesis of Tri-, Tetra-, and Penta-Deuterated Forms of Vitamin A," *Journal of Labelled compounds and Radiopharmaceuticals*, vol. 25, no. 1, 11-21 (1988).	
	10.	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, 562-564 (2004).	
	11.	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.* 19, 1664-1670 (2001).	
	12.	Capon, et al. "Sorsby's fundus dystrophy: a light and electron microscopic study," *Ophthalmology* 96, 1769-1777 (1989).	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12/733,631
	Filing Date	March 10, 2010
	First Named Inventor	Ilyas WASHINGTON
	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned
	Attorney Docket Number	C035795/0307366

	13.	Isotretinoin, [online], [retrieved on July 05, 2012] Retrieved from Chemocare.com using Internet <URL: http://www.chemocare.com/bio/isotretinoin.asp>.	
	14.	Chong, et al. "TIMP-3 collagen, and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy," *Invest Ophthamol Vis Sci* 41, 898-902 (2000).	
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	Application Number	12/733,631
	Filing Date	March 10, 2010
	First Named Inventor	Ilyas WASHINGTON
	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned
	Attorney Docket Number	C035795/0307366

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Name/Print	/Jihong Zang/	Registration Number	56,606

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	B2	WO 2002/072528	09/19/2002	Eli Lilly and Company		
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	C1	Radu, et al. "Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt's Macular Degeneration," PNAS 100(8): 4742-4747 (2003)	
	C2	Walker, "New/Old Findings on Unique Vitamin E," retrieved from the Internet: http://www.enerex.ca/articles/new_old_findings_on_ unique_vitamin_e.htm (01 Dec 2008)	

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Name/Print	Joseph A. Coppola	Registration Number	38413

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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 record s.

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).

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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.

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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12733631
Filing Date	2010-10-14
First Named Inventor	Ilyas Washington
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	13533/541US

U.S.PATENTS Remove

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	8124646	B2	2012-02-28	Liu	
	2	8263601	B2	2012-09-11	Tung	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	"What is Deuterium?" [retrieved on 2/11/2013], <URL: http://www.innovateus.net/print/science/what-deuterium>. 4 pages.	☐
	2	BAILLIE, Thomas A., "The Use of Stable Isotopes in Pharmacological Research", Pharmacological Reviews, Vol. 33, No. 2, pp. 81-132, 1981.	☐
	3	FOSTER, Allan, "Deuterium Isotope Effects in Studies of Drug Metabolism," TIPS-- December 1984.	☐
	4	HANDELMAN et al., "An Improved Protocol for Determining Ratios of Retinol-d4 to Retinol Isolated from Human Plasma", Anal. Chem., 65, 2024-2028, 1993.	☐
	5	HASKINS, N.J., "The Application of Stable Isotopes in Biomedical Research", Biomedical Mass Spectrometry, Vol. 9, No. 7, pp. 269-277, 1982.	☐
	6	KUSHNER et al., "Pharmacological uses and perspectives of heavy water and deuterated compounds," Can. J. Physiol. Pharmacol. 77: 79-88 (1999).	☐
	7	PARK, et al. "Metabolism of Fluorine-Containing Drugs," Annu. Rev. Pharmacol. Toxicol. (41) 443-70 (2001).	☐
	8	TANG, G. et al., "Deuterium enrichment of retinol in humans determined by gas chromatography electron capture negative chemical ionization mass spectrometry", J. Nutr. Biochem, 9:408-414, 1998.	☐
	9	TUNG, Office action for US Patent Application 12/874,783, Dated 08/16/2011.	☐
	10	WOLEN, Robert L., "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence", The Journal of Clinical Pharm., Vol.26, pp. 419-424, 1986.	☐

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	Application Number	12733631
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	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

If you wish to add additional non-patent literature document citation information please click the Add button		Add	
EXAMINER SIGNATURE			
Examiner Signature	/Zohreh Fay/	Date Considered	

*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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	Filing Date	2010-10-14
	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

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)	2013-02-26
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.**

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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.

OK TO ENTER: /Z.F./

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application No.: 12/733,631 | Confirmation No.: 4180

Filed: October 14, 2010 | Art Unit: 1621

For: Compositions and Methods for Treating Macular Degeneration | Examiner: Fay, Zohreh A.

VIA EFS-Web
MS: AF
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 May 30, ***2014.***

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

AMENDMENT AFTER FINAL

Dear Sir/Madam:

This paper is in response to the Final Office Action mailed December 27, 2013 and is intended to put the claims in better form for allowance. Enclosed herewith is a Petition for the Extension of Time.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12733631	WASHINGTON, ILYAS
	Examiner	**Art Unit**
	ZOHREH FAY	1621

CPC						
Symbol					**Type**	**Version**
A61K		31	/	135	F	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

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

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12733631	WASHINGTON, ILYAS
	Examiner	**Art Unit**
	ZOHREH FAY	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:
(Assistant Examiner) (Date)	27
/ZOHREH FAY/ Primary Examiner.Art Unit 1621	O.G. Print Claim(s): 1 / O.G. Print Figure: none
(Primary Examiner) (Date)	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12733631	WASHINGTON, ILYAS
	Examiner	**Art Unit**
	ZOHREH FAY	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	61	17	130												
2	115	18	131												
3	116	19	132												
4	117	20	133												
5	118	21	134												
6	119	22	135												
7	120	23	136												
8	121	24	137												
9	122	25	138												
10	123	26	139												
11	124	27	140												
12	125														
13	126														
14	127														
15	128														
16	129														

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

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BIB DATA SHEET

CONFIRMATION NO. 4180

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/733,631	10/14/2010 RULE	514	1621	13533/541US

APPLICANTS

INVENTORS
Ilyas Washington, New York, NY;

** **CONTINUING DATA** *************************
This application is a 371 of PCT/US2008/010676 09/12/2008
which claims benefit of 60/993,379 09/12/2007

** **FOREIGN APPLICATIONS** *************************

** **IF REQUIRED, FOREIGN FILING LICENSE GRANTED** ** ** SMALL ENTITY **
10/28/2010

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /ZOHREH A FAY/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	7	49	6

ADDRESS

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004
UNITED STATES

TITLE

COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

FILING FEE RECEIVED		
2466	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

BIB (Rev. 05/07).

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12733631	WASHINGTON, ILYAS
	Examiner	Art Unit
	ZOHREH FAY	1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	613	6/16/2014	ZF
514	671	6/16/2014	ZF
514	703	6/16/2014	ZF

SEARCH NOTES		
Search Notes	Date	Examiner
West	6/11/2013	ZF
Inventor search	6/11/2013	ZF
Updated	12/20/2013	ZF
Updated	6/16/2014	ZF

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	613	6/16/2014	ZF
514	671	6/16/2014	ZF
514	703	6/16/2014	ZF

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

26646 7590 05/30/2014

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
05/30/2014	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

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/733,631	**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 --

THE REPLY FILED 29 April 2014 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☐ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☒ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires 3 months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☒ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
13. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 4/29/2014
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: none.
    Claim(s) objected to: none.
    Claim(s) rejected: 1-13.
    Claim(s) withdrawn from consideration: none.

/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Continuation of 11. does NOT place the application in condition for allowance because: for the reasons of record. The presented references submitted in the Information Disclosure Statement of April 29, 2014 have been considered. Applicant's arguments have been considered. However, the newly submitted art raises new issues. Such documents were not presented prior to the Final action of 2/7/2014.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application No.: 12/733,631 | Confirmation No.: 4180

Filed: October 14, 2010 | Art Unit: 1621

For: Compositions and Methods for Treating Macular Degeneration | Examiner: Fay, Zohreh A.

VIA EFS-Web
MS: AF
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 May 30, ***2014.***

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

AMENDMENT AFTER FINAL

Dear Sir/Madam:

This paper is in response to the Final Office Action mailed December 27, 2013 and is intended to put the claims in better form for allowance. Enclosed herewith is a Petition for the Extension of Time.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1-60. (Cancelled)

61. (Currently amended) A method of retarding the accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid, wherein the C_{20}-D_{1-3}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinol, C_{20}-D_{1-3}-retinol ester, C_{20}-D_{1-3}-retinal and C_{20}-D_{1-3}-pro-vitamin A carotenoids, and a pharmaceutically acceptable carrier~~, provided that the C_{20}-D_{1-3}-retinoid is not a C_{20}-D_{1-3}-isotretinoin or a C_{20}-D_{1-3}-all trans-retinylamine~~.

62-114. (Cancelled)

115. (New) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-retinoid is a C_{20}-D_3-retinoid.

116. (New) The method according to Claim 61, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

117. (New) The method according to Claim 61, wherein the patient is in need of treatment for a macular degeneration.

118. (New) The method according to Claim 117, wherein the macular degeneration is age-related macular degeneration.

119. (New) The method according to Claim 118, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

120. (New) The method according to Claim 118, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-pro-vitamin A carotenoid.

121. (New) The method according to Claim 118, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

122. (New) The method according to Claim 121, wherein the C_{20}-D_3-retinal, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinal.

123. (New) The method according to Claim 118, wherein the patient is in need of treatment for dry (non-neovascular) age-related macular degeneration.

124. (New) The method according to Claim 61, wherein the patient is in need of treatment for Stargardt disease.

125. (New) The method according to Claim 124, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

126. (New) The method according to Claim 124, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-pro-vitamin A-carotenoid.

127. (New) The method according to Claim 124, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

128. (New) The method according to Claim 127, wherein the C_{20}-D_3-retinal, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinal.

129. (New) The method according to Claim 61, wherein the patient is in need of treatment for a macular degeneration selected from the group consisting of Vitelliform or Best disease, Sorsby's fundus dystrophy, retinitis pigmentosa, and Malattia Leventinese.

130. (New) The method according to Claim 129, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

131. (New) The method according to Claim 61, wherein the patient is in need of treatment for a macular degeneration characterized by one or more mutation(s) in the ABCA4 gene.

132. (New) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-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.

133. (New) The method according to Claim 61, further comprising an additional active.

134. (New) The method according to Claim 133, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

135. (New) The method according to Claim 134, 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.

136. (New) The method according to Claim 134, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

137. (New) The method according to Claim 134, wherein the negatively charged phospholipid is

selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

138. (New) The method according to Claim 134, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

139. (New) The method according to Claim 61, wherein the C_{20}-D_3-retinal, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinal.

140. (New) The method according to Claim 61, wherein the pharmaceutical composition is administered directly to the eye.

Remarks

Claim Amendments

Claims 50-60 and 62-114 have been cancelled in this Amendment. Claims 1-49 had previously been cancelled. Claim 61 has been amended. Claims 115-140 are new. Thus, if this Amendment is entered, Claims 61 and 115-140 will be pending. Support for the amendments to Claim 61 and for new Claims 115-140 is described in the following paragraphs.

Amended Claim 61 combines the features of former Claim 61 and now-cancelled Claim 70. Amended Claim 61 also further narrows "carotenoid" to those that are "pro-vitamin A". Support for this amendment is found in the specification, at page 19, line 8. Note that because none of the four retinoids now claimed in amended Claim 61 is either a C_{20}-D_{1-3}-all trans-retinylamine or C_{20}-D_{1-3}-isotretinoin, the final part of former Claim 61 "provided that the C_{20}-D_{1-3}-retinoid is not a C_{20}-D_{1-3}-isotretinoin or a C_{20}-D_{1-3}-all trans-retinylamine" has been deleted without broadening the scope of former Claim 61.

Claim 115 is essentially the same as former Claim 62 (adding "a" before "C_{20}-D_3-retinoid).

Claims 116-119 correspond to former Claims 64 and 66-68.

Claim 120 is essentially the same as former Claim 70 restricting "carotenoid" to "pro-vitamin A carotenoid". Support for this amendment is found in the specification, at page 19, line 8.

Claims 121-125 correspond to former Claims 71-76 (excluding Claim 73), wherein "retinaldehyde" was renamed to "retinal" for consistency with naming used in Figure 3 of the description.

Claim 126 is essentially the same as former Claim 78 restricting "carotenoid" to "pro-vitamin A carotenoid". Support for this amendment is found in the specification, at page 19, line 8.

Claims 127-129 correspond to former Claims 79-82 (excluding Claim 81) with the same "retinal" naming convention explained above, and wherein the diseases recited in Claim 129 are "macular degeneration".

Claim 130 is dependent on new Claim 129 and restricts the C_{20}-D_{1-3}-retinoid to C_{20}-D_3-retinol acetate.

Claim 131 corresponds to former Claim 83, wherein the disease caused by ABCA4 mutation(s) is a macular degeneration.

Claims 132-140 correspond to former Claims 98-107 (excluding Claim 105) with the same "retinal" naming convention explained above.

Interview summary

The Applicant thanks the Examiner for the telephonic interviews that were held on May 15, 22, and 27, 2014 and included the Examiner, Joseph Coppola (attorney for Applicant), Ilyas Washington (inventor), and Leonide Saad (CEO of licensee). The Examiner is thanked for granting the interviews and for her careful attention to the issues discussed.

During the interview, the rejections of record and possible claim language to overcome those rejections were discussed. It was agreed that the Applicant would file the enclosed set of amended claims in order to put the claims in better form for allowance.

In view of the enclosed amendments, the Applicant respectfully submits that the claims are in condition for allowance and requests that the enclosed amendments be entered.

The Examiner is invited to contact the undersigned by telephone if it is felt that such would advance the prosecution of the present application.

The time for responding to the Office Action was set for March 27, 2014. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Commissioner is authorized to charge Kenyon & Kenyon LLP's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: May 30, 2014

By: /Joseph A. Coppola/
Joseph A. Coppola
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One Broadway
New York, NY 10004
(212) 425-7200

CUSTOMER NO.: 26646

Electronic Patent Application Fee Transmittal

Application Number:	12733631
Filing Date:	14-Oct-2010
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:	13533/541US

Filed as Small Entity

U.S. National Stage under 35 USC 371 Filing Fees

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:				
Extension - 3 months with $0 paid	2253	1	700	700

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**700**

Electronic Acknowledgement Receipt

EFS ID:	19169059
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	13533/541US
Receipt Date:	30-MAY-2014
Filing Date:	14-OCT-2010
Time Stamp:	12:58:10
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$700
RAM confirmation Number	9066
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	Response After Final Action	13533-541US_Response-AF_5_30_2014.pdf	149815 9f6f72f20274c3553c911d465833dfe22a3c9858	no	8
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30286 e225dbd447b2738115df447c2fd6e6c4037a8fd2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	180101		

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.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/733,631	Filing Date 10/14/2010	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) 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

AMENDMENT **05/30/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 27	Minus	** 65	=	X $ =	
Independent (37 CFR 1.16(h))	* 1	Minus	***6	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
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
/KATRINA . TURNER/

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

26646 7590 05/01/2014

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
05/01/2014	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

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/733,631	**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 --

THE REPLY FILED 27 March 2014 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☒ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: of the reasons of record.
13. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 4/21/2014
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: nonr.
    Claim(s) objected to: none.
    Claim(s) rejected: 61-66,75-81 and 84-107.
    Claim(s) withdrawn from consideration: none.

/ZOHREH FAY/
Primary Examiner, Art Unit 1621

Continuation of 3. NOTE: the specific retinoids cited in claims 61 raise new issues, which require further consideration and search.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12733631
Filing Date	2010-10-14
First Named Inventor	Ilyas Washington
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	13533/541US

U.S.PATENTS Remove

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
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020169176	A1	2002-11-14	James T. Elder et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2006-526662	JP	A	2006-11-24	ACHKAR, Charles et al.	See English counterpart WO2005-000230	☐
	2	2005-000230	WO	A2	2005-01-06	ACHKAR, Charles et al.		☐
	3	2002-275095	JP	A	2002-09-25	Warner-Lambert Company	See English counterpart WO1996-024344	☐

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12733631
	Filing Date	2010-10-14
	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

	4	1996/024344	WO	A1	1996-08-15	Warner-Lambert Company		☐
	5	H10-513197	JP	A	1998-12-15	Warner-Lambert Company	See English counterpart US2002-0169176	☐

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NON-PATENT LITERATURE DOCUMENTS **Remove**

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Japanese Office Action with English translation from counterpart Japanese Application No.: 2012-260971 dated February 7, 2014.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/	Date Considered	

*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.

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12733631
	Filing Date	2010-10-14
	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

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)	2014-04-21
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.**

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

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 record s.

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.

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.

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PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12733631
Filing Date	2010-10-14
First Named Inventor	Ilyas Washington
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	13533/541US

U.S.PATENTS Remove

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					

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020169176	A1	2002-11-14	James T. Elder et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2006-526662	JP	A	2006-11-24	ACHKAR, Charles et al.	See English counterpart WO2005-000230	☐
	2	2005-000230	WO	A2	2005-01-06	ACHKAR, Charles et al.		☐
	3	2002-275095	JP	A	2002-09-25	Warner-Lambert Company	See English counterpart WO1996-024344	☐

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	Filing Date	2010-10-14
	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

	4	1996/024344	WO	A1	1996-08-15	Warner-Lambert Company		☐
	5	H10-513197	JP	A	1998-12-15	Warner-Lambert Company	See English counterpart US2002-0169176	☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Japanese Office Action with English translation from counterpart Japanese Application No.: 2012-260971 dated February 7, 2014.	☐

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Electronic Patent Application Fee Transmittal

Application Number:	12733631
Filing Date:	14-Oct-2010
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:	13533/541US

Filed as Small Entity

U.S. National Stage under 35 USC 371 Filing Fees

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($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	18818957
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	13533/541US
Receipt Date:	21-APR-2014
Filing Date:	14-OCT-2010
Time Stamp:	17:49:58
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$90
RAM confirmation Number	4493
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	Transmittal Letter	13533-541US-Supp-IDS-Trans-Ltr_4-21-2014.pdf	113996 345ff2a41e1429d299bbb8108043533ab51373f0	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	13533-541US_Supplemental-IDS-4-21-2014.pdf	612634 22dd3b6eb0d4b3722cef3242755d1543a0496e35	no	4
Warnings:					
Information:					
3	Foreign Reference	JP2006-526662T.pdf	5666136 6a45462688cd6e145fec7496121e0e57744f090f	no	31
Warnings:					
Information:					
4	Foreign Reference	WO-2005-00230-Eng-Ver-of-JP2006-526662.pdf	528124 a037d3afaa7b33489a3ec509a16b2268a354ca3d	no	54
Warnings:					
Information:					
5	Foreign Reference	JP2002-275095A.pdf	6387088 2e814602134cc2d77db4b1f9d8afeb40829b8a16	no	32
Warnings:					
Information:					
6	Foreign Reference	WO-1996-024344-Eng-Ver-of-JP2002-275095.pdf	648596 6682427354f088f4b35f64329bad19809e704011	no	77
Warnings:					
Information:					
7	Foreign Reference	JPH10-513197T.pdf	10524503 6ba972a830d39702fef97e8675e274b43fee0f0e	no	83
Warnings:					
Information:					
8	Non Patent Literature	JP-Office-Action-.pdf	917937 0bd68a4556e6959305235f58deba9fcd513e3bf0	no	7
Warnings:					
Information:					

9	Fee Worksheet (SB06)	fee-info.pdf	30599 c7b5c25ee2e374ac6b05c9dd29073412889503de	no	2

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Total Files Size (in bytes):	25429613

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application No.: 12/733,631 | Confirmation No.: 4180

Filed: October 14, 2010 | Art Unit: 1621

For: Compositions and Methods for Treating Macular Degeneration | Examiner: Fay, Zohreh A.

Via EFS-Web
MS: AF
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 **April 21, 2014.**

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir/Madam:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

Pursuant to 37 CFR §1.97(e)(1), it is hereby certified that each item of information contained in the Supplemental 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 Supplemental Information Disclosure Statement.

The fee set forth in 37 CFR 1.17(p) is submitted herewith.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 11-0600.

Dated: April 21, 2014

Respectfully submitted,

/Joseph A. Coppola/
Joseph A. Coppola
Registration No.: 38,413

KENYON AND KENYON LLP
One Broadway
New York, New York 10004-1050
(212) 425-7200
Customer No. 26646

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
13533/541US	12/733,631	October 14, 2010
First Named Inventor:	**Title:**	
Ilyas Washington	Compositions and Methods for Treating Macular Degeneration	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
   - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
   - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
     - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
     - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
       - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
       - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Joseph A. Coppola/	March 27, 2014
Name (Print/Typed)	**Practitioner Registration No.**
Joseph A. Coppola	38,413

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☐ * Total of _____ forms are submitted.

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application No.: 12/733,631 | Confirmation No.: 4180

Filed: October 14, 2010 | Art Unit: 1621

For: Compositions and Methods for Treating Macular Degeneration | Examiner: Fay, Zohreh A.

VIA EFS-Web
MS: AF
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 ***March 27, 2014.***

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

AMENDMENT AFTER FINAL

Dear Sir/Madam:

This Paper is in response to the Final Office Action mailed December 27, 2013. Authorization is hereby granted to charge any additional fees which may be required regarding this application, or credit any overpayment, to Deposit Account No. 11-0600. Applicant requests that this Response be examined in accordance with the After Final Pilot Program 2.0.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1-60. (Cancelled)

61. (Currently amended) A method of retarding the accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid, wherein the C_{20}-D_{1-3}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinol, C_{20}-D_{1-3}-retinol ester, C_{20}-D_{1-3}-retinal and C_{20}-D_{1-3}-pro-vitamin A carotenoids, and a pharmaceutically acceptable carrier~~, provided that the C_{20}-D_{1-3}-retinoid is not a C_{20}-D_{1-3}-isotretinoin or a C_{20}-D_{1-3}-all trans-retinylamine~~.

62-114. (Cancelled)

115. (New) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-retinoid is a C_{20}-D_3-retinoid.

116. (New) The method according to Claim 61, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

117. (New) The method according to Claim 61, wherein the patient is in need of treatment for a macular degeneration.

118. (New) The method according to Claim 117, wherein the macular degeneration is age-related macular degeneration.

119. (New) The method according to Claim 118, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

120. (New) The method according to Claim 118, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-pro-vitamin A carotenoid.

121. (New) The method according to Claim 118, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

122. (New) The method according to Claim 121, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

123. (New) The method according to Claim 118, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

124. (New) The method according to Claim 118, wherein the patient is in need of treatment for dry (non-neovascular) age-related macular degeneration.

125. (New) The method according to Claim 61, wherein the patient is in need of treatment for Stargardt disease.

126. (New) The method according to Claim 125, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

127. (New) The method according to Claim 125, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-pro-vitamin A-carotenoid.

128. (New) The method according to Claim 125, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

129. (New) The method according to Claim 128, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

130. (New) The method according to Claim 125, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

131. (New) The method according to Claim 61, wherein the patient is in need of treatment for a disease selected from the group consisting of Vitelliform or Best disease, Sorsby's fundus dystrophy, retinitis pigmentosa, and Malattia Leventinese.

132. (New) The method according to Claim 131, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

133. (New) The method according to Claim 61, wherein the patient is in need of treatment for a disease characterized by one or more mutation(s) in the ABCA4 gene.

134. (New) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-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.

135. (New) The method according to Claim 61, further comprising an additional active.

136. (New) The method according to Claim 135, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

137. (New) The method according to Claim 136, 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.

138. (New) The method according to Claim 136, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

139. (New) The method according to Claim 136, wherein the negatively charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

140. (New) The method according to Claim 136, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

141. (New) The method according to Claim 61, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

142. (New) The method according to Claim 61, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

143. (New) The method according to Claim 61, wherein the pharmaceutical composition is administered directly to the eye.

Remarks

Claim Amendments

Claims 50-60 and 62-114 have been cancelled in this Amendment. Claims 1-49 had previously been cancelled. Claim 61 has been amended. Claims 115-143 are new. Support for new Claims 115-143 is described in the following paragraphs.

Amended Claim 61 combines the features of former Claim 61 and now-cancelled Claim 70. Amended Claim 61 also adds "pro-vitamin A" before "carotenoid". Support for this amendment is found at page 19, line 8. Note that because none of the four retinoids now claimed in amended Claim 61 is either a C_{20}-D_{1-3}-all trans-retinylamine or C_{20}-D_{1-3}-isotretinoin, the final part of former Claim 61 "provided that the C_{20}-D_{1-3}-retinoid is not a C_{20}-D_{1-3}-isotretinoin or a C_{20}-D_{1-3}-all trans-retinylamine" has been deleted without broadening the scope of former Claim 61.

Claim 115 is essentially the same as former Claim 62 (adding "a" before "C_{20}-D_3-retinoid).

Claims 116-119 correspond to former Claims 64 and 66-68.

Claim 120 is essentially the same as former Claim 70 restricting "carotenoid" to "pro-vitamin A carotenoid". Support for this amendment is found at page 19, line 8.

Claims 121-126 correspond to former Claims 71-76.

Claim 127 is essentially the same as former Claim 78 restricting "carotenoid" to "pro-vitamin A carotenoid". Support for this amendment is found at page 19, line 8.

Claims 128-131 corresponds to former Claims 79-82.

Claim 132 is dependent on new Claim 131 and restricts the C_{20}-D_{1-3}-retinoid to C_{20}-D_3-retinol acetate.

Claim 133 corresponds to former Claim 83.

Claims 134-143 correspond to former Claims 98-107.

Interview Summary

On February 26, 2014 a telephonic interview was held between Examiner Zohreh A. Fay, Joseph A. Coppola (Attorney for Applicant), Steven G. Davis (Attorney for licensee of the subject application), Inventor Ilyas Washington and Leonide Saad (CEO of licensee). The Examiner is thanked for granting the interview and for her helpful comments during the interview.

During the interview, the rejections of record were discussed. It was agreed that incorporating the features of Claim 70 into 61 would likely advance prosecution, which is what essentially was done in amended Claim 61.

Rejection Under 35 USC 112, First Paragraph for Failing to Comply with the Enablement Requirement

The Examiner stated that the claims are drawn to a method of retarding the accumulation of lipofuscin pigment in a retina using a substituted C_{20}-D_{1-3} retinoid with the proviso that the C_{20}-D_{1-3} is not C_{20}-D_{1-3} isotretinoin or C_{20}-D_{1-3} all *trans* retinylamine. She stated further that Applicant excluded the retinoids used in the prior art rejection and indicated that such retinoids slow lipofuscin accumulation by slowing the visual cycle and causing night blindness. She concluded that Applicant has failed to provide an enabling disclosure to show lack of side effects of the rest of the retinoids.

Without acceding to the Examiner's objection, but in order to progress this application to grant, amended Claim 61 is more specifically defined with a recitation of only four retinoids, i.e., C_{20}-D_{1-3}-retinol, C_{20}-D_{1-3}-retinol ester, C_{20}-D_{1-3}-retinal and C_{20}-D_{1-3}-pro-vitamin A carotenoids. Each of these four listed retinoids belong to the class of "vitamin A compounds" and are known to transform into "C_{20}-D_{1-3}-retinal" in the eye and body. Indeed please refer for example to the webpage http://en.wikipedia.org/wiki/Vitamin_A enclosed herewith as Exhibit A. This Exhibit A shows that the claimed compounds are converted into the vision active aldehyde form, retinal. Retinal is processed in the eye to enable vision in a process called the "visual cycle".

Of these four retinoids, C_{20}-D_3-retinal (the active form in the eye) and C_{20}-D_3-retinol acetate (the form of vitamin A mostly found in food and supplements), were provided as two examples in the application. Using these retinoids the application showed that the accumulation of A2E and lipofuscin could be slowed in animal models of retinal degenerations characterized by accumulation of lipofuscin and other vitamin A dimers (see Examples 3-6). As explained above, both compounds are used in the eye as C_{20}-D_3-retinal and therefore act as substrates of the visual cycle, differing only from the natural vitamin A aldehyde substrate in the replacement of its three hydrogen atoms located on the carbon number twenty, with deuterium. Because it is well accepted in the art that replacement of hydrogen with its isotope deuterium will not generally affect the ability of the substituted compounds to interact with proteins, persons of ordinary skill in the art would immediately conclude that C_{20}-D_3-vitamin A will be used as natural substrates in the visual cycle and not cause any side effects in patients. Further, based on the theory of kinetic isotope effect, one of ordinary skill in the art would also understand that it is not necessary to substitute with 3 deuterium atoms and that substituting just one or two hydrogens with deuterium would suffice to slow down dimerization, albeit potentially to a lower extent. As such, the subject application is enabling for the use of C_{20}-D_{1-3}-vitamin A to inhibit A2E lipofuscin formation in the eye. Because the specifically defined deuterium-substituted retinoids, C_{20}-D_{1-3}-retinal, C_{20}-D_{1-3}-retinol ester, and C_{20}-D_{1-3}-pro-vitamin A carotenoids are all converted into C_{20}-D_{1-3}-retinal in the body, the full scope of amended Claim 61 is enabled. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 USC 112, First Paragraph for Failing to Comply with the Written Description Requirement

The Examiner raised a Written Description rejection, referring to the term "substituted C_{20}-D_{1-3}" in the claims. The Examiner stated that although the specification discloses examples of structures of some compounds within the scope of what is claimed, there is no evidence of any structure/function relationship between the disclosed substituted C_{20}-D_{1-3}-retinoid and any others that may be found using the claimed method. Without acceding to the Examiner's objection, but in order to progress this application to grant, Applicant has restricted the claims to four specifically defined retinoids. The structures and function of all four of the corresponding non-

substituted retinoids (i.e., retinoids with hydrogen instead of deuterium at carbon twenty) are known to the person of ordinary skill in the art as compounds commonly called "vitamin A". As discussed in the previous section of this Response, the subject application provides evidence that the specific substitution at carbon twenty of vitamin A by deuterium atom(s), results in substituted C_{20}-D_{1-3}-retinoids that can act as substrates of the visual cycle in the eye, as would the unsubstituted vitamin A, but the specific substitution of deuterium confers on the four claimed deuterium substituted retinoids the ability to slow down A2E/lipofuscin formation. As such, there is a structure/function relationship between these four retinoids and amended Claim 61 therefore satisfies the Written Description Requirement. Withdrawal of the rejection is therefore requested.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Commissioner is authorized to charge Kenyon & Kenyon LLP's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: March 27, 2014

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EXHIBIT A

Vitamin A

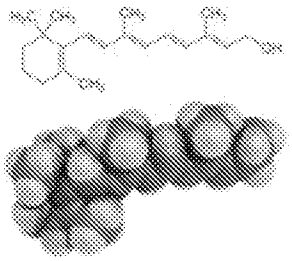
From Wikipedia, the free encyclopedia

Vitamin A is a group of unsaturated nutritional organic compounds, that includes retinol, retinal, retinoic acid, and several provitamin A carotenoids, among which beta-carotene is the most important.[1] Vitamin A has multiple functions: it is important for growth and development, for the maintenance of the immune system and good vision.[2] Vitamin A is needed by the retina of the eye in the form of retinal, which combines with protein opsin to form rhodopsin the light-absorbing molecule,[3] that is necessary for both low-light (scotopic vision) and color vision.[4] Vitamin A also functions in a very different role as an irreversibly oxidized form of retinol known as retinoic acid, which is an important hormone-like growth factor for epithelial and other cells.[5]

In foods of animal origin, the major form of vitamin A is an ester, primarily retinyl palmitate, which is converted to retinol (chemically an alcohol) in the small intestine. The retinol form functions as a storage form of the vitamin, and can be converted to and from its visually active aldehyde form, retinal. The associated acid (retinoic acid), a metabolite that can be irreversibly synthesized from vitamin A, has only partial vitamin A activity, and does not function in the retina for the visual cycle. Retinoic acid is used for growth and cellular differentiation.[2]

All forms of vitamin A have a beta-ionone ring to which an isoprenoid chain is attached, called a *retinyl group*. Both structural features are essential for vitamin activity.[6] The orange pigment of carrots – beta-carotene – can be represented as two connected retinyl groups, which are used in the body to contribute to vitamin A levels. Alpha-carotene and gamma-carotene

Vitamin A



Systematic (IUPAC) name	
(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol (Retinol)	
Clinical data	
Trade names	Aquasola
AHFS/Drugs.com	monograph
Pregnancy cat.	A (US)
Legal status	OTC (US)
Identifiers	
CAS number	68-26-8
ATC code	V04CB01
PubChem	CID 445354
DrugBank	DB00162
ChemSpider	393012
KEGG	D03365
ChEBI	CHEBI:17336
ChEMBL	CHEMBL986
NIAID ChemDB	008876
Chemical data	
Formula	$C_{20}H_{30}O$
Mol. mass	286.4516 g/mol
SMILES	
InChI	
(what is this?) (verify)	

also have a single retinyl group, which give them some vitamin activity. None of the other carotenes have vitamin activity. The carotenoid beta-cryptoxanthin possesses an ionone group and has vitamin activity in humans.

Vitamin A can be found in two principal forms in foods:

- Retinol, the form of vitamin A absorbed when eating animal food sources, is a yellow, fat-soluble substance. Since the pure alcohol form is unstable, the vitamin is found in tissues in a form of retinyl ester. It is also commercially produced and administered as esters such as retinyl acetate or palmitate.[7]
- The carotenes alpha-carotene, beta-carotene, gamma-carotene; and the xanthophyll beta-cryptoxanthin (all of which contain beta-ionone rings), but no other carotenoids, function as provitamin A in herbivores and omnivore animals, which possess the enzyme (15-15'-dioxygenase) which cleaves beta-carotene in the intestinal mucosa and converts it to retinol.[8] In general, carnivores are poor converters of ionone-containing carotenoids, and pure carnivores such as cats and ferrets lack 15-15'-dioxygenase and cannot convert any carotenoids to retinal (resulting in *none* of the carotenoids being forms of vitamin A for these species).

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History

The discovery of vitamin A may have stemmed from research dating back to 1816, when physiologist Magendie observed that dogs deprived of nutrition developed corneal ulcers and had high mortality rate.[9] In 1912, Frederick Gowland Hopkins demonstrated that unknown "accessory factors" found in milk, other than carbohydrates, proteins, and fats were necessary for growth in rats. Hopkins received a Nobel Prize for this discovery in 1929.[9][10] By 1917, one of these substances was independently discovered by Elmer McCollum at the University of Wisconsin–Madison, and Lafayette Mendel and Thomas Burr Osborne at Yale University who studied the role of fats in the diet. The "accessory factors" were termed "fat soluble" in 1918 and later "vitamin A" in 1920. In 1919, Harry Steenbock (University of Wisconsin) proposed a relationship between yellow plant pigments (beta-carotene) and vitamin A. In 1931, a Swiss Chemist Paul Karrer described the chemical structure of vitamin A.[9] Vitamin A was first synthesized in 1947 by two Dutch chemists; David Adriaan van Dorp and Jozef Ferdinand Arens.

Equivalencies of retinoids and carotenoids (IU)

As some carotenoids can be converted into vitamin A, attempts have been made to determine how much of them in the diet is equivalent to a particular amount of retinol, so that comparisons can be made of the benefit of different foods. The situation can be confusing because the accepted equivalences have changed. For many years, a system of equivalencies in which an international unit (IU) was equal to 0.3 μg of retinol, 0.6 μg of β-carotene, or 1.2 μg of other provitamin-A carotenoids was used.[11] Later, a unit called retinol equivalent (RE) was introduced. Prior to 2001, one RE corresponded to 1 μg retinol, 2 μg β-carotene dissolved in oil (it is only partly dissolved in most supplement pills, due to very poor solubility in any medium), 6 μg β-carotene in normal food (because it is not absorbed as well as when in oils), and 12 μg of either α-carotene, γ-carotene, or β-cryptoxanthin in food.

Newer research has shown that the absorption of provitamin-A carotenoids is only half as much as previously thought. As a result, in 2001 the US Institute of Medicine recommended a new unit, the retinol activity equivalent (RAE). Each μg RAE corresponds to 1 μg retinol, 2 μg of β-carotene in oil, 12 μg of "dietary" beta-carotene, or 24 μg of the three other dietary provitamin-A carotenoids.[12]

Substance and its chemical environment	Micrograms of retinol equivalent per microgram of the substance
retinol	1
beta-carotene, dissolved in oil	1/2
beta-carotene, common dietary	1/12
alpha-carotene, common dietary	1/24
gamma-carotene, common dietary	1/24
beta-cryptoxanthin, common dietary	1/24

Because the conversion of retinol from provitamin carotenoids by the human body is actively regulated by the amount of retinol available to the body, the conversions apply strictly only for vitamin A-deficient humans. The absorption of provitamins depends greatly on the amount of lipids ingested with the provitamin; lipids increase the uptake of the provitamin.[13]

The conclusion that can be drawn from the newer research is that fruits and vegetables are not as useful for obtaining vitamin A as was thought; in other words, the IUs that these foods were reported to contain were worth much less than the same number of IUs of fat-dissolved oils and (to some extent) supplements. This is important for vegetarians, as night blindness is prevalent in countries where little meat or vitamin A-fortified foods are available.

A sample vegan diet for one day that provides sufficient vitamin A has been published by the Food and Nutrition Board (page 120[12]). On the other hand, reference values for retinol or its equivalents, provided by the National Academy of Sciences, have decreased. The RDA (for men) of 1968 was 5000 IU (1500 μg retinol). In 1974, the RDA was set to 1000 RE (1000 μg retinol), whereas now the Dietary Reference Intake is 900 RAE (900 μg or 3000 IU retinol). This is equivalent to 1800 μg of β-carotene supplement (3000 IU) or 10800 μg of β-carotene in food (18000 IU).

Recommended daily intake

Vitamin A
Dietary Reference Intake:[14]

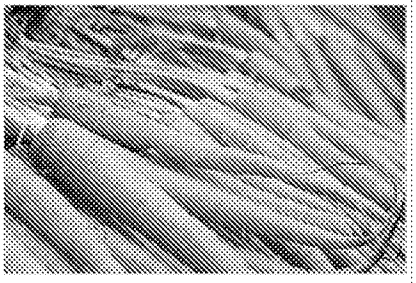
Life stage group	RDA Adequate intakes (AI*) µg/day	Upper limit µg/day
Infants		
0–6 months	400*	600
7–12 months	500*	600
Children		
1–3 years	300	600
4–8 years	400	900
Males		
9–13 years	600	1700
14–18 years	900	2800
19 – >70 years	900	3000
Females		
9–13 years	600	1700
14–18 years	700	2800
19 – >70 years	700	3000
Pregnancy		
<19 years	750	2800
19 – >50 years	770	3000
Lactation		
<19 years	1200	2800
19 – >50 years	1300	3000

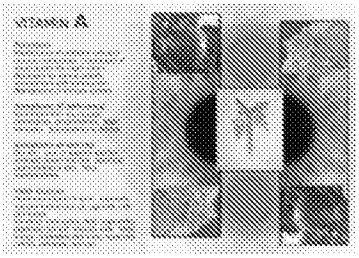
(The limit is for synthetic and natural retinol ester forms of vitamin A. Carotene forms from dietary sources are not toxic.[15][16])

According to the Institute of Medicine of the National Academies, "RDAs are set to meet the needs of almost all (97 to 98%) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevents being able to specify with confidence the percentage of individuals covered by this intake."[17]

Sources

Vitamin A is found naturally in many foods:


carrots



- cod liver oil (30000 µg)
- liver (turkey) (8058 µg 895%)
- liver (beef, pork, fish) (6500 µg 722%)
- liver (chicken) (3296 µg 366%)
- dandelion greens (5588 IU 112%)[18]
- sweet potato (961 µg 107%)
- carrot (835 µg 93%)
- broccoli leaf (800 µg 89%) – According to USDA database (http://www.nal.usda.gov/fnic/foodcomp/search/) broccoli florets have much less.[19]
- broccoli florets (31 µg 3%)
- butter (684 µg 76%)
- kale (681 µg 76%)
- spinach (469 µg 52%)
- pumpkin (400 µg 41%)
- collard greens (333 µg 37%)
- Cheddar cheese (265 µg 29%)
- cantaloupe melon (169 µg 19%)
- egg (140 µg 16%)
- apricot (96 µg 11%)
- papaya (55 µg 6%)
- mango (38 µg 4%)
- pea (38 µg 4%)
- milk (28 µg 3%)
- tomatoes
- Seaweed

Note: data taken from USDA database (http://www.nal.usda.gov/fnic/foodcomp/search/) bracketed values are retinol activity equivalences (RAEs) and percentage of the adult male RDA, per 100 grams of the foodstuff (average).

Conversion of carotene to retinol varies from person to person and bioavailability of carotene in food varies.[20][21]

Metabolic functions

Vitamin A plays a role in a variety of functions throughout the body, such as:

- Vision
- Gene transcription
- Immune function
- Embryonic development and reproduction
- Bone metabolism
- Hematopoiesis
- Skin and cellular health
- Antioxidant activity

Vision

The role of vitamin A in the visual cycle is specifically related to the retinal form. Within the eye, 11-*cis*-retinal is bound to protein "opsin" to form rhodopsin in rods[3] and iodopsin (cones) at conserved lysine residues. As light enters the eye, the 11-*cis*-retinal is isomerized to the all-"trans" form. The all-"trans" retinal dissociates from the opsin in a series of steps called photo-bleaching. This isomerization induces a nervous signal along the optic nerve to the visual center of the brain. After separating from opsin, the all-"trans"-retinal is recycled and converted back to the 11-"cis"-retinal form by a series of enzymatic reactions. In addition, some of the all-"trans" retinal may be converted to all-"trans" retinol form and then transported with an interphotoreceptor retinol-binding protein (IRBP) to the pigment epithelial cells. Further esterification into all-"trans" retinyl esters allow for storage of all-trans-retinol within the pigment epithelial cells to be reused when needed.[22] The final stage is conversion of 11-*cis*-retinal will rebind to opsin to reform rhodopsin (visual purple) in the retina. Rhodopsin is needed to see in low light (contrast) as well as for night vision. Kühne showed that the regeneration of rhodopsin only occurs when retina is attached to retinal pigmented epithelial (RPE).[3] It is for this reason that a deficiency in vitamin A will inhibit the reformation of rhodopsin and lead to one of the first symptoms, night blindness.[23]

Gene transcription

Main article: Gene transcription

Vitamin A, in the retinoic acid form, plays an important role in gene transcription. Once retinol has been taken up by a cell, it can be oxidized to retinal (retinaldehyde) by retinol dehydrogenases and then retinaldehyde can be oxidized to retinoic acid by retinaldehyde dehydrogenases.[24] The conversion of retinaldehyde to retinoic acid is an irreversible step, meaning that the production of retinoic acid is tightly regulated, due to its activity as a ligand for nuclear receptors.[22] The physiological form of retinoic acid (all-trans-retinoic acid) regulates gene transcription by binding to nuclear receptors known as retinoic acid receptors (RARs) which are bound to DNA as heterodimers with retinoid "X" receptors (RXRs). RAR and RXR must dimerize before they can bind to the DNA. RAR will form a heterodimer with RXR (RAR-RXR), but it does not readily

form a homodimer (RAR-RAR). RXR, on the other hand, may form a homodimer (RXR-RXR) and will form heterodimers with many other nuclear receptors as well, including the thyroid hormone receptor (RXR-TR), the Vitamin D_3 receptor (RXR-VDR), the peroxisome proliferator-activated receptor (RXR-PPAR) and the liver "X" receptor (RXR-LXR).[25] The RAR-RXR heterodimer recognizes retinoic acid response elements (RAREs) on the DNA whereas the RXR-RXR homodimer recognizes retinoid "X" response elements (RXREs) on the DNA; although several RAREs near target genes have been shown to control physiological processes,[24] this has not been demonstrated for RXREs. The heterodimers of RXR with nuclear receptors other than RAR (i.e. TR, VDR, PPAR, LXR) bind to various distinct response elements on the DNA to control processes not regulated by vitamin A.[22] Upon binding of retinoic acid to the RAR component of the RAR-RXR heterodimer, the receptors undergo a conformational change that causes co-repressors to dissociate from the receptors. Coactivators can then bind to the receptor complex, which may help to loosen the chromatin structure from the histones or may interact with the transcriptional machinery.[25] This response can upregulate (or downregulate) the expression of target genes, including Hox genes as well as the genes that encode for the receptors themselves (i.e. RAR-beta in mammals).[22]

Dermatology

Vitamin A, and more specifically, retinoic acid, appears to maintain normal skin health by switching on genes and differentiating keratinocytes (immature skin cells) into mature epidermal cells.[26] Exact mechanisms behind pharmacological retinoid therapy agents in the treatment of dermatological diseases are being researched. For the treatment of acne, the most prescribed retinoid drug is 13-cis retinoic acid (isotretinoin). It reduces the size and secretion of the sebaceous glands. Although it is known that 40 mg of isotretinoin will break down to an equivalent of 10 mg of ATRA — the mechanism of action of the drug (original brand name Accutane) remains unknown and is a matter of some controversy. Isotretinoin reduces bacterial numbers in both the ducts and skin surface. This is thought to be a result of the reduction in sebum, a nutrient source for the bacteria. Isotretinoin reduces inflammation via inhibition of chemotactic responses of monocytes and neutrophils.[22] Isotretinoin also has been shown to initiate remodeling of the sebaceous glands; triggering changes in gene expression that selectively induce apoptosis.[27] Isotretinoin is a teratogen with a number of potential side-effects. Consequently, its use requires medical supervision.

Retinal/retinol versus retinoic acid

Vitamin A deprived rats can be kept in good general health with supplementation of retinoic acid. This reverses the growth-stunting effects of vitamin A deficiency, as well as early stages of xerophthalmia. However, such rats show infertility (in both male and females) and continued degeneration of the retina, showing that these functions require retinal or retinol, which are intraconvertable but which cannot be recovered from the oxidized retinoic acid. The requirement of retinol to rescue reproduction in vitamin A deficient rats is now known to be due to a requirement for local synthesis of retinoic acid from retinol in testis and embryos.[28][29]

Deficiency

Main article: Vitamin A deficiency

Vitamin A deficiency is estimated to affect approximately one third of children under the age of five around the world.[30] It is estimated to claim the lives of 670,000 children under five annually.[31] Approximately 250,000–500,000 children in developing countries become blind each year owing to vitamin A deficiency, with the highest prevalence in Southeast Asia and Africa.[32]

Vitamin A deficiency can occur as either a primary or a secondary deficiency. A primary vitamin A deficiency occurs among children and adults who do not consume an adequate intake of provitamin A carotenoids from fruits and vegetables or preformed vitamin A from animal and dairy products. Early weaning from breastmilk can also increase the risk of vitamin A deficiency.

Secondary vitamin A deficiency is associated with chronic malabsorption of lipids, impaired bile production and release, and chronic exposure to oxidants, such as cigarette smoke, and chronic alcoholism. Vitamin A is a fat soluble vitamin and depends on micellar solubilization for dispersion into the small intestine, which results in poor use of vitamin A from low-fat diets. Zinc deficiency can also impair absorption, transport, and metabolism of vitamin A because it is essential for the synthesis of the vitamin A transport proteins and as the cofactor in conversion of retinol to retinal. In malnourished populations, common low intakes of vitamin A and zinc increase the severity of vitamin A deficiency and lead physiological signs and symptoms of deficiency.[22] A study in Burkina Faso showed major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children.[33]

Due to the unique function of retinal as a visual chromophore, one of the earliest and specific manifestations of vitamin A deficiency is impaired vision, particularly in reduced light – night blindness. Persistent deficiency gives rise to a series of changes, the most devastating of which occur in the eyes. Some other ocular changes are referred to as xerophthalmia. First there is dryness of the conjunctiva (xerosis) as the normal lacrimal and mucus-secreting epithelium is replaced by a keratinized epithelium. This is followed by the build-up of keratin debris in small opaque plaques (Bitot's spots) and, eventually, erosion of the roughened corneal surface with softening and destruction of the cornea (keratomalacia) and leading to total blindness.[34] Other changes include impaired immunity (increased risk of ear infections, urinary tract infections, Meningococcal disease), hyperkeratosis (white lumps at hair follicles), keratosis pilaris and squamous metaplasia of the epithelium lining the upper respiratory passages and urinary bladder to a keratinized epithelium. With relations to dentistry, a deficiency in Vitamin A leads to enamel hypoplasia.

Adequate supply, but not excess vitamin A, is especially important for pregnant and breastfeeding women for normal fetal development and in breastmilk. Deficiencies cannot be compensated by postnatal supplementation.[35][36] Excess vitamin A, which is most common with high dose vitamin supplements, can cause birth defects and therefore should not exceed recommended daily values.[24]

Vitamin A metabolic inhibition as a result of alcohol consumption during pregnancy is the elucidated mechanism for fetal alcohol syndrome and is characterized by teratogenicity closely matching maternal vitamin A deficiency.[37]

Vitamin A supplementation

Global efforts to support national governments in addressing vitamin A deficiency are led by the Global Alliance for Vitamin A (GAVA), which is an informal partnership between A2Z, the Canadian International Development Agency, Helen Keller International, the Micronutrient Initiative, UNICEF, USAID, and the World Bank. Joint GAVA activity is coordinated by the Micronutrient Initiative.

While strategies include intake of vitamin A through a combination of breast feeding and dietary intake, delivery of oral high-dose supplements remain the principal strategy for minimizing deficiency.[38] A meta-analysis of 43 studies showed that vitamin A supplementation of children under five who are at risk of deficiency reduces mortality by up to 24%.[39] About 75% of the vitamin A required for supplementation activity by developing countries is supplied by the Micronutrient Initiative with support from the Canadian International Development Agency.[40] Food fortification approaches are becoming increasingly feasible[41] but cannot yet ensure coverage levels.[38]

The World Health Organization estimates that Vitamin A supplementation has averted 1.25 million deaths due to vitamin A deficiency in 40 countries since 1998.[42] In 2008 it was estimated that an annual investment of US$60 million in vitamin A and zinc supplementation combined would yield benefits of more than US$1 billion per year, with every dollar spent generating benefits of more than US$17.[43] These combined interventions were ranked by the Copenhagen Consensus 2008 as the world's best development investment.[43]

Toxicity

Main article: Hypervitaminosis A

Since vitamin A is fat-soluble, disposing of any excesses taken in through diet takes much longer than with water-soluble B vitamins and vitamin C. This allows for toxic levels of vitamin A to accumulate.

In general, acute toxicity occurs at doses of 25,000 IU/kg of body weight, with chronic toxicity occurring at 4,000 IU/kg of body weight daily for 6–15 months.[44] However, liver toxicities can occur at levels as low as 15,000 IU per day to 1.4 million IU per day, with an average daily toxic dose of 120,000 IU per day, particularly with excessive consumption of alcohol .[*citation needed*] In people with renal failure, 4000 IU can cause substantial damage. Children can reach toxic levels at 1,500 IU/kg of body weight.[45]

Excessive vitamin A consumption can lead to nausea, irritability, anorexia (reduced appetite), vomiting, blurry vision, headaches, hair loss, muscle and abdominal pain and weakness, drowsiness, and altered mental status. In chronic cases, hair loss, dry skin, drying of the mucous membranes, fever, insomnia, fatigue, weight loss, bone fractures, anemia, and diarrhea can all be evident on top of the symptoms associated with less serious toxicity.[46] Some of these symptoms are also common to acne treatment with Isotretinoin. Chronically high doses of vitamin A, and also pharmaceutical retinoids such as 13-cis retinoic acid, can produce the syndrome of pseudotumor cerebri.[47] This syndrome includes headache, blurring of vision and confusion, associated with increased intracerebral pressure. Symptoms begin to resolve when intake of the offending substance is stopped.[48]

Chronic intake of 1500 RAE of preformed vitamin A may be associated with osteoporosis and hip fractures because it suppresses bone building while simultaneously stimulating bone breakdown.[49]

High vitamin A intake has been associated with spontaneous bone fractures in animals. Cell culture studies have linked increased bone resorption and decreased bone formation with high intakes. This interaction may occur because vitamins A and D may compete for the same receptor and then interact with parathyroid hormone, which regulates calcium.[45] Indeed, a study by Forsmo *et al.* shows a correlation between low bone mineral density and too high intake of vitamin A.[50] Sufficiently high levels of vitamin D may be protective against the bone density lowering effects of high vitamin A, while inadequate levels of vitamin D may exacerbate those effects.[51][52][53][54]

Toxic effects of vitamin A have been shown to significantly affect developing fetuses. Therapeutic doses used for acne treatment have been shown to disrupt cephalic neural cell activity. The fetus is particularly sensitive to vitamin A toxicity during the period of organogenesis.[22] These toxicities only occur with preformed (retinoid) vitamin A (such as from liver). The carotenoid forms (such as beta-carotene as found in carrots), give no such symptoms, except with supplements and chronic alcoholism, but excessive dietary intake of beta-carotene can lead to carotenodermia, which causes orange-yellow discoloration of the skin.[55][56][57]

Hepatic (liver) injury has been found in human and animal studies where consumption of alcohol is paired with high dose vitamin A and beta-carotene supplementation.

Researchers have succeeded in creating water-soluble forms of vitamin A, which they believed could reduce the potential for toxicity.[58] However, a 2003 study found water-soluble vitamin A was approximately 10 times as toxic as fat-soluble vitamin.[59] A 2006 study found children given water-soluble vitamin A and D, which are typically fat-soluble, suffer from asthma twice as much as a control group supplemented with the fat-soluble vitamins.[60]

In some studies, the use of Vitamin A supplements has been linked to an increased rate of mortality,[61] but there is minimal evidence to show this.[62]

Vitamin A and derivatives in medical use

Retinyl palmitate has been used in skin creams, where it is broken down to retinol and ostensibly metabolised to retinoic acid, which has potent biological activity, as described above.

The retinoids (for example, 13-cis-retinoic acid) constitute a class of chemical compounds chemically related to retinoic acid, and are used in medicine to modulate gene functions in place of this compound. Like retinoic acid, the related compounds do not have full vitamin A activity, but do have powerful effects on gene expression and epithelial cell differentiation.[63]

Pharmaceutics utilizing mega doses of naturally occurring retinoic acid derivatives are currently in use for cancer, HIV, and dermatological purposes.[64] At high doses, side-effects are similar to vitamin A toxicity. Severe side effects related to vitamin A toxicity, and a small optimal range of use are key obstacles in developing vitamin A-derived pharmaceutics for therapeutic use.

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Further reading

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External links

- Vitamin A (//www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Vitamin+A) at the US National Library of Medicine Medical Subject Headings (MeSH)
- The Micronutrient Initiative (http://www.micronutrient.org/english/view.asp?x=1)
- UNICEF (http://www.unicef.org)
- Helen Keller International (http://www.hki.org/)
- A2Z (http://www.a2zproject.org/)
- World Health Organization Database on Vitamin A Deficiency (http://www.who.int/vmnis/vitamina/data/en/index.html)

Retrieved from "http://en.wikipedia.org/w/index.php?title=Vitamin_A&oldid=600826195"
Categories: Vitamins

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Electronic Acknowledgement Receipt

EFS ID:	18606611
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	13533/541US
Receipt Date:	27-MAR-2014
Filing Date:	14-OCT-2010
Time Stamp:	18:43:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	After Final Consideration Program Request	AF-Request-for-Reconsideration.pdf	226420 b85fff04151c824b8a1db7864bf7a68fb7a841bf	no	2

Warnings:

Information:

2	Response After Final Action	13533-541US_Response-AF_3-27-2014.pdf	6173986 c36986f9cd0645ccab7309c2a088f39472c0fb68	no	26

Warnings:	
Information:	
Total Files Size (in bytes):	6400406

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.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/733,631	Filing Date 10/14/2010	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) 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

AMENDMENT **03/27/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 30	Minus	** 65	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***6	= 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

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
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
/GLORIA ANTHONY/

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.**
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

26646 7590 12/27/2013

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
12/27/2013	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. 12/733,631	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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *9/16/2013*.

☐ 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) *50-114* is/are pending in the application.

5a) Of the above claim(s) *50-60,67-74,82 and 108-114* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *61-66, 75-81 and 83-107* 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)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

Claims 61-66, 75-81 and 84-107are presented for examination.

The amendments and remarks filed on September 16, 2013 have been received and entered.

Claim Rejections - 35 USC § 112

The following is a quotation 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 35 U.S.C. 112 (pre-AIA), first paragraph:
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 61-66, 75-81 and 84-107are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to “a method of retarding the accumulation of lipofuscin pigment in a retina using a substituted C20-D1-3 retinoid with the provision that the C20-D1-3 is not a C20-D1-3-isotretinoin or a C20-D1-3-all trans–retinylamine. Applicant has excluded the retinoids used in the art rejection in the office action of June 14, 2013 indicating that such compounds will slow the lipofuscin accumulation by slowing visual cycle and causing

night blindness. However, applicant has failed to provide an enabling disclosure to show the lack of side effects of the rest of retinoids, other than the ones excluded by the applicant. Since applicant argues that the retinoids covered by the relied upon references, substituated at the 20 position have adverse effect on the retina, without showing the broadly claimed substituted C20-D1-3-retinoids do not have such effect on the retina, applicant has failed to provide an enabling disclosure for the use of a substituted C20-D1-3-retinoids in retarding accumulation of lipofuscin pigment in the retina.

Claim Rejections - 35 USC § 112

The following is a quotation 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 35 U.S.C. 112 (pre-AIA), first paragraph:
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 61-66, 75-81 and 84-107 are 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 claims are directed to “A

method of retarding the accumulation of a lipofuscin pigment in a retina" using a "substituted C20-D1-3 retinoid" and a pharmaceutically acceptable carrier. The specification discloses examples of structures of some 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 C20-D1-3 retinoid and any others that might be found using the claimed method. Structural identifying characteristics of group of substituted C20-D1-3 retinoid 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. Applicant has failed to establish the correlation between being a substituted C20-D1-3 retinoid and retarding accumulation of lipofuscin pigment in the retina. Actually, applicant's specification teaches that not all retinoids are safe and without side effect in retarding accumulation of the lipofuscin pigment in a retina.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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
/Zohreh A Fay/
Primary Examiner, Art Unit 1621

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12733631	WASHINGTON, ILYAS
	Examiner	Art Unit
	ZOHREH FAY	1629

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	6/11/2013	ZF
Inventor search	6/11/2013	ZF
Updated	12/20/2013	ZF

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application No.: 12/733,631 | Confirmation No.: 4180

Filed: October 14, 2010 | Art Unit: 1629

For: Compositions and Methods for Treating Macular Degeneration | Examiner: Fay, Zohreh A.

VIA EFS-Web
MS: Amendment
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 September 16, 2013.

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

RESPONSE TO OFFICE ACTION

Dear Sir/Madam:

This Paper is in response to the Office Action mailed June 14, 2013. Authorization is hereby granted to charge any additional fees which may be required regarding this application, or credit any overpayment, to Deposit Account No. 11-0600.

Also enclosed herewith are:

Exhibit A (IUPAC, "Nomenclature of Retinoids," *Pure and Applied Chemistry* 55:721-26 (1983);

Exhibit B (Radu *et al.*, Investigative Ophthalmology & Visual Science *46*:4393 (2005);

Exhibit C ("Nomenclature of Carotenoids", 1974); and

Exhibit D (https://en.wikipedia.org/wiki/Isotretinoin).

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

Remarks begin on page 9 of this paper

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1-49. (Cancelled)

50. (Withdrawn-Currently Amended) A pharmaceutical composition comprising a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier, provided that the C_{20}-D_{1-3}-retinoid is not a C_{20}-D_{1-3}-isotretinoin or a C_{20}-D_{1-3}-all trans-retinylamine.

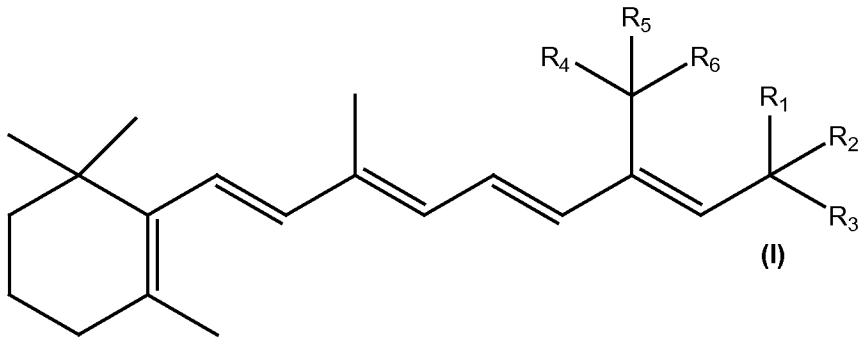
51. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is a C_{20}-D_3-retinoid.

52. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 51 in a unit dosage form.

53. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 51, which is a vitamin supplement.

54. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

55. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is according to formula I :



(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 H or D, wherein R_4, R_5, and R_6 are not each H.

56. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal or a C_{20}-D_3-carotenoid.

57. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 50, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

58. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 57, wherein the C_{20}-D_3-retinol acetate inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinol acetate.

59. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 57, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

60. (Withdrawn-Previously Presented) The pharmaceutical composition according to Claim 50, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

61. (Currently Amended) A method of retarding the ~~treating or ameliorating the effects of a disease characterized by an~~ accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier, provided that the C_{20}-D_{1-3}-retinoid is not a C_{20}-D_{1-3}-isotretinoin or a C_{20}-D_{1-3}-all trans-retinylamine.

62. (Previously Presented) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinoid.

63. (Previously Presented) The method according to Claim 61, wherein the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

64. (Previously Presented) The method according to Claim 61, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

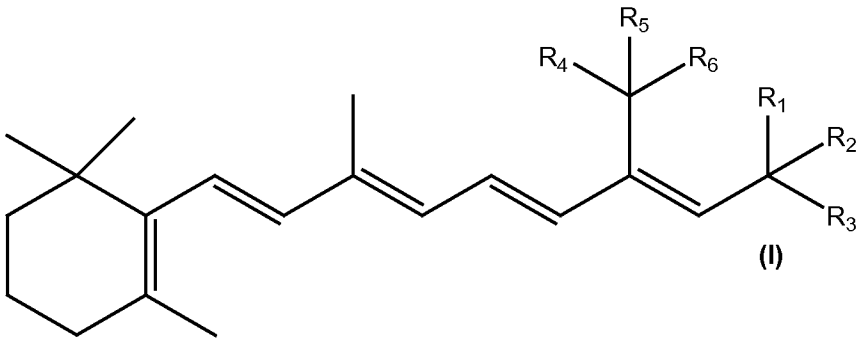
65. (Previously Presented) The method according to Claim 61, wherein the pharmaceutical composition is administered as a unit dosage form.

66. (Currently Amended) The method according to Claim 61, wherein the patient is in need of treatment for ~~disease is~~ a macular degeneration.

67. (Withdrawn-Previously Presented) The method according to Claim 66, wherein the macular degeneration is age-related macular degeneration.

68. (Withdrawn-Previously Presented) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

69. (Withdrawn-Previously Presented) The method according to Claim 67, wherein the substituted C_{20}-D_{1-3}-retinoid is 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 H or D, wherein R_4, R_5, and R_6 are not each H.

70. (Withdrawn-Previously Presented) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-carotenoid.

71. (Withdrawn-Previously Presented) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

72. (Withdrawn-Previously Presented) The method according to Claim 71, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

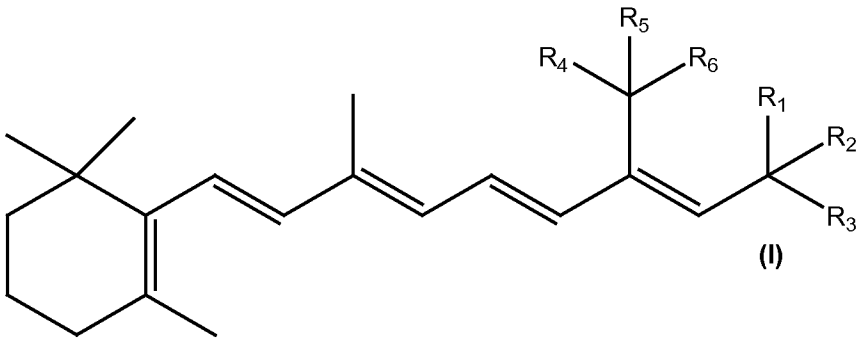
73. (Withdrawn-Previously Presented) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

74. (Withdrawn-Currently Amended) The method according to Claim 67, wherein the patient is in need of treatment for ~~the disease is~~ dry (non-neovascular) age-related macular degeneration.

75. (Currently Amended) The method according to Claim 61, wherein the patient is in need of treatment for ~~disease is~~ Stargardt disease.

76. (Previously Presented) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

77. (Previously Presented) The method according to Claim 75, wherein the substituted C_{20}-D_{1-3}-retinoid is according to formula I :



(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 H or D, wherein R_4, R_5, and R_6 are not each H.

78. (Previously Presented) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-carotenoid.

79. (Previously Presented) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

80. (Previously Presented) The method according to Claim 79, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

81. (Previously Presented) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

82. (Withdrawn-Currently Amended) The method according to Claim 61, wherein the patient is in need of treatment for a disease ~~is~~ selected from the group consisting of Vitelliform or Best disease, Sorsby's fundus dystrophy, retinitis pigmentosa, and Malattia Leventinese.

83. (Currently Amended) The method according to Claim 61, wherein the patient is in need of treatment for a disease ~~is~~ characterized by one or more mutation(s) in the ABCA4 gene.

84. (Previously Presented) The method according to Claim 61 further comprising administering to the patient 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.

85. (Previously Presented) The method according to Claim 84, wherein the visual cycle antagonist is selected from the group consisting of TDH, TDT, 13-cis-retinoic acid, ret-NH_2, and

combinations thereof.

86. (Previously Presented) The method according to Claim 84, wherein the molecule that inhibits influx of a retinoid into an eye is fenretinide.

87. (Previously Presented) The method according to Claim 84 further comprising one or more additives.

88. (Previously Presented) The method according to Claim 87, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.

89. (Previously Presented) The method according to Claim 88, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 80 mg.

90. (Previously Presented) The method according to Claim 88, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 10 mg.

91. (Previously Presented) The method according to Claim 88, wherein the zinc is present in the pharmaceutical composition at between about 10 to about 80 mg.

92. (Previously Presented) The method according to Claim 88, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 3,000 mg.

93. (Previously Presented) The method according to Claim 88, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 15 mg.

94. (Previously Presented) The method according to Claim 88, wherein the vitamin E is present in the pharmaceutical composition at between about 15 to about 3,000 mg.

95. (Previously Presented) The method according to Claim 88, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.1 mg.

96. (Previously Presented) The method according to Claim 88, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.015 mg.

97. (Previously Presented) The method according to Claim 88, wherein the vitamin D is present in the pharmaceutical composition at between about 0.015 to about 0.1 mg.

98. (Previously Presented) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-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.

99. (Previously Presented) The method according to Claim 61 further comprising an additional active.

100. (Previously Presented) The method according to Claim 99, wherein the additional active is

selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

101. (Previously Presented) The method according to Claim 100, 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.

102. (Previously Presented) The method according to Claim 100, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

103. (Previously Presented) The method according to Claim 100, wherein the negatively charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

104. (Previously Presented) The method according to Claim 100, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

105. (Previously Presented) The method according to Claim 61, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

106. (Previously Presented) The method according to Claim 61, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

107. (Previously Presented) The method according to Claim 61, wherein the pharmaceutical composition is administered directly to the eye.

108. (Withdrawn-Previously Presented) A method of retarding formation of a lipofuscin pigment in a retina comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

109. (Withdrawn-Previously Presented) The method according to Claim 108, wherein the C_{20}-D_{1-3}-retinoid is a C_{20}-D_3-retinoid.

110. (Withdrawn-Previously Presented) The method according to Claim 108, wherein the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

111. (Withdrawn-Previously Presented) The method according to Claim 108, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

112. (Withdrawn-Previously Presented) The method according to Claim 108, wherein the pharmaceutical composition is administered as a unit dosage form.

113. (Withdrawn-Previously Presented) A method of retarding formation of a lipofuscin pigment selected from the group consisting of A2E, ATR-dimer, and combinations thereof, the method comprising replacing a retinoid with a pharmaceutical composition comprising a C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier, under conditions sufficient to impede formation of A2E, ATR-dimer, or both A2E and ATR-dimer.

114. (Withdrawn-Previously Presented) A method of retarding formation of A2E in a retina comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

Claim Amendments:

Claims 50 and 61 have been amended to exclude C_{20}-D_{1-3}-isotretinoin and C_{20}-D_{1-3}-all-trans-retinylamine. Support for these amendments is found at paragraphs [0011] and [0014], which discuss the disadvantages of isotretinoin and all-trans-retinylamine when used to inhibit A2E formation, in contrast with the substituted C_{20}-retinoids of the disclosed invention. These passages teach that use of isotretinoin and all-trans-retinylamine causes delayed dark adaptation and thus indicate a clear intention to ***not*** include these compounds in the claimed subject matter. One of ordinary skill in the art would understand that avoiding delayed dark adaptation is one of the advantages of the claimed invention. See paragraph [0040] of the present application.[1]

In view of the above considerations, case law holds that the present application contains an adequate written description for the exclusion of isotretinoin and all-trans-retinylamine from the claims since the instant specification describes a reason to exclude isotretinoin and all-trans-retinylamine. See *Santarus Inc. v. Par Pharmaceuticals Inc.,* 694 F.3d 1344, 1351 (Fed. Cir. 2012):

> Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation. Such written description support need not rise to the level of disclaimer. ... The claim limitation that the Phillips formulations contain no sucralfate is adequately supported by statements in the specification expressly listing the disadvantages of using sucralfate.

Claim 61 has been amended to delete "treating or ameliorating the effects of a disease characterized by".

Claims 66, 74, 75, 82 and 83 have been amended to be consistent with this change to Claim 61.

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[1] [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. [underscoring added]

General Remarks:

Retinoids are a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner. See Exhibit A (1983, IUPAC, "Nomenclature of Retinoids"). Per the same nomenclature, retinoids that convert into retinol in the body are those that have the activity of vitamin A. They include retinol, retinol esters, retinal, etc. In the eye, these retinoids are used for vision and undergo a series of transformation between retinal, retinol and retinol ester, called "the visual cycle". Improper functioning of the visual cycle, due to age, genetics, chemicals, environmental or yet unknown factors, is known to result in degeneration of the retina, or of its central part, the macula. When the aldehyde retinal is not cleared fast enough, it has time to dimerize with another retinal molecule through a non-enzymatic mechanism, forming a vitamin A dimer. Vitamin A dimers, such as A2E or all-trans-retinal (ATR) dimers, are pigments of lipofuscin and known to be related to the formation of lipofuscin in the retina. Diseases such as Stargardt's disease, Best disease, Cone-Rod dystrophy, Retinitis Pigmentosa, Age-related macular degeneration (including its late stage form called "geographic atrophy") have been characterized by the accumulation of lipofuscin in the retina (See Exhibit B (Radu *et al.*, Investigative Ophthalmology & Visual Science *46*:4393 (2005), last paragraph of page 4399). As such, compounds that could slow the formation of vitamin A dimers and/or lipofuscin have been sought as treatments for diseases characterized by the accumulation of lipofuscin, and/or vitamin A dimers such as A2E.

In this application, the Applicant discloses **retinoids selectively substituted at the retinoid's carbon number 20, the C_{20} position. In particular, the claims currently amended focus only on retinoids whereby the protium (^{1}H or H) at the carbon 20 position have been replaced with deuterium (^{2}H or D)**. These retinoids are used as therapeutic compositions to replace non-substituted vitamin A in a patient, by its equivalent, substituted with deuterium at the C_{20} position. These "substituted C_{20}-D_{1-3}-retinoids" have been found by the Applicant to slow the rate at which vitamin A dimerizes without inhibiting the visual cycle. Inhibiting the visual cycle is one of the major drawbacks of other molecules that attempt to prevent vitamin A dimers and lipofuscin formation. Indeed, this inhibition of the visual cycle leads to visual side effects such as night blindness and dark adaptation problems, in addition to possible long term ocular or

systemic toxicity, as discussed above and as described in the document cited as number 27 of the present application and enclosed herewith as Exhibit B, page 4399, right panel:

> However, since isotretinoin acts as a competitive inhibitor, high intracellular drug concentrations are required to achieve efficacy. The doses used in our previous study on mice … were far higher than doses used for treating acne in humans … Treatment of macular degeneration patients with isotretinoin at the high doses used in mice would result in unacceptable systemic toxicity.

The Applicant's results disclosed in the application as filed demonstrate that:

1) vitamin A dimerizes via cleavage of one of the C_{20}-carbon–hydrogen bonds of vitamin A, and that this cleavage is the rate limiting factor of the dimerization reaction.

2) substituting one or several protiums specifically on the carbon C_{20} with deuterium atoms results in significant slowing of vitamin A dimerization.

3) administering C_{20}-D_3-vitamin A (or other retinoid equivalents) to animals results in a significant reduction in the accumulation of vitamin A dimers, such as A2E or ATR-dimer, as well as in the accumulation of lipofuscin in the retina, both in animals with genetically defective visual cycle ($ABCR^{-/-}$ knock-out mice, a model of Stargardt's disease), or in wild-type mice or rats with no genetic defect (a model of the aging eye such as age-related macular degeneration).

4) In view of 1) and 2), the person skilled in the art would understand that substituting the retinoids' C_{20} hydrogen atoms (1 or more hydrogens) by other atoms that reinforce the C_{20}-H bond, would also result in substituted C_{20}-retinoids that slow down vitamin A dimerization. In order to work, those substituted retinoids would need to replace the body's non substituted vitamin A.

5) Since the C_{20}-carbon–hydrogen bonds are not involved in normal vitamin A processing, deuterium incorporation is not expected to affect the vitamin's properties such as its pharmacokinetics or pharmacodynamics, nor would it disrupt the visual cycle, resulting in a compound that could reduce lipofuscin and vitamin A dimers without visual side effects or any more toxicity than non-substituted vitamin A itself.

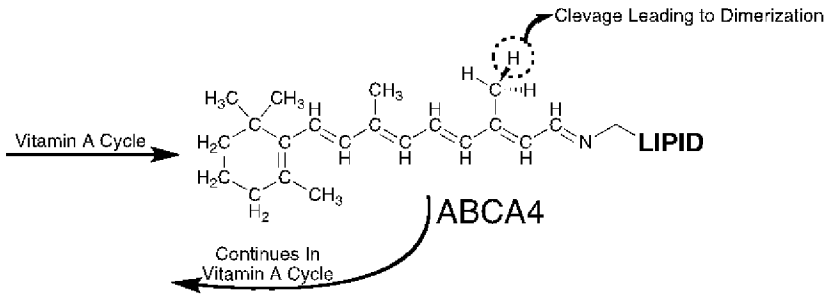


Figure 1 – The application shows that: 1) through the cleavage of a C_{20} C-H bond, vitamin A can react with another molecule of vitamin A to form toxic vitamin A dimers; 2) changing these specific hydrogens to a deuterium reinforces this C_{20} C-H bond, slowing vitamin A dimerization.

According to the IUPAC 1984 nomenclature, "substituted-C_{20}-retinoid" should be interpreted as substituted derivatives of retinoids, wherein the substitution is made selectively at the level of the carbon number 20 of such retinoid. **A "C_{20}-D_{1-3}-retinoid" is therefore a retinoid, whereby one or more H at the carbon C_{20} position, has/have been replaced by 1, 2 or 3 deuterium (D) atoms, and wherein the non-substituted atoms remain unchanged**.

A. Rejection Under 35 USC 112, First Paragraph for Failing to Comply with the Written Description Requirement

The Examiner rejected Claims 61-66, 75-81 and 84-107 for failing to comply with the Written Description requirement for two reasons.

First reason: the Examiner apparently objects to the term "C_{20}-D_{1-3}-retinoid" and asserts that although "[t]he specification discloses structures of some compounds within the scope of what is claimed", there is "no evidence that there is any per se structure/function relationship between the disclosed C_{20}-D_{1-3}-retinoid and others that might be found using the claimed method". The Examiner also stated that "structural identifying characteristics of group of substituted C_{20}-D_{1-3}-retinoid are not disclosed". For reasons provided below, Applicant respectfully disagrees.

Response to Examiner's Reasoning: In order to provide an adequate written description, the specification must reasonably convey to the artisan that the inventor had possession of the

claimed subject matter. *Fiers v. Revel*, 984 F. 2d 1164, 1170 (Fed. Cir. 1993). The Written Description Guidelines (Federal Register, Vol. 66, pages 1099-1111, 2001) repeatedly state that a rejection for lack of written description should not be based on the absence of disclosure pertaining to well known subject matter. See page 1105, sentence bridging center and right columns: "the absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. §112, ¶1, for lack of adequate written description." See also page 1105, right column:

> Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification.

See also page 1106, left column: "The description need only describe in detail that which is new or not conventional. … What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail."

Retinoids are an extremely well known and well studied class of compounds. As evidence of this, Applicant submits as Exhibit A a paper from the International Union of Pure and Applied Chemistry (IUPAC), recognized as the world authority on chemical nomenclature (*Pure and Applied Chemistry* 55:721-26 (1983). It should be readily appreciated from this paper that among those of ordinary skill in the art, "retinoids" are recognized as a known, well-defined and distinct class of compounds with numerous known specific examples. Retinoids are defined as a "class of compounds consisting of four isoprenoid units joined in a head-to-tail manner". Similarly, vitamin A is defined in the text as "the generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol" (section 1.1). The same document highlights "substituted retinoids" (section 4.4) as "substituted derivatives of retinoids". The numbering of atoms is also disclosed at the top left corner of page 723. The Applicant follows all nomenclature and numbering conventions of the IUPAC. Similar IUPAC nomenclature and numbering apply for carotenoids and are attached as Exhibit C "Nomenclature of Carotenoids", 1974. Therefore the terms "retinoids", "substituted-retinoids", or the position C_{20}, would be clear for a person of ordinary skill in the art.

Moreover, Exhibit A shows that the nomenclature of retinoids is well accepted and that in particular, one of ordinary skill in the art would understand what is meant by "substituted-

retinoid" and "substituted C_{20}-D_{1-3}-retinoid". Applicant has also exemplified several deuterated C_{20} retinoids but would not need to disclose every molecule of the retinoids class, an impossible task.

It is axiomatic in patent law that an application need not disclose that which is known to one of ordinary skill in the art. As such, Applicant does not agree with the Examiner that the claims lack adequate written description because of their use of the term "retinoid", "substituted C_{20}-retinoid" or "substituted C_{20}-D_{1-3}-retinoid".

Applicant further exemplifies methods to make the appropriate substituted C_{20}-retinoid compounds, in particular with substitution with deuterium (D), tritium (T) and halogens (X) in paragraph [0059], further providing an adequate description of the genus, restricted in the current claims list to deuterium substitution. Further, Applicant has provided a correlation between physical or chemical properties and functional characteristics by disclosing that the appropriate substitution is at the location of the hydrogen that undergoes migration ([1,5] hydrogen shift), such that the dimerization of the corresponding retinoid-aldehyde is slowed (paragraph [0043]). Based on the results described in the application, it would be well understood by a person of ordinary skill in the art that partial substitution (e.g., D_1H_2 or D_2H), combination of substitutions (e.g., D_2F, DF_2), or any other substitution at C_{20} that can slow or prevent hydrogen abstraction at the C_{20} position would also result in slowing of vitamin A dimerization and in lipofuscin accumulation ([0061]). Given this structure/function correlation taught by the present application, the skilled person would understand that the Applicant broadly possessed the genus of "substituted C_{20}-D_{1-3}-retinoid[s]".

The C_{20}-D_{1-3}-retinoid is administered to a patient, so as to replace endogenous retinal as described in [0030], so that the corresponding C_{20}-D_{1-3}-retinal would slow down dimerization in the eye. A person skilled in the art would understand that the claimed genus is that of retinoids substituted at the carbon 20 position, that replace the body's retinal by the corresponding substituted C_{20}-D_{1-3}-retinal, wherein such substituted C_{20}-D_{1-3}-retinal results in reduced formation of A2E and accumulation of lipofuscin. The provided description places specific limitations on the claimed genus and is therefore exactly informative of the genus itself.

The structure/function relationship is clear: the retinoid substituted with 1, 2 or 3 molecules of deuterium at the C_{20} position is expected to result in slowed A2E formation and reduced lipofuscin accumulation, so as to ameliorate diseases manifested by lipofuscin accumulation and will not significantly inhibit the visual cycle or vision. The person skilled in the art would understand that the function, i.e., slowing of the formation of A2E and other dimers and thus slowing of lipofuscin accumulation, results from the kinetic isotope effect described in [0045] due to substitution with deuterium at the C_{20}.

Given that retinoids are well known in the art, and that the present specification teaches the structure/function correlation that substituting deuterium at position 20 leads to the desired function of retarding lipofuscin accumulation, one of ordinary skill in the art would understand that the Applicant possessed the entire scope of the claimed subject matter "substituted C_{20}-D_{1-3}-retinoid."

As such, Applicant requests withdrawal of this Written Description rejection.

Second reason: the Examiner also objected to "a disease characterized by an accumulation of a lipofuscin pigment in the retina". The Examiner asserted that the "specification discloses a few disorders within the scope of what is claimed".

Response to Examiner's Reasoning: Although Applicant disagrees with the rejection, the claims have been amended in order to expedite prosecution so as to delete the term "treating or ameliorating the effects of a disease characterized by" from Claim 50 and 61. With this amendment, it is believed that the Examiner's concerns have been addressed. Withdrawal of the rejection is requested.

B. Rejection of Claims 61-66, 75-81 and 84-107 Under 35 U.S.C. 103

Claims 61-66, 75-81 and 84-107 were rejected as being obvious in view of Radu *et al.,* Proc. Natl. Acad. Sci USA *100*:4742 (2003) (hereinafter "Radu"), WO95/04018 (hereinafter "Boehm"), WO2005/065669 (hereinafter "Lang") and US2007/0015827 (hereinafter "Widder").

Advantages of the Claimed Invention

The claimed methods of treatment are based on the discovery that retinoids deuterated at the C_{20} position inhibit the formation of A2E dimers in $ABCR^{-/-}$ mice. $ABCR^{-/-}$ mice lack the ABCR gene, which leads to impaired ability to properly transport vitamin A in the eye, which leads to accelerated accumulation of A2E dimers and lipofuscin (lipofuscin are pigments that store A2E) in the eyes. As a result, $ABCR^{-/-}$ mice are an accepted animal model for testing approaches that would limit A2E dimer and/or lipofuscin formation. Because A2E and lipofuscin have been shown to be toxic to the retina, agents that could slow or reduce A2E/lipofuscin formation in the eyes could be used in the treatment of diseases characterized by accumulation of A2E dimer and/or lipofuscin in the eye, such as Stargardt's disease, macular degeneration and other macular dystrophies (Best disease, Cone-Rod dystrophy, Retinitis Pigmentosa, etc.) (See Exhibit B, last paragraph of page 4399[2]).

The Examiner is referred to Example 4, on page 36 of the present specification, which describes an experiment wherein a retinoid deuterated at the C_{20} position, C_{20}-D_3-retinol acetate, was compared with the corresponding non-deuterated retinol acetate (corresponding to normal dietary vitamin A) with respect to its ability to inhibit formation of the A2E dimer in adult $ABCR^{-/-}$ mice switched from normal retinol acetate diet to deuterated retinol acetate. Mice fed the C_{20}-D_3-retinol acetate for a short period of three months had approximately 44-58% less A2E-lipofuscin as compared with mice fed the corresponding non-deuterated retinol acetate (page 36, [0093]).

The Examiner is also referred to Example 5 on page 36-37, which describes a similar experiment in $ABCR^{-/-}$ mice reared on C_{20}-D_3-retinol acetate from birth. In this Example 5, the amount of lipofuscin pigments deposited in the eyes of the mice was determined using HPLC. Results show that lipofuscin was practically undetectable in mice fed C_{20}-D_3-retinol-acetate from birth (see figure 5 reproduced below, curve B), but were in significantly higher levels in mice on the retinol acetate diet (curve A below). Figure 5 panel C shows that the quantity of vitamin A

[2] Exhibit B and the Radu reference cited in the obviousness rejection are different publications, although they have the same first author.

(absorbance at 325nm) in the eyes of both groups was identical, so that a diet rich in C_{20}-D_3-retinol acetate would not alter the quantity of vitamin A in the eyes.

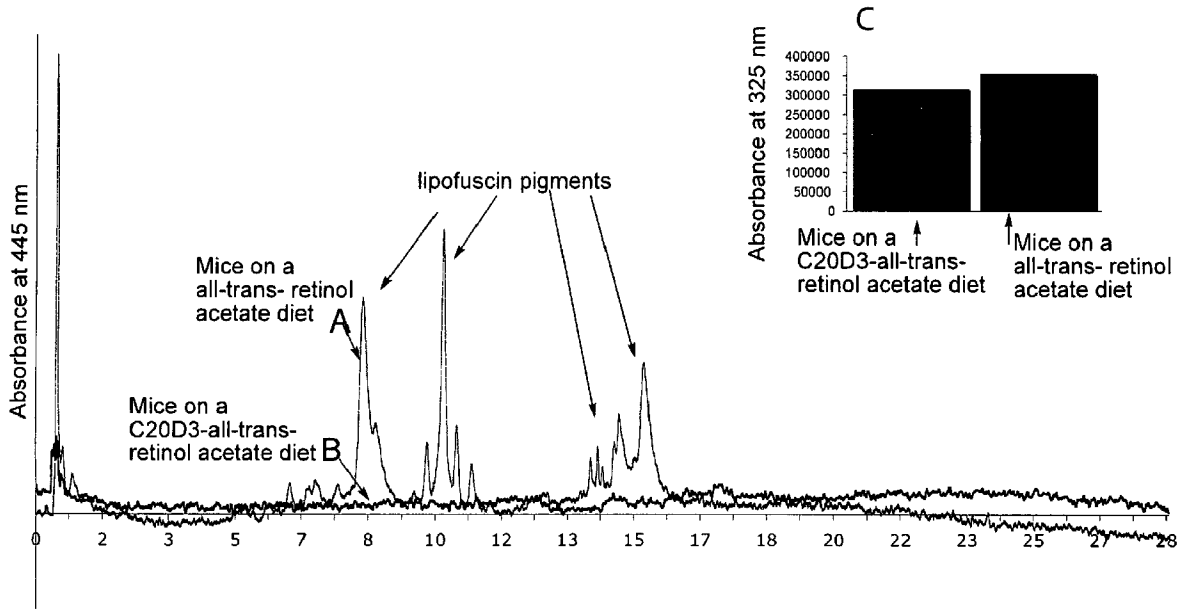


FIG 5.

The effect of retinoids deuterated at C_{20} in reducing A2E formation is not limited to ABCR-/- mice, the mouse model of Stargardt's disease. Experiments performed in wild type mice and rats without genetic defects also showed benefit, as explicated in Example 6 (wild type rats) and Example 3 (CD-1, ICR mice). As an extension, the person skilled in the art would understand that all diseases characterized by accumulation of lipofuscin or A2E could benefit from a treatment using the disclosed retinoids deuterated at C_{20}.

The biochemical pathway by which A2E dimer is hypothesized to form is shown schematically in Figure 2 of the subject application, which is also reproduced below:

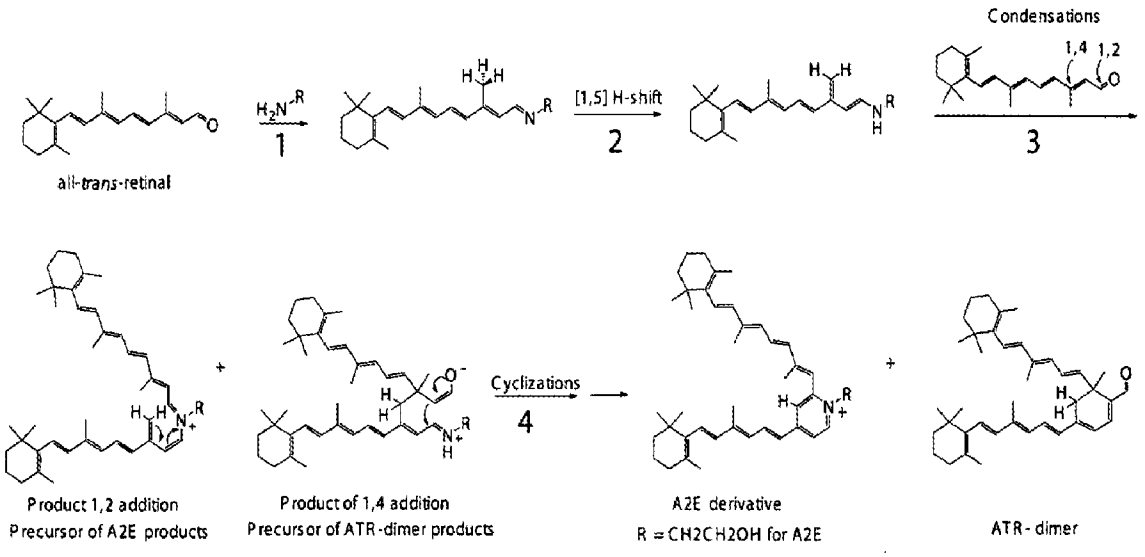


FIG 2.

It is noted that step 2 from the figure above would involve ***the loss of <u>one</u> of the C20 hydrogen atoms***. The decreased A2E and lipofuscin dimer formation associated with deuterated C_{20} retinoids would come from the slower loss of C_{20} hydrogen atom when the hydrogen (as protium) is replaced in majority by a deuterium (kinetic isotope effect). As a result, the use of one, two or three deuteriums is expected to be beneficial.

In contrast with the mechanism of A2E and lipofuscin formation, retinoids themselves do not lose any C_{20}-hydrogen atoms in the retinoid pathway of the retina and of the retinal pigment epithelium (RPE). Support for this assertion is provided by the schematic from Figure 1A of Radu, which is reproduced below:

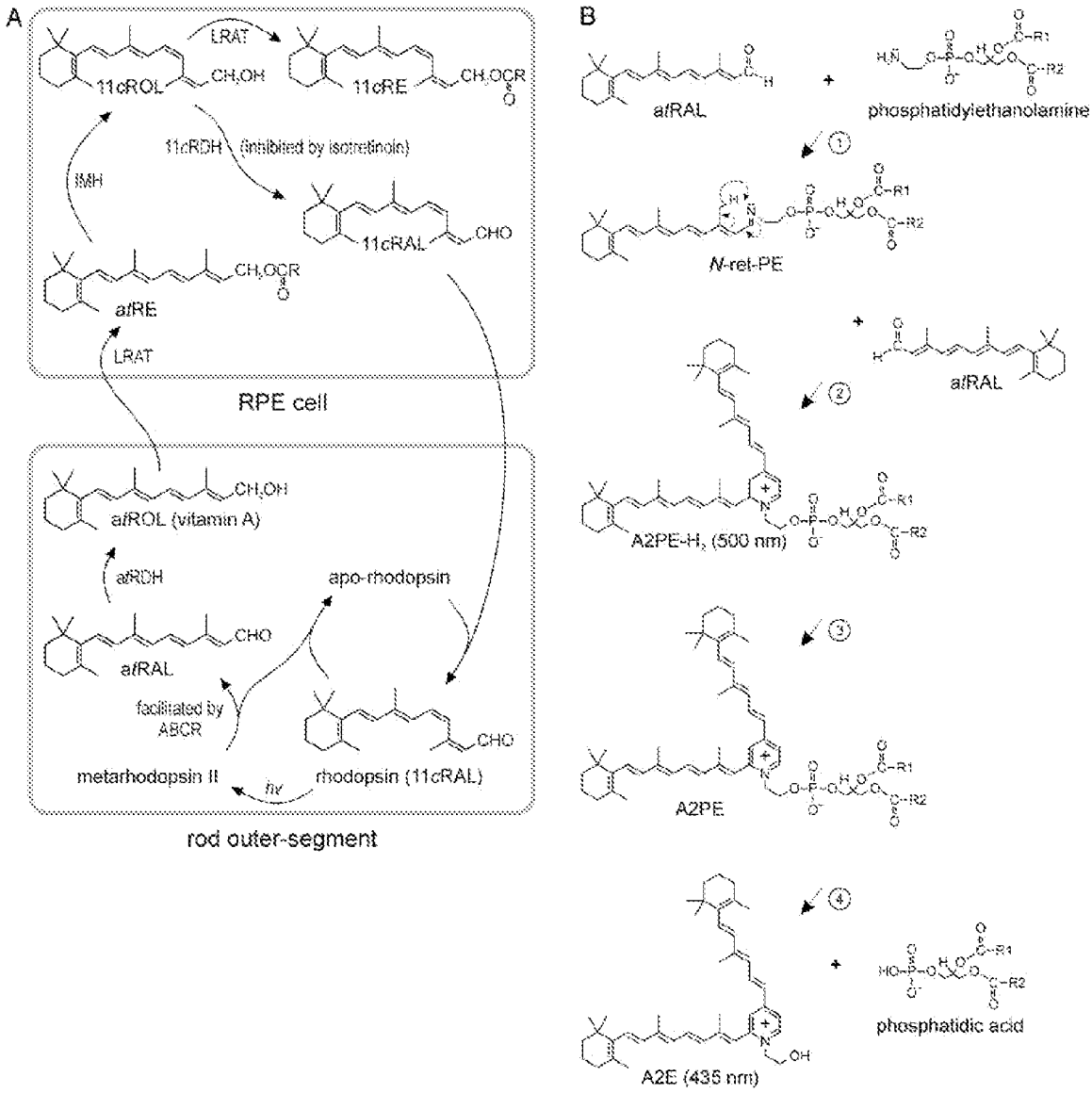


Figure 1 from Radu

It is clear from this schematic that ***no C_{20} hydrogen bonds are broken in these retinoid pathways.*** As such, use of retinoids substituted with deuterium at the C_{20} position in place of the corresponding non-deuterated retinoids is unlikely to alter the retinoid pathway and to cause any side effects in the eye. Indeed, it is well established that molecules with deuterium have substantially the same properties as the corresponding non-deuterated compounds and that any effect as substantial as that measured in the present application would be surprising and inventive. Similarly, deuterated drugs in most instances have substantially the same properties as

the corresponding non deuterated drugs, except where a carbon/deuterium bond is being broken during metabolism instead of a carbon/hydrogen bond, and then only in certain instances.

In addition, in Example 5, figure 5C, there was no observable difference in the quantity of total vitamin A contained in the eyes of mice treated with either deuterated or non deuterated vitamin A, so that visual side effects as usually experienced by those treated with other A2E-reducing retinoids, would be avoided.

Therefore, the results in Examples 4 and 5 in the subject application, discussed above, reasonably correlate to the ability to treat disease characterized by excessive formation in the eye of A2E or lipofuscin with little if any side effects.

As summarized above, the present specification teaches that the claimed invention involves substitution at the C_{20} position of retinoids, in order to slow the condensation reaction that produces A2E (and thus lipofuscin). In view of this, the claim limitation "substituted C_{20}-D_{1-3}-retinoid" should be interpreted in light of the specification as referring to retinoids where at least one protium (^1H or H) at the carbon 20 position has been replaced with deuterium (^2H or D). As discussed below, none of the art cited in the obviousness rejection discloses or suggests this limitation.

The Examiner's Reasoning

The Examiner asserts that "Radu teaches the use of isotretinoin, a C_{20}-retinoid for inhibition of lipofuscin pigment in a retina. Such reference suggests that treatment with isotretinoin may inhibit lipofuscin accumulation and thus delay the onset of visual loss in Stargardt's patient".

The Examiner then acknowledges that "Radu differs from the claimed invention in using substituted C_{20}-D_{1-3}". However, the Examiner then noted that Boehm discloses a substituted C_{20} retinoid" and that "tritium labeled is taught in page 5, line 13-19, formula V", and "deuterium labeled is taught on page 6, lines 15-37". The Examiner then concludes that "it would have been obvious to a person skilled in the art to use labeled retinoid instead of retinoid for the inhibition of lipofuscin and treat a disease, such as, stargardt's characterized by lipofuscin accumulation

and to improve efficacy of treatment, motivated by Boehm, which teaches the advantage of radio labeled retinoid in bind to the retinoid receptors".

Response to Examiner's Reasoning

1. It is first noted that the claims have been amended to specifically exclude isotretinoin, the pharmacological active agent tested by Radu. For this reason alone, the claimed methods are non-obvious over the combination of references cited by the Examiner.

Although Radu teaches that 13-*cis*-retinoic acid (also known as isotretinoin), a non-substituted retinoid, inhibits formation of A2E dimers and lipofuscin, isotretinoin however does so by a very different mechanism than retinoids deuterated at the C_{20} position. Isotretinoin is a retinoid that inhibits lipofuscin accumulation by slowing the visual cycle, which is known to lead to side effects such as night blindness and slowed dark adaptation. Radu specifically writes that "isotretinoin (Accutane) has been shown to slow the synthesis of 11-*cis*-retinaldehyde and regeneration of rhodopsin by inhibiting 11-*cis*-retinol dehydrogenase in the visual cycle." For added clarity, we direct the Examiner to panel A on Figure 1 of Radu, which shows the portion of the schematic which indicates that isotretinoin inhibits the retinoid pathway in the eye and retinal pigment epithelium by inhibiting the enzyme 11cRDH. Applicant has cited this work as document number 24 in the present specification. The Applicant is also well aware that not just isotretinoin but several other retinoids and non-retinoid small molecules [0009] have been used to slow the accumulation of lipofuscin by inhibiting specific visual cycle enzymes involved in vitamin A processing in the eye [0019].

As stated in the application, proper working of the visual cycle is necessary for good vision and slowing down of the visual cycle leads to unwanted visual side effects. These side effects, first noticed when these compounds were used in humans for other diseases (e.g., isotretinoin is used to treat acne), led researchers to hypothesize that these compounds were slowing the visual cycle and could potentially be used to slow the processing of vitamin A in the eye in order to slow its dimerization.

In contrast, Applicant discovered that instead of inhibiting the visual cycle, the described C_{20}-deuterated retinoids (excluding at least isotretinoin and retinylamine, which would inhibit the retinoid pathway), could replace vitamin A with a C_{20}-deuterated vitamin A, which in itself would dimerize in the eye more slowly than non-deuterated vitamin A, because deuterium atoms are lost more slowly from the C_{20} position than protium during vitamin A dimerization. In addition, using a heavy hydrogen (deuterium) substitution, the resulting C_{20}-D_{1-3}-retinoids would be identical in terms of electronic cloud to that of the non-substituted retinoids so that they would themselves not disrupt the visual cycle [0027].

It is important to note that A2E is formed by a purely chemical mechanism, i.e., a non-enzymatic mechanism, and that C_{20} substituted retinoids would inherently, i.e., without the need of an enzyme, slow down A2E formation. This was demonstrated in Example 1 of the present application, wherein deuterated C_{20} retinaldehyde formed A2E much more slowly than non-deuterated retinaldehyde in a test tube absent any enzyme.

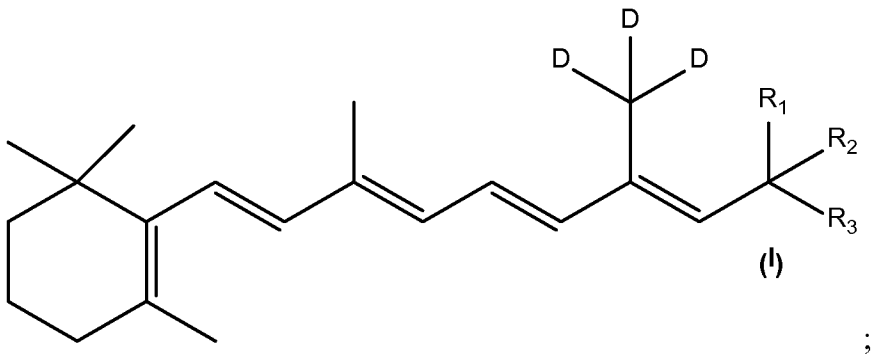
Further, the C_{20}-substituted retinoid is designed so as to replace, or function as, retinal in a patient [0030]. A person skilled in the art would therefore understand that this provided description places specific limitations and is very informative of the genus.

These differences highlight a further distinguishing feature between isotretinoin, which inhibits an enzyme of vision, and retinoids labeled with deuterium at the C_{20} position, which do not. The description as filed, and now the claims, exclude isotretinoin described by Radu as a suitable retinoid candidate because of the known side effects of isotretinoin. Actually, deuteration of isotretinoin would not diminish or alter the ability of isotretinoin to inhibit this pathway, and therefore would not diminish these side effects. As discussed in the advantages section above, Example 4 and 5 of the subject application correlate with the ability of deuterated C_{20}-retinoids to inhibit A2E and lipofuscin formation without causing the side effects of isotretinoin, by simply changing the vitamin A that reaches the retina.

2. Second, Applicant also disagrees with the Examiner's reliance on Boehm. While it is true that Boehm discloses a labeled retinoid, the labeling is not at the C_{20} position but at the C_{11} position, and such labeled retinoids do not fall into the claimed genus, retinoids specifically substituted at the carbon C_{20} position with deuterium. We invite the Examiner to quickly review

Boehm, compound V, page 5, to confirm this.

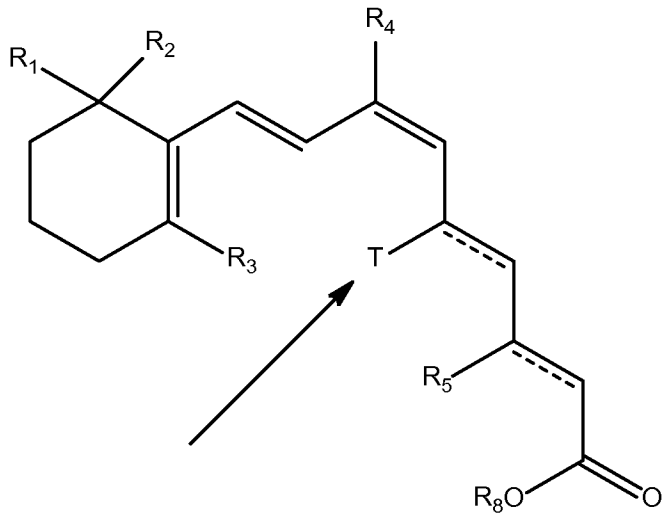
Applicant's C_{20}-D_3 deuterated compound is shown below:



(I)

;

In contrast, the labeled structure from Boehm is shown below (see page 5, Structure V):



The tritiated position is indicated by the arrow and clearly shows that the tritium in Boehm's structure is ***not*** in the C_{20} position (which would be at R5 on the figure above).

Moreover, tritium or deuterium in any position other than C_{20} would not be expected to have any effect on A2E or lipofuscin formation. This is because, as shown above in the schematic from figure 2 of the subject application, carbon-hydrogen breakage would occur only at the C_{20} position for the chemical synthesis of A2E.

Besides, Boehm provides no guidance with respect to how to modify the tritium or deuterium labeled retinoids disclosed therein to obtain a deuterium or tritium labeled retinoid

that could slow A2E formation. In particular, Boehm provides no reason to think that substituting deuterium at position 20 would reduce lipofuscin accumulation or lead to any other desirable result. Thus, Boehm provides no motivation to modify Radu's isotretinoin by substituting deuterium at position 20.

In fact, the teachings of Boehm are directed to using these retinoids as tools to better understand cellular retinoid receptors and for metabolic studies. The Examiner is directed to the paragraph bridging pages 6 and 7 of Boehm, reproduced below:

> It while also be understood, that while the process and compounds of the present invention have been illustrated with a tritium label, that deuterium could also be employed to provide isotopically labeled materials ***which are useful for mass spectral metabolism studies regarding the oxidative metabolites of such labeled compounds, and their corresponding non-labeled versions.***

Further, Boehm reports that the disclosed tritiated and deuterated retinoid binds with the same affinity as the non-substituted hydrogen analogs. It is well established that labeled compounds are useful as tracers for metabolic studies only if the isotopic label does not alter metabolism. Support for this assertion is provided by Baillie *et al.,* Pharmacology Rev., *33*:61 (1981) and Haskins et al., *Biomedical Spetrometry 9:*269(1982). Both references are cited in the Information Disclosure Statement filed February 26, 2013 in the present application. The Baillie reference states:

> An absolute requirement of the direct stable isotope dilution approach, of course, is that labeled and unlabelled forms of the drug are metabolized in an identical fashion, i.e. there is no isotope effect on metabolism. (Pharmacological Reviews, Vol. 33, No. 2 at page 92, right column)

The Haskins references states:

> Caution must be exercised to ensure that no isotope effects occur." (Biomedical Mass Spectrometry, Vol. 9, at page 273, left column).

Therefore, the person of ordinary skill in the art would understand the teachings of Boehm to mean that the tritium and deuterium labeled retinoids disclosed therein were meant not to alter metabolism, including the route of A2E dimer and lipofuscin formation. Because deuterium labeled tracer compounds are meant not to alter metabolism relative to the corresponding unlabeled compound, the person of ordinary skill in the art would have no reason

to believe that changing the site of deuterium or tritium labeling would in any way diminish A2E dimer and lipofuscin formation. Nor would a person skilled in the art have any reason to select the C_{20} site as having such an effect as disclosed in the present application. For these reasons also, the claimed invention is non-obvious in view of Radu and Boehm.

The C_{20} deuterium labeled retinoids recited in the claimed methods of treatment also have unexpected advantages over isotretinoin. Although both reduce A2E lipofuscin dimer formation, isotretinoin has serious side effects. For example, Radu mentions impaired night vision in the first full paragraph in right hand column on page 4742:

> A side effect of treatment with isotretinoin is reduced night vision because of its inhibitory effect on 11-*cis*-retinol dehydrogenase in RPE cells.

Further evidence in support of this assertion is provided by https://en.wikipedia.org/wiki/Isotretinoin, enclosed herewith as Exhibit D. The Examiner is referred to the table therein showing the numerous side effects, all of which are not seen with use of a deuterated intermediate in a patient's normal metabolism.

As was discussed above, isotretinoin inhibits the retinoid pathway in the eye and retinal pigment epithelium, which is believed to account for the side effects associated with isotretinoin. The present disclosure shows that the precise deuteration at the C_{20} position can slow lipofuscin formation. Because no carbon/hydrogen bond is broken at the C_{20} position in the retinoid pathway, the disclosed C_{20}-D_{1-3}-retinoids should have no effect on the retinoid pathway and are therefore not expected to reduce night vision nor to have the other side effects associated with isotretinoin. For this reason also, the claimed methods are further non-obvious in view of Boehm and Radu.

In summary:

- Radu's isotretinoin is specifically excluded from the present claims;
- Radu does not disclose or suggest any deuterated retinoids;
- Boehm does not disclose or suggest deuterium substitutions at C_{20};
- Radu and Boehm are directed to very different problems – Radu to treating visual system diseases by slowing the visual cycle, Boehm to understanding cellular retinoid receptors and to metabolic studies - and thus would not be combined.

Given the above, the combination of Radu and Boehm does not disclose or suggest the limitation of the present claims of "a substituted C_{20}-D_{1-3}-retinoid." Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner's Reasoning

The Office Action then proceeds to cite Lang (WO2005/065669) and Widder (US20070015827) in the obviousness rejection. Lang is cited because it teaches a "composition for retarding formation of lipofuscin pigment in the retina comprising retinoid and a pharmaceutically acceptable carrier" and the "dosage forms, vitamins and supplements". Widder is cited because it teaches the "use of phospholipids in combination with retinoids for treatment of ophthalmic conditions, such as stargardt's disease".

Response to Examiner's Reasoning

However, neither of these two references overcome the combined deficiencies of Radu because neither reference teaches how to reduce formation of A2E lipofuscin dimers with deuterium incorporation into the C_{20} position of retinoids, how to reduce formation of A2E dimers without inhibiting the retinoid pathway in the eye and retinal pigment epithelial nor how to treat ophthalmic condition associated with increased A2E dimer or lipofuscin formation without causing the side effects that are associated with isotretinoin. For at least these reasons, the claimed methods are non-obvious in view of the combination of Radu, Boehm, Lang, and Widder.

Restriction Requirement

The Examiner maintained the restriction requirement. She noted Applicant's argument that the shared technical feature between the method claims and the pharmaceutical composition claims is the pharmaceutical composition comprising a C_{20} deuterated retinoid. The Examiner rejected this argument because she believes that WO95/04018 (Boehm) discloses such a composition. However, for reasons discussed in the section of this Paper that respond to the obviousness rejection, although WO95/04018 (Boehm) discloses deuterated retinoids, Boehm does not disclose retinoids ***substituted with deuterium at the C_{20} position.*** Moreover, as also

discussed in the section of this Paper responding to the obviousness rejection, a pharmaceutical composition comprising a C_{20} deuterium enriched retinoid and a pharmaceutically acceptable carrier or diluent is novel and non-obvious, not only in view of WO95/04018, but also in view of the combination of WO95/04018, Radu, Lang and Widder.

Withdrawal of the restriction requirement and examination of both method and pharmaceutical composition claims is therefore respectfully requested.

CONCLUSION

In view of the above, applicant believes the pending claims are in condition for allowance.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Commissioner is authorized to charge Kenyon & Kenyon LLP's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: September 16, 2013

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EXHIBIT A

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PROVISIONAL

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

and

INTERNATIONAL UNION OF BIOCHEMISTRY

JOINT COMMISSION ON BIOCHEMICAL NOMENCLATURE*

NOMENCLATURE OF RETINOIDS

Comments on these recommendations are welcome and should be sent within 8 months from April 1983 to the Secretary of the Commission

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Tennis Court Road
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UK

Comments from the viewpoint of languages other than English are especially encouraged. These may have special significance regarding the publication in various countries of translations of the nomenclature eventually approved by IUPAC.

*Membership of the Commission for 1981-83 is as follows:

Chairman: P. KARLSON (FRG); *Secretary:* H. B. F. DIXON (UK); *Members:* C. LIÉBECQ (Belgium — as Chairman of IUB Committee of Editors of Biochemical Journals); K. L. LOENING (USA); G. P. MOSS (UK); J. REEDIJK (Netherlands); S. F. VELICK (USA); J. F. G. VLIEGENTHART (Netherlands).

Additional contributors to the formulation of these recommendations:

Nomenclature Committee of IUB (those additional to JCBN); H. BIELKA (GDR); N. SHARON (Israel).

PROVISIONAL

IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN)

Nomenclature of Retinoids

Recommendations 1981

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PREAMBLE

Funk [1] suggested in 1912 the term 'vitamine' to describe a growth factor present in food which was essential for life. It later became clear that there was more than one growth factor, and McCollum [2] divided them into two classes, 'fat-soluble A' and 'water-soluble B'. Objecting to the chemical implications of the suffix '-ine', Drummond [3] suggested deletion of the final 'e', renamed McCollum's two groups vitamin A and vitamin B, and proposed that further members of this series be called vitamin C, vitamin D, etc.

In 1934 Wald [4] isolated from animal retina a substance he called retinene. Morton [5] suggested that this compound was the aldehyde of vitamin A, and [6] called it retinaldehyde (rather than retinal). The correct structure of vitamin A was deduced in 1931 by Karrer [7] who proposed [8] the name axerophthol (*Axerophtol* in German), based on its action in preventing the eye disease xerophthalmia. A second vitamin A, isolated by Morton and others, was called vitamin A_2 [9].

Recommendations for the nomenclature of the vitamins were published by IUPAC in 1960 [10]. These included names for the three parent compounds – retinol, retinal and retinoic acid – as well as for their 3-dehydro analogues. A revised and enlarged version of these recommendations was published by the IUPAC-IUB Commission on Biochemical Nomenclature (CBN) in 1965 [11]. With the publication by the IUPAC Commission on the Nomenclature of Organic Chemistry (CNOC) and CBN of the 'Nomenclature of carotenoids' [13] and by CNOC of 'Section F' (Natural products and related compounds) [14] of the 'Nomenclature of Organic Chemistry' [15] it was decided by JCBN that a separate document should be published extending section M-1 of the 1965 document. The present recommendations are based on drafts prepared by G. P. Moss in consultation with several active workers in the field and with CNOC.

RECOMMENDATIONS

Ret-1. CLASS OF COMPOUNDS

Retinoids are a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner. All retinoids may be formally derived from a monocyclic parent compound containing five carbon-carbon double bonds and a functional group at the terminus of the acyclic portion. To avoid confusion with previously used names in this field no parent hydrocarbon is named (see Ret-4.1).

1.1. *Vitamin A*

The term vitamin A should be used as the generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol. This term should be used in derived terms such as vitamin A activity, vitamin A deficiency, vitamin A antagonist [16].

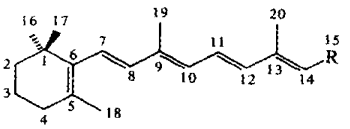
Ret-2. STEREOPARENTS

A stereoparent is a parent compound whose name implies stereochemistry, which will not need to be stated explicitly.

Document of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), whose members are: P. Karlson (chairman), H. B. F. Dixon, C. Liébecq (as chairman of the IUB Committee of Editors of Biochemical Journals), K. L. Loening, G. P. Moss, J. Reedijk, S. F. Velick, and J. F. G. Vliegenthart. JCBN thanks other members of the Nomenclature Committee of IUB (H. Bielka and N. Sharon) for consultation. Comments and suggestions for future revisions of these recommendations may be sent to its secretary, H. B. F. Dixon, University Department of Biochemistry, Tennis Court Road, Cambridge, England CB2 1QW, or to any member.

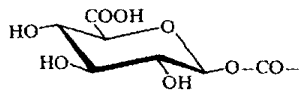
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by courtesy of Springer-Verlag, Heidelberg, FRG.

It is convenient to omit the explicit representation of C and H atoms in the skeletal formulae of retinoids as follows:



(*1*) R = CH_2OH
(*2*) R = CHO
(*3*) R = CO_2H
(*4*) R = CH_3
(*5*) R = CH_2OCOCH_3
(*6*) R = CH_2NH_2
(*7*) R = CH=NOH
(*8*) R = $CH{=}N[CH_2]_4CHNH_2CO_2H$
(*9*) R = $CO_2C_2H_5$

(*10*) R- =



2.1. *Retinol*

The compound (*1*) (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraen-1-ol[1], also known as vitamin A, vitamin A alcohol, vitamin A_1, vitamin A_1 alcohol, axerophthol or axerol, should be designated retinol[2].

2.2. *Retinal*

The compound (*2*) also known as vitamin A aldehyde, vitamin A_1 aldehyde, retinene or retinene$_1$ should be designated retinal[3] or, if liable to be confused with the adjective retinal (pertaining to the retina), retinaldehyde[4].

2.3. *Retinoic Acid*

The compound (*3*) also known as tretinoin[2], vitamin A acid or vitamin A_1 acid should be designated retinoic acid.

Ret-3. NUMBERING

The basic system of numbering is that shown in structures (*1*) to (*10*). This follows the system outlined in the carotenoid rules in Rule Car-4 and Rule Car-12.4 [13].

Ret-4. MODIFICATION OF STEREOPARENT

4.1. *Basic Hydrocarbon*

The hydrocarbon (*4*), also known as axerophthene, should be designated deoxyretinol[5]. This hydrocarbon cannot be considered as the stereoparent for the stem 'retin-' as it would then need to be called retinene, a name already used as a misleading synonym for retinal (Ret-2.2). A name such as retinane is inappropriate as it would imply a saturated hydrocarbon (Rule F-2.3 in [14]).

[1] The numbering system of the systematic name is different from above. See Ret-3.

[2] WHO-approved nonproprietary names.

[3] Recommended for chemical usage.

[4] Recommended for nutritional usage [16].

[5] The prefix deoxy may be either detachable or non-detachable (see Rule C-16.11 [15]). In this document it is treated as a non-detachable prefix and, so that the locant 15 is not needed, it is always placed next to the stem name (cf. Rule C-16.32 [15]).

4.2. *Change of the Functional Group*

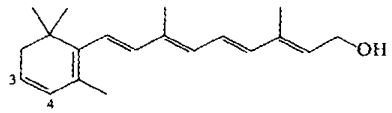
4.2.1. Functional substitution at the 15 position of the basic hydrocarbon is denoted by the use of the group names retinyl (R is CH_2-) or retinylidene (R is CH=), with retention of the original numbering of the basic hydrocarbon. For example (*5*) is retinyl acetate and (*6*) is retinylamine.

4.2.2. A compound derived from retinal is named either as an aldehyde derivative (following Rule C-842, Rule C-922 or Rule C-982 in [15]), or as a compound substituted by the bivalent radical retinylidene (Rule A-4.1 in [15]). For example (*7*) is retinal oxime and (*8*) is N^6-retinylidene-L-lysine.

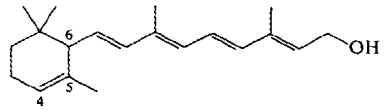
4.2.3. Derivatives of retinoic acid named as carboxylic acid derivatives following Rule C-4.6 or Rule C-403 [15]. For example (*9*) is ethyl retinoate and (*10*) is 1-*O*-retinoyl-β-D-glucopyranuronic acid.

4.3. *Changes in the Hydrogenation Level*

Retinoids that differ in hydrogenation level from the corresponding stereoparents defined by Rule Ret-2 are named by use of the prefixes 'hydro' and 'dehydro' together with locants specifying the carbon atoms at which hydrogen atoms have been added or removed. These prefixes are nondetachable, and, if both occur in one name, are cited in the order dehydro before hydro (multiplying prefixes do not affect the order); see Rule Car-6 [13]. Examples:



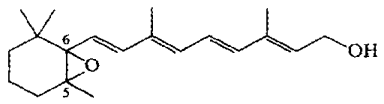
3,4-Didehydroretinol (also known as dehydroretinol[4] or vitamin A_2)



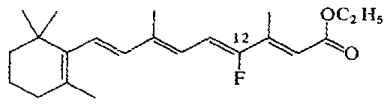
4,5-Didehydro-5,6-dihydroretinol (also known as α-vitamin A)

4.4. *Substituted Retinoids*

Substituted derivatives of retinoids are named by the use of prefixes according to the rules of general organic chemical nomenclature, see Rule C-0.1 [15]. The use of suffixes is not possible since the stereoparents defined by Rule Ret-2 include a suffix concerned with the function at C-15. Examples:



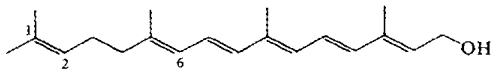
5,6-Epoxy-5,6-dihydroretinol (also known as hepaxanthin)



Ethyl 12-fluororetinoate

4.5. *Seco Retinoids*

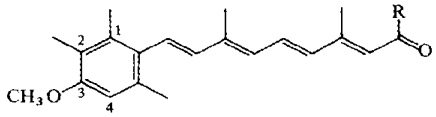
Fission of the ring, with addition of one or more hydrogen atoms at each terminal group thus created, is indicated by the prefix 'seco', the original retinoid numbering being retained (see Rule F-4.7 [14]). Example:



1,6-Seco-1,2-didehydroretinol (also known as γ-vitamin A)

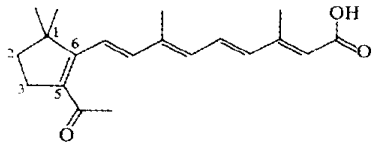
4.6. *Nor Retinoids*

Elimination of a CH_3, CH_2, CH or C group from a retinoid is indicated by the prefix 'nor', which is preceded by the locant of the carbon atom removed. When alternatives are possible, the locant selected is the highest possible, and the basic numbering of the retinoid is retained. The prefix is nondetachable (see F-4.2, F-4.4 [14]). Note that this recommendation follows rules F-4.2 and F-4.4, rather than the carotenoid recommendation (Car-5.1 [13]), which specifies the lowest possible locant. We propose that Car-5.1 should be changed to conform to the general practice when the carotenoid recommendations are next revised. Examples:



R = NHC_2H_5 *N*-Ethyl-3-methoxy-2-methyl-17-nor-1,2,3,4-tetradehydroretinamide (also known as motretinide[2])

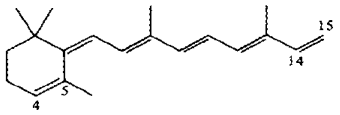
R = OC_2H_5 Ethyl 3-methoxy-2-methyl-17-nor-1,2,3,4-tetradehydroretionate (also known as etretinate[2])



5-Acetyl-4,18-dinor-retinoic acid

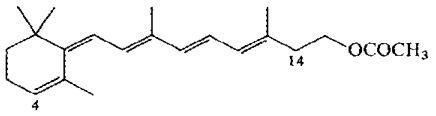
4.7. Retro *Retinoids*

The prefix '*retro*' (printed in italics) and a pair of locants indicate a shift by one position of the conjugated polyene system between the positions indicated by the locants. The first locant indicates the carbon atom that has lost a proton and the second the carbon atom that has gained one. This prefix is nondetachable (see Rule Car-9 [13]). Examples:



4,5-Didehydro-15,5-*retro*-deoxyretinol (also known as anhydro vitamin A)

Note. This semisystematic name is preferred over 14,15-didehydro-4,14-*retro*-deoxyretinol as it has the lower set of locants, see A-2.2, C-13.11 [15].



4,14-*retro*-Retinyl acetate

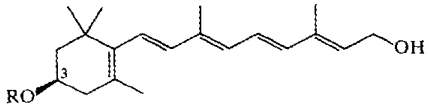
4.8. *Other Modifications*

Other modifications may be indicated by the appropriate prefix. For example; cyclo (see Rule F-4.1 [14]); homo (see Rule F-4.5 [14]); hetero atoms (see Rule F-4.11 [12], Rule B-4 and Rule C-0.6 [14]); and additional rings (see Rule 2S Appendix [17]).

Ret-5. STEREOCHEMISTRY

5.1. *Chiral Groups*

The absolute configuration at chiral centres is designated by use of the *RS* convention, the symbols being placed, with the corresponding locants, before the retinoid name (see Rule E-4.9 [18]). Examples:

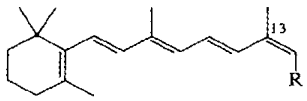


R = H (3*R*)-3-Hydroxyretinol

R = $COCH_3$ (3*R*)-3-Acetoxyretinol

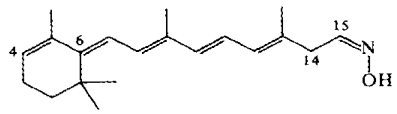
5.2. *Double Bonds*

The stereoparent name defined by Rule Ret-2 implies that the polyene chain has the *trans* configuration about all double bonds unless the contrary is indicated. Following the designation of absolute configuration (if any), *cis* double bonds are indicated. The stereochemical prefixes *E* or *Z* (see Rule E-2 [18]) may be used, and should always be used where *cis* or *trans* might be ambiguous. However it should be noted that substitution may result in a change from *E* to *Z* or *vice versa* even though there is no change in configuration of the stereoparent polyene chain. Hence it is recommended that the stereochemistry of all double bonds should be cited when this system is used. For example compound (9) is ethyl (*all-E*)-retinoate. Replacement of the hydrogen at C-12 by fluorine gives the compound used to illustrate rule Ret-4.4 which may be described as ethyl (7*E*,9*E*,11*Z*,13*E*)-12-fluororetinoate. Examples:



R = CH_2OH 13-*cis*-Retinol or (7*E*,9*E*,11*E*,13*Z*)-retinol (also known as neovitamin A)

R = CO_2H 13-*cis*-Retinoic acid or (7*E*,9*E*,11*E*,13*Z*)-retinoic acid (also known as isotretinoin[2])



(6*E*,8*E*,10*E*,12*E*,15*Z*)-4,14-*retro*-Retinal oxime

Note that if it is necessary to indicate the stereochemistry of the 6(7)-double bond of a *retro*-retinoid this should be stated so that, for example, the compound given with Ret-4.7 is (6*Z*,8*E*,10*E*,12*E*)-4,14-*retro*-retinyl acetate.

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APPENDIX

Some Related Terpenoids Containing less than Twenty Carbon Atoms

The term carotenoid is usually restricted to terpenoids that retain the two central methyl groups of the parent C_{40} compound. However the definitions in Rule Car-1 and Rule Car-10 [13] permit an extension of the apo nomenclature to include retinoids (e.g. retinal would be 15-apo-β-caroten-15-al) and a range of smaller molecules. Many of these compounds exhibit plant hormone action or are important essential oil components. The list of trivial names in this Appendix is given for convenience but is not intended as official recognition of these names.

Trivial name	Semisystematic name
(+)-Abscisic acid	(7E,9*Z*)-(6*S*)-6-hydroxy-3-oxo-11-apo-ε-caroten-11-oic acid
(−)-Actinidiolide	(5*R*)-3,4-didehydro-5,8-dihydro-8-apo-β-caroten-8,5-olide
Actinidol	5,8-epoxy-3,4-didehydro-5,8-dihydro-9-apo-β-caroten-9-ol
Blumenol A	(6*S*,9*R*)-6,9-hydroxy-9-apo-ε-caroten-3-one
Blumenol B	(6*S*,9*R*)-6,9-dihydroxy-7,8-dihydro-9-apo-ε-caroten-3-one
Blumenol C	9-hydroxy-7,8-dihydro-9-apo-ε-caroten-3-one
β-Cyclocitral	7-apo-β-caroten-7-al
β-Cyclogeraniol	7-apo-β-caroten-7-ol
β-Cyclogeranic acid	7-apo-β-carotin-7-oic acid
Damascenone	(8*E*)-3,4,8,9-tetradehydro-7,8-dihydro-9-apo-β-caroten-7-one
Digiprolactone	see Loliolide
Grasshopper ketone	(3*S*,5*R*,6*R*)-3,5-dihydroxy-6,7-didehydro-5,6-dihydro-9-apo-β-caroten-9-one
(+)-α-Ionone	(6*R*)-9-apo-ε-caroten-9-one
β-Ionone	9-apo-β-caroten-9-one
(−)-γ-Ionone	(6*S*)-9-apo-γ-caroten-9-one
ψ-Ionone	9-apo-ψ-caroten-9-one
(+)-*cis*-α-Irone	(2*R*,6*S*)-2-methyl-9-apo-ε-caroten-9-one
(−)-*trans*-α-Irone	(2*R*,6*R*)-2-methyl-9-apo-ε-caroten-9-one
(+)-β-Irone	(2*R*)-2-methyl-9-apo-β-caroten-9-one
β-Ionylideneacetaldehyde	11-apo-β-caroten-11-al
β-Ionylideneacetic acid	11-apo-β-caroten-11-oic acid
β-Ionylideneethanol	11-apo-β-caroten-11-ol

(continuation)

Trivial name	Semisystematic name
(−)-Loliolide	(3*S*,5*R*)-3-hydroxy-5,8-dihydro-8-apo-β-caroten-8,5-olide
Latia luciferin	(9*E*)-7,8-dihydro-10-apo-β-caroten-10-yl formate
(−)-Phaseic acid	(7*E*,9*Z*)-(1*R*,5*R*,6*S*)-5,16-epoxy-6-hydroxy-3-oxo-5,6-dihydro-11-apo-β-caroten-11-oic acid
Pseudoionone	see ψ-Ionone
Safranal	3,4-didehydro-7-apo-β-caroten-7-al
(−)-Theaspirone	(6*S*,9*S*)-6,9-epoxy-7,8-dihydro-9-apo-ε-caroten-3-one
Trisporic acid B	(1*S*)-4,13-dioxo-11,12-dihydro-13-apo-β-caroten-16-oic acid
Trisporic acid C	(1*S*,13*R*)-13-hydroxy-4-oxo-11,12-dihydro-13-apo-β-caroten-16-oic acid
Trisporol B	(1*S*)-16-hydroxy-11,12-dihydro-13-apo-β-carotene-4,13-dione
Trisporol C	(1*S*,13*R*)-13,16-dihydroxy-11,12-dihydro-13-apo-β-caroten-4-one
Trisporone	(1*S*)-11,16-dihydroxy-11-apo-β-caroten-4-one
Vomifoliol	see Blumenol A
(−)-Xanthoxin	(7*E*,9*Z*)-(3*S*,5*R*,6*S*)-5,6-epoxy-3-hydroxy-5,6-dihydro-11-apo-β-caroten-11-al

EXHIBIT B

Reductions in Serum Vitamin A Arrest Accumulation of Toxic Retinal Fluorophores: A Potential Therapy for Treatment of Lipofuscin-Based Retinal Diseases

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Purpose. Excessive accumulation of lipofuscin is observed in numerous degenerative retinal diseases. A toxic vitamin A–based fluorophore (A2E) present within lipofuscin has been implicated in the death of RPE and photoreceptor cells. Here, we used an animal model that manifests accelerated lipofuscin accumulation (*ABCA4*−/− mutant) to evaluate the efficacy of a therapeutic approach based on reduction of serum retinol.

Methods. *N*-(4-hydroxyphenyl)retinamide (HPR) potently and reversibly reduces serum retinol. The interaction of HPR with retinol binding protein (RBP) and transthyretin was studied by spectrofluorometry and size-exclusion chromatography. To assess the effects of HPR on visual cycle retinoids and A2E biosynthesis, HPR was chronically administered to *ABCA4*−/− mice. Mice were evaluated using biochemical, electrophysiological, and morphologic techniques.

Results. Administration of HPR to *ABCA4*−/− mice caused immediate, dose-dependent reductions in serum retinol and RBP. Chronic administration produced commensurate reductions in visual cycle retinoids and arrested accumulation of A2E and lipofuscin autofluorescence in the RPE. Physiologically, HPR treatment caused modest delays in dark adaptation. Chromophore regeneration kinetics, light sensitivity of photoreceptors, and phototransduction processes were normal. Histologic examinations showed no alteration of retinal cytostructure or morphology.

Conclusions. These findings demonstrate the vitamin A–dependent nature of A2E biosynthesis and validate a novel therapeutic approach with potential to halt the accumulation of lipofuscin fluorophores in the eye. (*Invest Ophthalmol Vis Sci.* 2005;46:4393–4401) DOI:10.1167/iovs.05-0820

Mutations in the *ABCR* (*ABCA4*) gene are responsible for several inherited retinal and macular degenerations, including recessive Stargardt disease (STGD1) and subsets of cone-rod dystrophy (CRD), retinitis pigmentosa (RP), and age-related macular degeneration (AMD).[1] These diseases share the phenotype of lipofuscin pigment accumulation in cells of the retinal pigment epithelium (RPE).[2,3] The RPE plays a critical role in the support of photoreceptor cells,[4] which includes synthesis of visual chromophore and phagocytosis of diurnally shed photoreceptor outer segments.[5,6] Lipofuscin arises in the RPE from incomplete digestion of these retinaldehyde-rich outer-segment fragments. Lipofuscin pigments are autofluorescent because of their high retinoid content. The major fluorophore of lipofuscin is the *bis*-retinoid, *N*-retinylidene-*N*-retinylethanolamine (A2E).[7] Dramatic accumulation of A2E has been observed in the RPE of *ABCA4* knockout mice, which represent an animal model for *ABCA4*-mediated macular and retinal degenerations.[8–10] Still higher rates of A2E accumulation have been reported in transgenic mice with a mutation in the *elovl4* gene, an animal model for dominant Stargardt disease,[11] and in knockout mice with mutations in the *ccl2 and ccr2* genes, as animal models for AMD.[12] Further, postmortem specimens of RPE from patients with STGD1 contained greatly elevated A2E compared to age-matched controls.[8]

Retinal fluorophores such as A2E can be visualized in patients as fundus autofluorescence (FAF) using confocal scanning laser ophthalmoscopy (cSLO). FAF analyses in STGD1 and AMD patients have shown prominent autofluorescence and retinal dysfunction in regions immediately surrounding atrophic areas.[13–17] Interestingly, new atrophic areas emerge within regions of intense autofluorescence, demonstrating that FAF precedes the onset of geographic atrophy.[13,15,17] Measuring FAF by cSLO is now accepted as a diagnostic tool to monitor disease progression in STGD and AMD patients.

The biological properties of A2E have been extensively studied. Notably, A2E has been shown to possess several modes of cytotoxicity to RPE cells. For example, A2E inhibits lysosomal degradative functions in RPE phagosomes[18] and predisposes RPE cells to blue light–induced apoptosis.[19] At higher concentrations, A2E behaves as a cationic detergent, dissolving cellular membranes.[20] The first event in A2E biogenesis is condensation of all-*trans* retinaldehyde (*at*RAL) with phosphatidylethanolamine in photoreceptor outer segments. This process occurs spontaneously after light exposure. For this reason, normal mice and humans accumulate small amounts of A2E in RPE cells in an age- and light-dependent manner.[8,10] The much faster accumulation of A2E in the above-described mouse models and humans with several forms of macular and retinal degeneration results in compromised RPE function and ultimately blindness due to photoreceptor death. Thus, the targeting of A2E accumulation in RPE cells appears a reasonable therapeutic strategy to slow the progression of visual loss in these patients.

Because A2E biosynthesis relies ultimately on circulating retinol, therapies that lower retinol should lower A2E levels. For example, leupeptin-induced lipofuscin and autofluorescence were dramatically reduced during dietary retinol deficiency.[21–23] However, deleterious systemic effects associated

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with long-term retinol deficiency invalidate limiting dietary vitamin A as a treatment strategy. Alternatively, serum retinol can be regulated by pharmacological means. *N*-(4-hydroxyphenyl) retinamide (HPR) has been widely used as a chemotherapeutic agent for a variety of cancers, and is known reversibly to reduce serum retinol and retinol-binding protein (RBP) levels.[24–27] Numerous clinical trials conducted over the past 20 years have shown minimal systemic effects with HPR treatment in humans.[28]

HPR exerts its effect on retinol levels by competing for binding sites on RBP.[29] Dietary retinol is secreted from the liver bound to RBP. The RBP-retinol holoprotein (~21 kDa) is retained in blood by virtue of increased molecular size after binding with transthyretin (TTR, ~51 kDa).[30] The bulky phenyl-hydroxyl moiety of HPR (Fig. 1) may prevent the RBP-HPR complex from binding with TTR. Consequently, RBP-HPR complexes are lost to the urine through glomerular filtration. The net effect is lowered retinol and RBP in the circulation. Unlike other organs, the uptake of retinol by the eye is largely dependent on delivery by RBP.[31] Consistently, mice with a knockout mutation in the *rbp* gene have a phenotype confined to the eyes, with no systemic signs of vitamin A deficiency.[31]

In the present study, we used *ABCA4* knockout mice to explore the potential activity of HPR to inhibit the accumulation of A2E and lipofuscin in cells of the RPE. These treated mice were evaluated biochemically, electrophysiologically, and histologically. The results suggest that HPR is effective in blocking formation of A2E and other lipofuscin fluorophores with no deleterious effects on visual function or retinal morphology.

Materials and Methods

Materials

Holo-RBP and HPR were purchased from Sigma Chemical Co. (St. Louis, MO). *N*-(4-methoxyphenyl)retinamide (MPR) was a gift from Robert W. Curley, Jr. (Ohio State University, Columbus, OH). 11-*cis*-Retinaldehyde (11cRAL) was obtained from Rosalie Crouch (Storm Eye Institute, Charleston, SC) and the National Eye Institute. HPLC grade solvents were purchased from Fisher Scientific (Houston, TX). All other reagents were of highest possible purity.

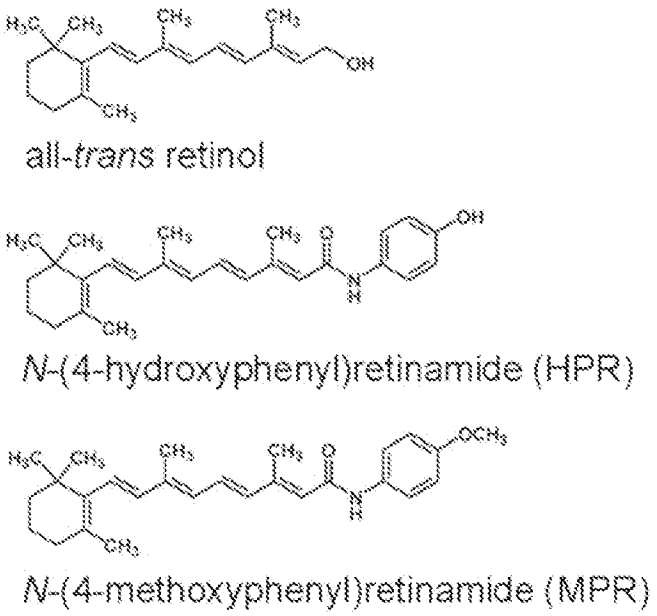


FIGURE 1. Structural similarities between all-*trans* retinol (retinol), HPR, and MPR. Each of the compounds is comprised of a β-ionone ring and a conjugated, double-bond polyene chain. HPR and MPR are distinct from retinol by virtue of their amide-linked phenyl moiety. MPR, the primary metabolite of HPR in serum, possesses a terminal methoxy group, while HPR possesses a hydroxyl group.

Mice

Animal studies were designed to conform with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Dimethyl sulfoxide (DMSO) and HPR were administered daily to wild-type and *ABCA4*−/− mice by intraperitoneal (IP) injection. The phenotypic attributes of *ABCA4*−/− mice have been described elsewhere.[9] Mice were 1 to 2 months of age at study onset and were either pigmented (129/SV) or albino (BALB/c) strains. Genotyping was performed to confirm that all mice carried the leucine (wild-type) *RPE*65 allele. All comparisons of the effects of HPR versus DMSO within a particular dosage group were made among littermates. HPR was delivered at concentrations of 1.5 to 15.0 μg/μL in 25 μL DMSO. Littermate controls received an equivolume of DMSO. Mice were raised under a 12-hour light–dark cycle (30–50 lux) during the treatment period and were anesthetized by IP injection of ketamine (200 mg/kg) plus xylazine (10 mg/kg) before death by cervical dislocation.

Fluorescence Quenching Spectroscopy

Fluorescence spectroscopy was performed using a commercial fluorometer (Fluorolog FL-3-22; Jobin Yvon, Edison, NJ). All titration and kinetic measurements were performed in PBS (pH 7.4) at 37°C with intermittent stirring in a 1-cm cuvette. Samples were excited at 280 nm and emission data were acquired from 290 to 550 nm with excitation and emission bandpass of 2 nm. Fluorescence emission spectra for holo-RBP (0.5 μM) were monitored over a 30-minute period. Displacement of retinol from holo-RBP was examined by adding 1 μM HPR or MPR in EtOH (0.05%, v:v) to a fresh mixture of 0.5 μM holo-RBP, followed by analysis for 30 minutes. Apo-RBP was prepared from a sample of holo-RBP (Sigma) after bleaching at 330 nm for 60 minutes (10°C) to destroy the endogenous retinol. Apo-RBP was purified and concentrated from the bleached sample using size-exclusion chromatography (SEC) as described below. Titrations of apo-RBP with MPR, HPR and retinol were performed by mixing apo-RBP (0.5 μM) with the indicated ligands (0.25–4 μM) at room temperature for 60 minutes. The fluorescence emission spectra were then acquired as described above.

Size-Exclusion Chromatography

The ability of RBP-retinol, RBP-HPR, and RBP-MPR to interact with TTR was examined by SEC. Samples were analyzed by fast protein liquid chromatography (Biological Duo Flow system; BioRad, Hercules, CA) using a 300- × 7.8-mm size-exclusion column (SEC 125; BioRad). The mobile phase (PBS, pH 7.4; 2mM NaN_3) was delivered at 1.0 mL/min. In these experiments, apo-RBP (5 μM) and the indicated ligand (10 μM) were mixed and incubated at room temperature for 30 minutes. After the incubation period, each sample was divided into two equal aliquots. TTR was added to one aliquot (final [TTR] = 5 μM), while the other aliquot received only TTR buffer. The samples were mixed, and incubation was resumed at room temperature for 30 minutes. After incubation, equivolume portions were removed from each sample and analyzed by SEC.

Extraction and Analysis of Serum Retinoids

Whole blood was collected from tail veins of DMSO- and HPR-treated mice at the indicated times to determine levels of serum retinol. Serum was prepared from the blood samples and retinoids were extracted using methods described by Formelli et al.[24,25] Briefly, serum was obtained from whole blood after centrifugation at 1500 *g* for 10 minutes. Serum proteins were precipitated with the addition of an equivolume of ice-cold acetonitrile and centrifugation (10,000*g* for 10 minutes). An aliquot was removed from the soluble phase and analyzed

by HPLC using a capillary liquid chromatograph (Agilent 1100 Series; Agilent Technologies, Palo Alto, CA) equipped with a diode-array detector. Retinoids were separated on a Zorbax SB C18 5-μm column (150- × 0.5-mm; Agilent Technologies) equilibrated with acetonitrile/water/glacial acetic acid (80:18:2, v:v) at a flow rate of 10 μL/min.

Extraction and Analysis of Retinoids, A2E, and A2E Precursors

Steady-state levels of retinoids, A2E, and A2E precursors (A2PE and A2PE-H_2) in *ABCA4*−/− mice were determined after daily administration (28 days) of either DMSO or HPR (2.5–20 mg/kg). To examine the effects of HPR on regeneration of visual chromophore, levels of 11*c*RAL and a*t*RAL were measured in dark-adapted mice and during recovery from a photobleach (~1000 lux, 5 minutes), which bleached ~50% of the rhodopsin. At the indicated times, the mice were killed, the eyes were enucleated, and the posterior portion of each eye was used for extraction of retinoids or A2E and precursors. Methodologies used for extraction of A2E, A2E precursors, and retinoids from eye tissue and HPLC analysis techniques have been previously described.[8–10] All samples were analyzed by HPLC using absorbance and fluorescence detection. In these analyses, a column thermostat was used to maintain the solvent and column temperature at 40°C. Identity of the indicated compounds was confirmed by online spectral analysis and by coelution with authentic standards.

Electroretinography

Electroretinograms (ERGs) were obtained from *ABCA4* knockout mice treated with either DMSO or HPR (10 mg/kg) for 35 days (n = 4/group). ERGs were recorded using previously described methods.[32,33] Briefly, after overnight dark adaptation, mice were anesthetized with ketamine and xylazine, their pupils were dilated with 1% atropine sulfate, and they were placed in a Ganzfeld dome (LKC Technologies, Gaithersburg, MD). ERGs were recorded from the corneal surface using a gold-loop corneal electrode and mouth-reference plus tail-ground electrodes. Responses were amplified (Grass CP511 AC amplifier; Grass Instruments, Quincy, MA) and digitized (PCI-1200; National Instruments, Austin, TX) using custom software (LabWindows/CVI; National Instruments).

Single-Flash Responses

After complete dark adaptation, rod-mediated ERGs were recorded to short-wavelength (Kodak Wratten 47A or 47B) flashes of light up to a maximum intensity of 3.32 log scot td · s. At the highest intensities, the leading edge of the *a*-wave of the ERG was fitted with a computational model to provide estimates of rod sensitivity S and Rm_{P3}, the maximum saturated photoresponse.[34–36] Over a range of intermediate intensities, *b*-wave intensity-response functions were fitted with a Naka-Rushton relation to estimate V_{max}, the saturated *b*-wave amplitude, and k, the semisaturation intensity. Light-adapted cone ERGs were obtained with white flashes of light after 10 minutes of exposure to a rod-saturating background (30 cd/m^2).

Recovery from Photobleach

The kinetics of recovery from a photobleach were examined by exposing the dark-adapted mice with dilated pupils to light at 500 lux for 30 seconds, which caused ~40% bleaching of rhodopsin. The time course of rod recovery was examined by monitoring the growth of the rod ERG *a*-wave to a bright probe flash (3.0 log scot td · s) in mice at different times after returning to darkness from 5 to 30 minutes.

Light Microscopy

ABCA4−/− pigmented and albino mice were treated with either DMSO or HPR (10 mg/kg per d) for 42 days. Mice were then deeply anesthetized with 25% Avertin in PBS (pH 7.2). Whole-body perfusion was performed with a 21°C mixture of 0.1 M sodium phosphate (pH 7.4), 2% formaldehyde, and 2.5% glutaraldehyde. After 5 minutes of perfusion, the eyes were removed, and a corneal window was cut in each eye to allow further fixation by immersion overnight at 4°C. The cornea was subsequently removed, and the hemispheres were marked for orientation. The hemispheres were fixed additionally in PBS (pH 7.4) and 1% osmium tetroxide for 1 hour, dehydrated in ethanol, and treated with propylene oxide. The hemispheres were embedded in Epon 812/Araldite 502 (2:1), and sections were cut at a thickness of 1 μm along the vertical meridian from the superior to inferior retinal margin. The sections were stained with toluidine blue for light microscopic analysis. Images were collected with a Zeiss Axioplan microscope fitted with a Planapo 63X oil-immersion lens and a CoolSNAP digital camera.

Fluorescence Microscopy

ABCA4−/− albino mice were treated with either DMSO or HPR (10 mg/kg) for 42 days. Mice were then deeply anesthetized and perfused as described above, except that the fixative was 2% formaldehyde and 1% glutaraldehyde. The eyes were removed, marked for orientation, and divided along the vertical meridian. The hemispheres were dehydrated in ethanol and embedded in LR White resin. One-micrometer-thick sections were prepared and imaged in a Zeiss Microsystems 410 confocal microscope at a laser excitation of 488 nm and emission bandwidth of 515 to 565 nm. The images were taken with a Planapo 63X oil-immersion lens and digitally processed.

Results

HPR Mechanism of Action

The capacity of HPR to bind apo-RBP and subsequently affect binding to a TTR affinity resin has been reported.[37,38] However, little information is available regarding the capacity of HPR to displace retinol from holo-RBP, the interaction of RBP-HPR with native TTR under physiological conditions, and the interaction of MPR, the principal metabolite of HPR (Fig. 1), with RBP and TTR. This latter issue is particularly important as serum concentration of MPR approaches that of HPR during chronic treatment.[24,39] We used fluorescence-based binding assays to study RBP-ligand interaction and chromatographic techniques using native proteins to examine interaction of the RBP-ligand complexes with TTR.

We first examined the binding affinity (K_d) of MPR, HPR and retinol for RBP by measuring the degree of RBP fluorescence quenching during ligand titration. Both retinol and HPR demonstrated similar affinities for RBP (60 and 30 nM, respectively; Fig. 2A). MPR was also observed to bind to RBP, albeit with reduced affinity (K_d ~ 100 nM). We next addressed the issue of retinol displacement from holo-RBP. In these studies, HPR and MPR were added to a solution of RBP-retinol. The protein and retinoid fluorescence intensities were then monitored over time. The fluorescence spectra from a solution containing only RBP-retinol (0.5 μM) is shown in Figure 2B. The 340-nm emission is a result of direct excitation of aromatic residues in RBP. The 470-nm emission is the result of fluorescence resonance energy transfer from RBP to retinol, which absorbs maximally at 330 nm and emits in the range of 420 to 540 nm. Figure 2C shows the effect of adding 1 μM HPR to a solution of RBP-retinol (0.5 μM). Like retinol, HPR absorbs maximally in the range of RBP fluorescence emission. Unlike retinol, however, HPR does not fluoresce. Therefore, the time-dependent decreases in both protein and retinol fluorescence indicate displacement of retinol by HPR. Similarly, MPR (1 μM) also displaced retinol from RBP, but to a lesser extent than observed for HPR (Fig. 2D).

The ability of the three RBP-ligand species (RBP-retinol, RBP-HPR, and RBP-MPR) to complex with TTR was examined by SEC (Fig. 3). Unbound TTR (55 kDa) elutes at ~8 minutes and displays a single absorbance maximum at 280 nm (Fig. 3A

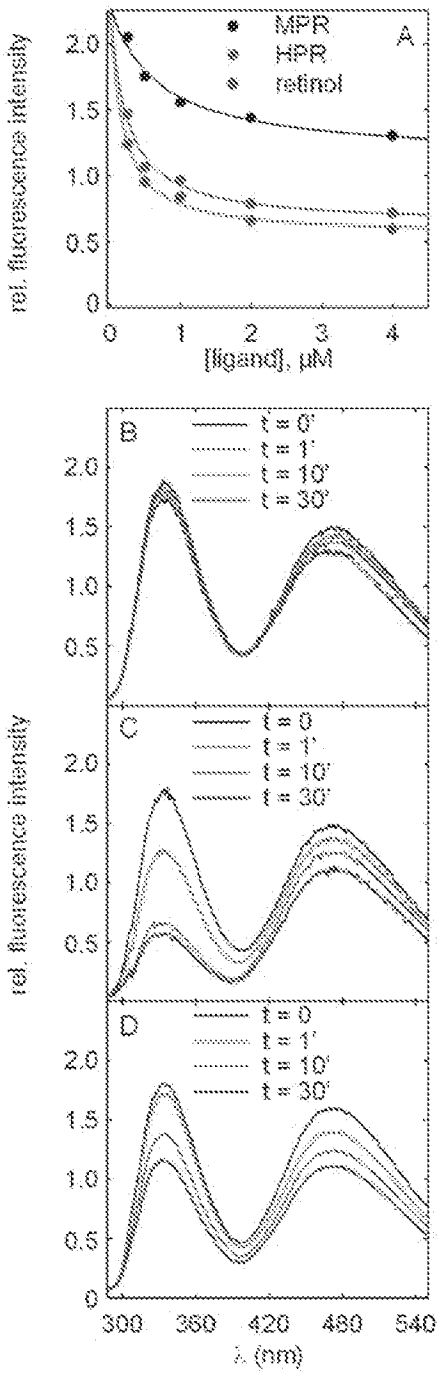


FIGURE 2. Binding of HPR, MPR, and retinol to RBP. (**A**) The binding affinity of HPR, MPR, and retinol for RBP (0.5 μM) was determined by measuring the extent of RBP fluorescence quenching (280 nm excitation) in the presence of increasing concentrations of the indicated ligands. Calculation of the dissociation constants (K_d) for binding to RBP revealed similar values for retinol and HPR (~30–60 nM). The affinity of MPR for RBP was approximately twofold lower (~100 nM). Displacement of retinol from RBP-retinol was examined during time-based analysis of protein and retinoid fluorescence quenching. (**B**) Fluorescence spectra from a solution of RBP-retinol (280 nm excitation). The 340-nm emission is due to RBP, and the 470-nm emission is due to retinol. (**C**) Effect of adding 1.0 μM HPR to 0.5 μM RBP-retinol. Time-dependent decreases in both protein and retinoid fluorescence indicate displacement of retinol from RBP-retinol by HPR. (**D**) Like HPR, MPR can also displace retinol from holo-RBP, albeit to a lesser extent than HPR.

and inset). Under identical chromatographic conditions, RBP-retinol (21 kDa) elutes at ~10 minutes and demonstrates absorbance maxima at 280 and 330 nm (Fig. 3B and inset). To demonstrate interaction between TTR and RBP-retinol, representative samples of the TTR and RBP-retinol solutions (Figs. 3A and 3B, respectively) were mixed and analyzed. The resulting chromatogram showed a marked decrease in the RBP-retinol absorbance peak, an increase in the TTR absorbance peak, and an additional absorbance band (at 330 nm) in the

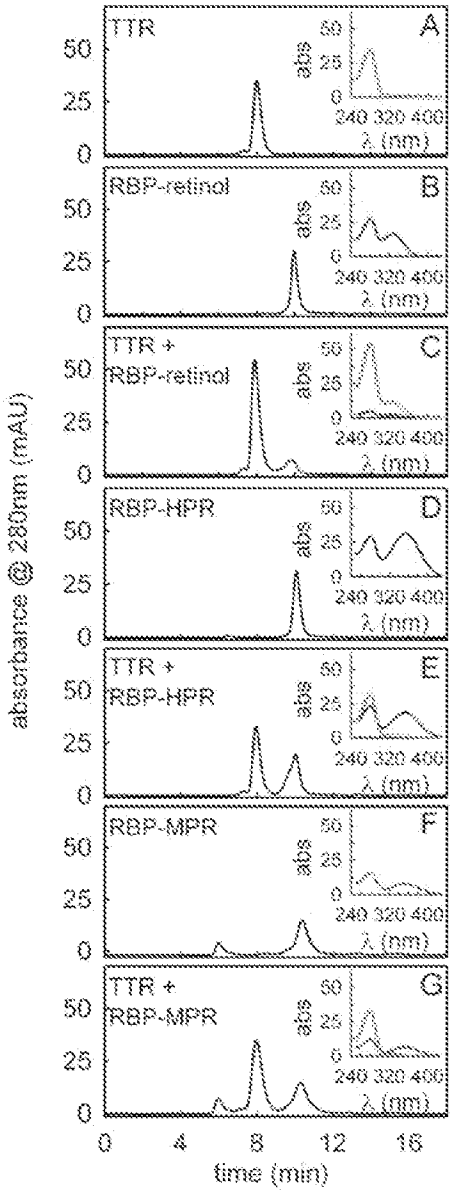


FIGURE 3. Interaction of RBP-ligand complexes with TTR. The ability of RBP-retinol, RBP-HPR, and RBP-MPR to bind with TTR was examined by size exclusion chromatography. Eluted peaks were detected by absorbance at 280 nm. Absorbance spectra (240–420 nm; *insets*) were obtained at the apex of each eluted peak: TTR (*dark red*), RBP-retinol (*blue*), RBP-HPR (*black*), and RBP-MPR (*green*). (**A**) Chromatographic and spectral properties of TTR; the indicated RBP-ligand complexes were analyzed before (**B**, **D**, **F**) and after (**C**, **E**, **G**) mixing with an equimolar amount of TTR. Interaction of RBP-retinol with TTR is readily observed as a decrease in the RBP-retinol absorbance, increase in the TTR absorbance, and the appearance of retinoid in the TTR spectra (*red*; **C**, *inset*). Mixtures of TTR + RBP-HPR (**E**) and TTR + RBP-MPR (**G**) showed no interaction, as evidenced by unchanged TTR absorbance and spectral properties.

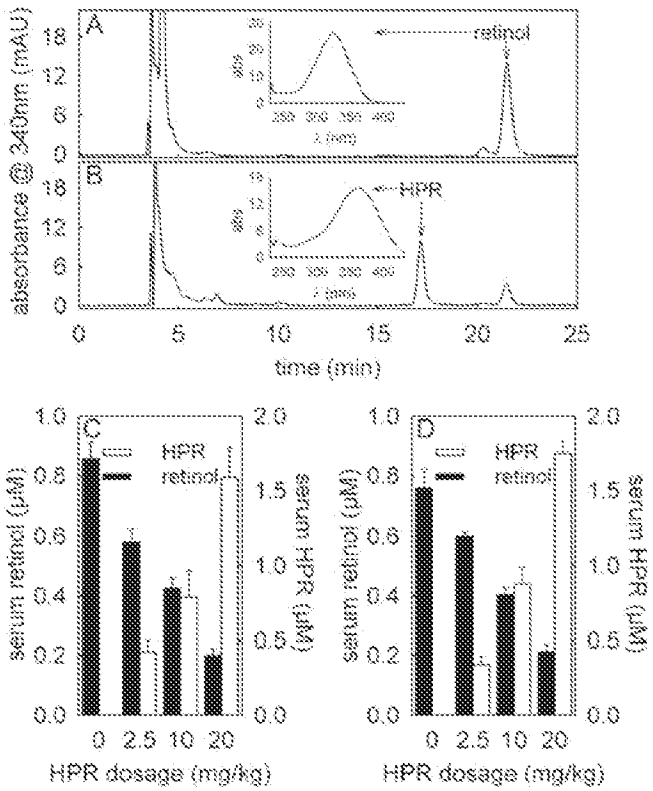


FIGURE 4. HPR-mediated reductions in serum retinol. Wild-type and *ABCA4*−/− mice were administered the indicated dose of HPR in DMSO (IP) daily for 28 days (n = 4 mice/dosage group). Spectra show HPLC identification of retinol and HPR from sera of wild-type mice treated with either DMSO (**A**) or 20 mg/kg HPR (**B**). Histograms show an HPR dose-dependent reduction in serum retinol in wild-type (**C**) and *ABCA4*−/− mice (**D**). Reductions in serum retinol correlated proportionally with reductions in RBP (not shown).

TTR absorbance spectrum (Fig. 3C and inset). These effects could only occur with the binding of RBP-retinol to TTR.

Notably, under the same experimental conditions, the RBP-HPR complex (Fig. 3D) showed no interaction with TTR (Fig. 3E). Similarly, the RBP-MPR complex did not interact with TTR (Figs. 3F and 3G). It should be noted that the lower binding affinity of MPR for RBP and its decreased water solubility (log P = 5.672) relative to HPR (log P = 4.956) contribute to aggregate formation. These MPR aggregates elute at ~6 minutes (Figs. 3F and 3G) and are well resolved from the TTR peak. Despite the relative loss of MPR due to aggregate formation, sufficient RBP-MPR was available for TTR binding; however, no binding was observed. Collectively, the data reveal that both HPR and MPR bind RBP with high affinity and generate complexes that do not associate with TTR.

HPR-Mediated Reductions in Serum Retinol

We examined the effects of HPR (2.5–20 mg/kg) on serum retinol by HPLC (Fig. 4). *ABCA4*−/− mice and age- and strain-matched wild-type mice were treated with the indicated dose of HPR in DMSO daily for 28 days. Chromatographic separation and spectral identification of retinol and HPR from sera of a representative wild-type mouse treated with either DMSO (Fig. 4A) or 20 mg/kg HPR (Fig. 4B) are shown. Quantitative analysis revealed a dose-dependent reduction in serum retinol for both wild-type (Fig. 4C) and *ABCA4*−/− mice (Fig. 4D). HPR doses of 2.5, 10, and 20 mg/kg reduced serum retinol by ~25%, 50%, and 75%, respectively. In all cases, reductions in serum retinol were associated with corresponding reductions in RBP as determined by an RIA specific for mouse RBP (not shown). All subsequent in vivo analyses were performed using the intermediate HPR dose (10 mg/kg) for at least 28 days in *ABCA4*−/− mice, unless otherwise indicated.

Effects of HPR on Visual Cycle Retinoids and Chromophore Regeneration

The profound HPR-induced reductions in serum retinol led us to explore the possibility that steady-state levels of visual cycle retinoids and/or visual chromophore biosynthesis might also be affected. To this end, we measured retinoid content in eyecups from light-adapted mice and chromophore regeneration in dark-adapted mice after a photobleach. The steady-state light-adapted retinoid levels in eyecup extracts are shown in Figure 5A. HPR produced a marked reduction (~50%) in each retinoid species examined and accumulated within the eye during the treatment period. It is noteworthy that the reduction of visual cycle retinoids in HPR-treated mice matched the reduction in serum retinol at this dose (Fig. 4D).

To determine whether HPR treatment caused alterations in visual chromophore (11*c*RAL) regeneration, we dark-adapted mice overnight and then monitored regeneration of 11*c*RAL and mobilization of bleached chromophore (*at*RAL) after a photobleach. Steady-state dark-adapted levels of 11*c*RAL were ~33% lower in HPR-treated compared to DMSO-treated mice; however, there were no significant differences in regeneration kinetics after a photobleach that bleached ~50% of the dark-adapted rhodopsin (Figs. 5B and 5C).

Retinal Physiology

We examined the effects of HPR treatment on retinal structure and function by electroretinography. Parameters derived from the fit of a rod model to the leading edge of the ERG *a*-wave did not reveal differences between DMSO- and HPR-treated mice (Figs. 5D and 5E, respectively) in either the structure or function of rod photoreceptors. Correspondingly, an analysis of the rod- and cone-mediated *b*-wave intensity-response functions (Figs. 5F and 5G, respectively) also revealed no differences, indicating that retinal cells downstream of photoreceptors that contribute to the ERG were functioning normally.

The only physiological manifestation of HPR treatment was observed during recovery from a photobleach. In this series of experiments, HPR-treated mice demonstrated a delay in return of the rod photoresponse to the dark-adapted baseline levels after a 30-second photobleach (Fig. 5H). This latter result is consistent with the biochemical data showing reduced retinoid and visual chromophore levels in the HPR-treated mice.

Effects of HPR on A2E and A2E Precursor Levels

We next examined the effect of HPR on accumulation of lipofuscin fluorophores (A2E, A2PE, and A2PE-H_2) in *ABCA4*−/− mouse eyecups. Analytes were separated by HPLC and measured by absorbance and fluorescence detection (Fig. 6). Representative chromatograms obtained from mice treated with either DMSO or HPR for 28 days are shown (Figs. 6A and 6B, respectively). Absorbance spectra for the indicated peaks are also provided (Fig. 6A, inset). The chromatographic tracings show that absorbance and fluorescence intensities of A2E, A2PE, and A2PE-H_2 track with each other and are dramatically reduced in the HPR-treated mouse. A2PE-H_2 is converted through an A2PE intermediate into A2E[8] and appears before the accumulation of A2E in *ABCA4*−/− mice (Mata NL et al., unpublished observation, 2005). For these reasons, we believe that A2PE-H_2 is a key A2E precursor. Accordingly, we monitored the accumulation rates of A2PE-H_2 and A2E as a function of time and HPR dose to better understand the effect of HPR on A2E biosynthesis.

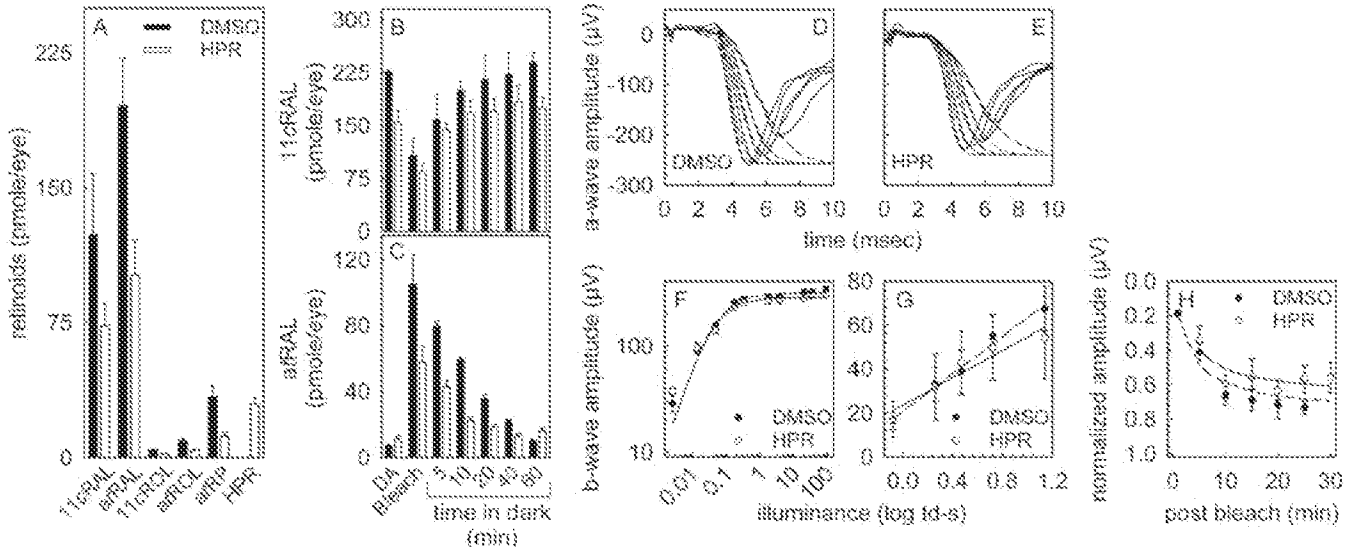


FIGURE 5. Effects of HPR on visual cycle retinoids, chromophore regeneration, and retinal physiology. Retinoid profiles were obtained for *ABCA4* −/− mice treated with either DMSO or HPR (10 mg/kg) daily for 28 days. (**A**) Steady state, light-adapted retinoid levels. HPR produced a profound reduction (~50%) in visual cycle retinoids and accumulated within the eye during the treatment period. (**B**) Chromophore levels in dark-adapted mice, and (**C**) regeneration kinetics after a photobleach (~1000 lux, 5 minutes). HPR treatment did not significantly affect the kinetics of chromophore regeneration (**B**) or mobilization of the bleached chromophore (**C**). Electroretinography was performed on *ABCA4* −/− mice treated with either DMSO or HPR (10 mg/kg) daily for 35 days. No differences were observed between DMSO- and HPR-treated mice in the parameters derived from an analysis of the rod ERG *a*-waves (**D**, **E**) or rod- and cone-mediated *b*-wave intensity-response functions (**F**, **G**). Analysis of the recovery of the rod photoresponse after photobleaching revealed a delay in return to prebleach baseline levels in HPR-treated mice (**H**).

We administered increasing doses of HPR in DMSO (2.5–20 mg/kg), or DMSO alone, to *ABCA4*−/− mice daily for 28 days. At the indicated times, representative mice were taken from each group for analysis. The data show significant time- and dose-dependent reductions in A2PE-H_2 (Figs. 6C, 6E, and 6G) and A2E (Figs. 6D, 6F, and 6H). Interestingly, HPR doses of 2.5,

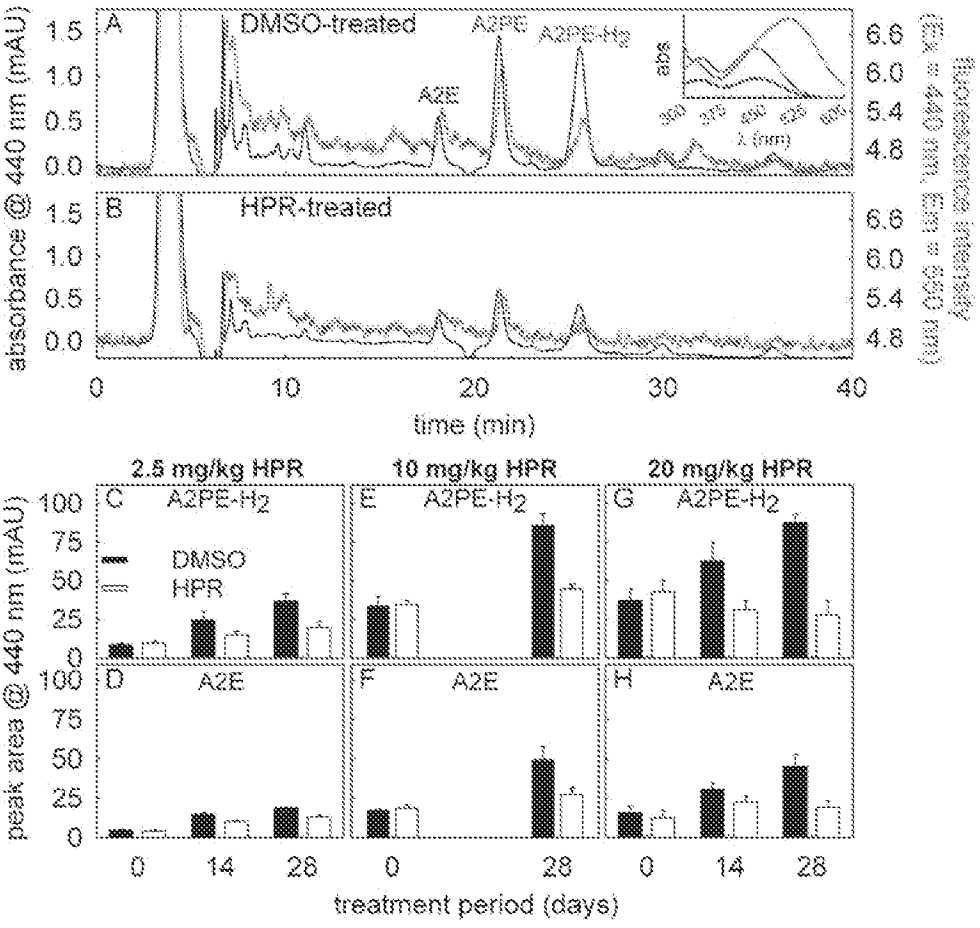


FIGURE 6. Effects of HPR on A2E and A2E precursor levels. A2E and A2E precursors (A2PE and A2PE-H_2) were extracted from eyecups of *ABCA4*−/− mice and analyzed by HPLC using absorbance and fluorescence detection. Spectra are representative chromatograms from mice treated with either DMSO (**A**) or HPR (10 mg/kg; **B**) daily for 28 days. The traces show absorbance at 440 nm (*black*) and the fluorescence intensity obtained using 440 ± 25 nm excitation and 550 ± 25 nm emission (*orange*). The identity of the indicated peaks (A2E, A2PE, and A2PE-H_2) was confirmed by acquiring the absorbance spectra at the peak apex. The chromatographic data show significantly reduced A2E and precursor fluorophores in the HPR-treated mouse. An analysis of A2PE-H_2 (**C**, **E**, **G**) and A2E (**D**, **F**, **H**) accumulation as a function of HPR dose and treatment time was also performed. Mice were administered DMSO or the indicated dose of HPR daily for 28 days (n = 16 mice/treatment group). At study onset, mice in the 2.5 mg/kg group were aged 1 month, mice in the other treatment groups were aged 2 months. Eyecup extracts (2 eyes/sample) were prepared from representative mice in each group (n = 4 mice/time point) and analyzed by HPLC. The raw data obtained from HPLC peak areas (**C**–**H**) reveal a dose- and time-dependent reduction of A2E and A2PE-H_2 in HPR-treated mice.

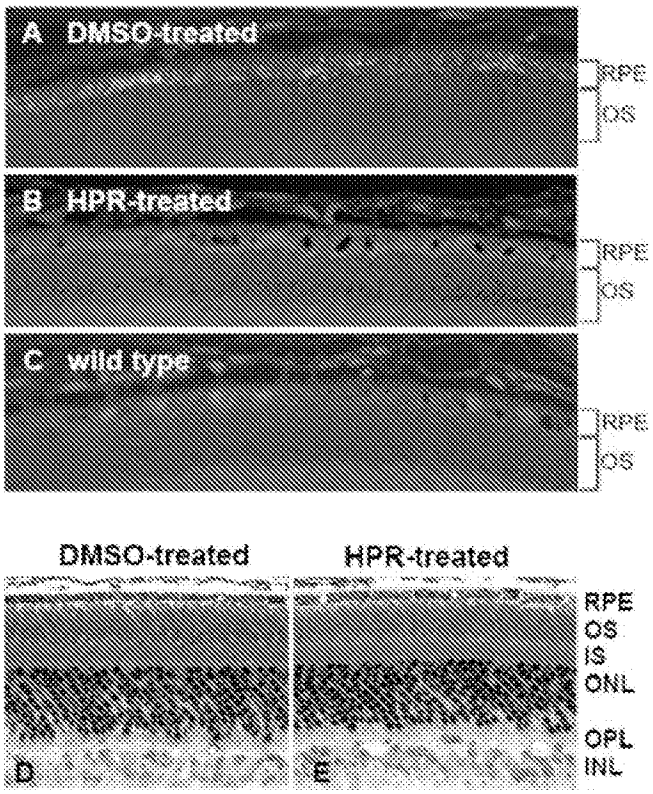


FIGURE 7. Microscopic analysis of lipofuscin autofluorescence and cytostructure of the retina. Tissue sections were prepared from the eyes of *ABCA4* −/− albino and pigmented mice that had been treated with either DMSO or HPR (10 mg/kg) for 42 days. Sections from albino mice were analyzed by fluorescence microscopy, while sections from pigmented mice were used for light microscopy. Analysis of lipofuscin autofluorescence revealed considerable accumulation within the RPE of DMSO-treated mice (**A**). In contrast, HPR-treated mice showed significantly reduced levels of lipofuscin fluorophores (**B**). Tissue sections prepared from an age- and strain-matched wild-type mouse are shown for comparison (**C**). Analysis of RPE and retina cytostructure by light microscopy revealed no aberrant morphology associated with either DMSO (**D**) or HPR treatment (**E**). INL, inner nuclear layer; IS, inner segment; ONL, outer nuclear layer; OPL, outer plexiform layer; OS, outer segment.

10, and 20 mg/kg, which reduced serum retinol by ~25%, 50% and 75%, produced reductions in A2E of 29%, 45% and 60%. Thus, the percent reduction in serum retinol at each dose was comparable to the percent reduction in A2E obtained at that dose. The same trend was observed for reduction of A2PE-H_2. It is apparent from these data that a direct effect of HPR on RBP, rather than inhibition of the visual cycle, is the principal mechanism of HPR action. These findings support therapeutic efficacy for HPR to reduce accumulation of lipofuscin fluorophores and illustrate the dependence of A2E biosynthesis on serum retinol levels.

Microscopic Analysis of Lipofuscin Autofluorescence and Retinal Cytostructure

In a final study, we used fluorescence and light microscopy to examine the eyes of *ABCA4*−/− mice treated with either DMSO or HPR for 42 days. The impetus for this study was to confirm data obtained from biochemical analyses of lipofuscin fluorophores and to examine the integrity of the retina and RPE after chronic HPR treatment. Analysis by fluorescence microscopy showed significant fluorophore accumulation within the RPE layer of DMSO-treated mice (Fig. 7A). In contrast, mice treated with HPR demonstrated significantly reduced fluorophore levels (Fig. 7B). A tissue section prepared from an untreated age- and strain-matched wild-type mouse is provided for comparison (Fig. 7C). These data are entirely consistent with the biochemical data, which show profound reductions of A2E-based fluorophores in HPR-treated *ABCA4*−/− mice.

Analysis of the retina and RPE cytostructure by light microscopy revealed no aberrant morphology associated with either DMSO or HPR treatment (Figs. 7D and 7E, respectively). Thus, despite the significant reduction in visual cycle retinoids, and the presence of HPR in the RPE, there is no evidence of retinotoxicity as a result of chronic HPR treatment.

DISCUSSION

HPR Mechanism of Action and Therapeutic Approach

We previously established that direct inhibition with isotretinoin (*Accutane*) of 11-*cis*-retinol dehydrogenase, which catalyzes the final enzymatic step in the visual cycle, reduces A2E and lipofuscin accumulation in the *ABCA4*−/− mouse.[40,41] Isotretinoin acts here to slow the synthesis of visual chromophore and thus to lower levels of *at*RAL, which is the primary reactant in A2E biosynthesis. However, since isotretinoin acts as a competitive inhibitor, high intracellular drug concentrations are required to achieve efficacy. The doses used in our previous study on mice (20–40 mg/kg per d)[40,41] were far higher than doses used for treating acne in humans (0.5–2.0 mg/kg per d). Treatment of macular degeneration patients with isotretinoin at the high doses used in mice would result in unacceptable systemic toxicity. Nevertheless, these studies were useful in establishing a therapeutic approach based on modulation of intracellular retinoid concentrations.

Our investigation of alternative therapies led to HPR, a retinoic acid analog, which has been widely used over the past 20 years as a chemopreventive agent in numerous phase II and phase III cancer trials. These trials were multicenter investigations enrolling thousands of patients (aged 35–70 years) for periods up to 5 years.[24–27] HPR was administered in doses of 200 to 800 mg/d (~2.5–10 mg/kg per d) and was deemed to be safe and well tolerated. Clinically, investigators noted reductions in serum retinol, RBP, and delayed dark adaptation.[27] Subsequent investigations showed a high correlation between HPR-induced reductions in serum RBP-retinol levels and manifestation of delayed dark adaptation.[42,43]

In the present study, we performed a comprehensive analysis of the HPR mechanism of action and its capacity to reduce the accumulation of A2E-based lipofuscin fluorophores. Our investigation showed that HPR, and its primary metabolite, MPR, bind apo-RBP in a concentration-dependent manner and efficiently displace retinol from native holo-RBP under physiological conditions. Our data further showed that, unlike RBP-retinol, RBP-HPR and RBP-MPR do not associate with native TTR. These effects explain the reduction in retinol and RBP observed in clinical trials. Notably, we also found that HPR-mediated reductions in serum retinol led to proportionate reductions in toxic A2E-fluorophores. HPR doses as low as 2.5 mg/kg produced significant reductions in A2E (~30%) and precursor compounds (~50%). Finally, electrophysiologic and histologic analyses showed no deleterious functional or morphologic effects in the retina of chronic HPR treatment.

Relation between Lipofuscin Autofluorescence and Retinal Disease

Excessive accumulation of lipofuscin fluorophores in the RPE is observed in several degenerative retinal diseases (e.g., STGD1, CRD, RP, and AMD). Although the biochemical etiologies underlying these diseases are diverse, a growing body of

clinical evidence suggests that lipofuscin fluorophores contribute directly to the pathogenesis of these diseases. For example, in patients with early AMD, increased FAF is associated with reduced light sensitivity before significant retinal degeneration.[44] These fluorescent changes likely represent an early manifestation of the disease process. In addition, recent studies have established that FAF precedes the death of RPE and photoreceptor cells in STGD1 and AMD.[13–17]

Relationship between A2E and Lipofuscin Autofluorescence

Is the FAF observed in STGD and AMD patients due to A2E and related *bis*-retinoid compounds? A2E accumulates in the RPE during normal aging,[7] in STGD1 patients,[8] and in several animal models of macular degeneration.[9–12] Analysis of postmortem STGD and AMD eyes for A2E and related molecules has never been reported. However, striking similarities have been observed in the fluorescence spectra of ocular tissues from STGD and AMD patients compared to spectra from cellular structures that are known to contain A2E. For example: A2E and A2E-like compounds are the dominant fluorophores in human lipofuscin granules;[16] RPE tissue from AMD-affected eyes contains fluorophores very similar to fluorophores present in lipofuscin granules[45] and in the RPE of *ABCA4*-null mice (Mata NL, unpublished observation, 2005); and the spectral properties of the long wavelength-emitting fluorophore in human fundi are similar to the spectral properties of the A2E precursor, A2PE-H_2.[46,47]

It is well established that the genesis of ocular lipofuscin fluorophores is dependent on the presence of retinol and/or retinaldehyde (e.g., *at*RAL).[8,10,21–23] In a recent study, a protease inhibitor was used to induce lipofuscin accumulation in the RPE of *Rpe*65-null mutant mice, which cannot generate 11*c*- or *at*RAL. While lipofuscin debris was observed to accumulate, there were no fluorescent species present within the debris.[48] Thus, retinaldehyde per se appears to be the requisite substrate for the formation of all lipofuscin fluorophores. It follows that therapies directed at reducing retinaldehyde content are likely to have a benefical effect on all diseases characterized by accumulation of lipofuscin fluorophores. The fact that the percent reduction of retinaldehyde in the eyes of HPR-treated *ABCA4*−/− mice (51%) was nearly identical with the percent reduction of ocular fluorophores (~50%) further supports this contention.

A final consideration is the potential for HPR to induce or inhibit mixed function oxidase systems (e.g., cytochromes) during chronic treatment. Involvement of cytochrome P_{450}, for example, would likely alter the pharmacokinetics of HPR and its metabolites (e.g., MPR) and therefore affect the therapeutic response. It has been shown that a 3-day pretreatment of mice with HPR (10 mg/kg) has no effect on the disposition or metabolism of HPR administered in subsequent doses or on hepatic levels of cytochrome P_{450} or b_5.[49] Thus, cytochrome induction is not likely to be an issue for the direct inverse relation between HPR and serum retinol observed in the present study. Moreover, pharmacokinetic data obtained from human subjects participating in a 5-year study of HPR efficacy for the treatment of breast cancer have revealed constant drug plasma levels and constant retinol level reduction throughout the treatment period.[24,25] In these studies, HPR and MPR levels demonstrated a direct dose–response relationship with HPR intake, and the $t_{1/2}$s of HPR and MPR did not change siginificantly over the treatment period.[25] While these data are promising for long-term treatment of lipofuscin-based retinal disease in patients in the 30- to 60-year age group, a reevaluation of HPR pharmacokinetics will be necessary for future clinical trials involving a predominantly elderly population.

Acknowledgments

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EXHIBIT C

INTERNATIONAL UNION OF
PURE AND APPLIED CHEMISTRY
AND
INTERNATIONAL UNION OF BIOCHEMISTRY

NOMENCLATURE OF CAROTENOIDS

(RULES APPROVED 1974)

Issued by the
IUPAC Commission on the Nomenclature of Organic Chemistry
and the
IUPAC–IUB Commission on Biochemical Nomenclature

LONDON
BUTTERWORTHS

NOMENCLATURE OF CAROTENOIDS

(RULES APPROVED 1974)

Issued by the
IUPAC Commission on Nomenclature of Organic Chemistry
and the
IUPAC–IUB Commission on Biochemical Nomenclature

INTRODUCTION

Definitive Rules for the Nomenclature of Carotenoids were approved at the IUPAC 14th Conference (London, 1947; *Comptes Rendus*, pp 142–143) and the 16th Conference (New York, 1951; *Comptes Rendus*, p 110). Many recent developments in the carotenoid field have resulted in situations that are not covered adequately by the existing rules; since these rules were adopted, the number of known naturally occurring carotenoids has increased from some 80 to about 300. In 1965, the IUPAC Commission on Nomenclature of Organic Chemistry (CNOC) and the IUPAC–IUB Commission on Biochemical Nomenclature (CBN) approved the formation of a subcommittee to revise the carotenoid rules. The subcommittee consisted of Professor W. Klyne (representative of CBN; and Chairman), Professor S. Veibel (representative of CNOC), Professor C. Bodea, Professor T. W. Goodwin, Dr F. Haxo, Dr O. Isler, Dr S. Liaaen-Jensen, Dr W. Powell, Dr W. Quackenbush, Professor N. A. Sørensen, and Professor B. C. L. Weedon.

The subcommittee met in Trondheim in 1966 and considered a number of approaches to the naming of carotenoids. Subsequently the set of proposals selected by the Trondheim subcommittee was refined by an *ad hoc* 'working party' (S. Liaaen-Jensen, B. C. L. Weedon, W. Klyne and L. C. Cross) to give a set of tentative rules for the nomenclature of this group of naturally occurring chemical compounds that was in accord with both the general traditions of biochemical usage and principles of organic chemical nomenclature[1].

These rules are now issued in revised form[1] jointly by the IUPAC Commission on Nomenclature of Organic Chemistry[2] and the IUPAC–IUB

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[1] Tentative Nomenclature Appendix No. 19 (February 1972) to IUPAC *Information Bulletin.* The revised rules shall be known as the IUPAC–IUB 1974 Recommendations.

[2] Those who have served on the Commission on the Nomenclature of Organic Chemistry for varying periods during 1967–1973 are the following (present members are shown by an asterisk): P. E. Verkade (Chairman to 1971), N. Lozac'h* (Chairman from 1971), K. Bláha*, L. C. Cross*, G. M. Dyson, H. Grünewald*, S. P. Klesney*, W. Klyne, K. L. Loening*, H. S. Nutting, J. Rigaudy*, Associate members: R. S. Cahn, K. Hirayama*, S. Veibel*. Observer: K. A. Jensen.

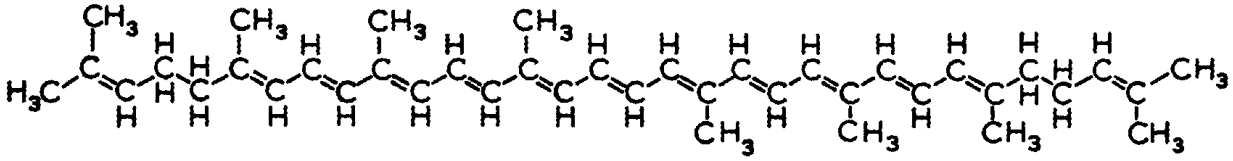
Commission on Biochemical Nomenclature[3]. Comments should be sent to one or other of the Commission Chairmen or Secretaries[4].

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Rule Carotenoid 1. Class of compound

Carotenoids are a class of hydrocarbons (carotenes) and their oxygenated derivatives (xanthophylls) consisting of eight isoprenoid units joined in such a manner that the arrangement of isoprenoid units is reversed at the centre of the molecule so that the two central methyl groups are in a 1,6-positional relationship and the remaining nonterminal methyl groups are in a 1,5-positional relationship. All carotenoids may be formally derived from the acyclic $C_{40}H_{56}$ structure (I below), having a long central chain of conjugated double bonds, by (i) hydrogenation, (ii) dehydrogenation, (iii) cyclization, or (iv) oxidation, or any combination of these processes.



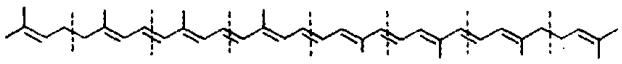
(I)

[3] Those who have served on the Commission on Biochemical Nomenclature for varying periods during 1967–1973 are the following (present members are shown by an asterisk): O. Hoffmann-Ostenhof (Chairman), A. E. Braunstein*, W. E. Cohn*, J. S. Fruton, B. L. Horecker*, P. Karlson*, B. Keil*, W. Klyne*, C. Liébecq*, E. C. Slater, E. C. Webb*, W. J. Whelan. Observer: S. Veibel*.

[4] Chairman (CNOC): Professor N. Lozac'h, Ecole nationale supérieure de Chimie, 5 Avenue d'Edimbourg, 14032 Caen Cedex, France; Secretary: S. P. Klesney, Central Report Index, 566 Building, The Dow Chemical Company, Midland, Michigan 48640, U.S.A. Chairman (CBN): Professor O. Hoffmann-Ostenhof, Institut für allgemeine Biochemie der Universität Wien, Währingerstrasse 38, A1090 Vienna, Austria; Secretary: Dr. Waldo E. Cohn, Oak Ridge National Laboratory, Post Office Box Y, Oak Ridge, Tennessee 37830, U.S.A.

This class also includes certain compounds that arise from certain rearrangements of the carbon skeleton (I), or by the (formal) removal of part of this structure.

For convenience carotenoid formulae are often written in a shorthand form as

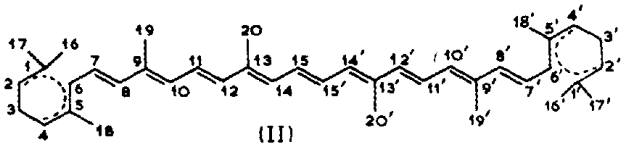


(IA)

(General formula ; broken lines indicate formal division into isoprenoid units).

Rule Carotenoid 2. The stem name

All specific names are based on the stem name 'carotene', which corresponds to the structure and numbering shown in II, where the broken lines at the two terminations are intended only to represent two 'double-bond equivalents'. Individual compounds may have C_9 acyclic end groups with two double bonds at positions 1,2 and 5,6 (e.g., III) or cyclic end groups (such as IV, V, VI, VII, VIII and IX).



(II)

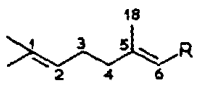
Rule Carotenoid 3. Specific names; End-group designations

3.1. The name of a specific carotenoid hydrocarbon is constructed by adding two Greek letters as prefixes to the stem name 'carotene' (defined in Rule Carotenoid 2), these prefixes being characteristic of the two C_9 end groups.

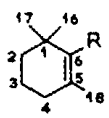
3.2. The prefixes are

Type	Prefix	Formula	Structure
Acyclic	ψ	C_9H_{15}	III
Cyclohexene	β, ε	C_9H_{15}	IV, V
Methylenecyclohexane	γ	C_9H_{15}	VI
Cyclopentane	κ	C_9H_{17}	VII
Aryl	φ, χ	C_9H_{11}	VIII, IX

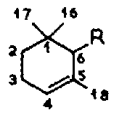
and correspond to the following end-group modifications



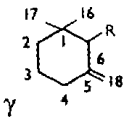
III; ψ



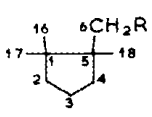
IV; β



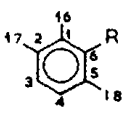
V; ε



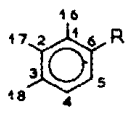
VI; γ



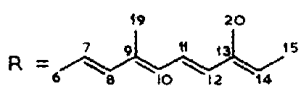
VII; κ



VIII; φ



IX; χ

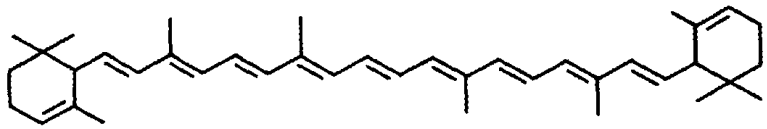


Note: The choice of locants 16 and 17 for the two methyl groups at C-1 is considered in connection with stereochemistry in Rule Carotenoid 12.4.

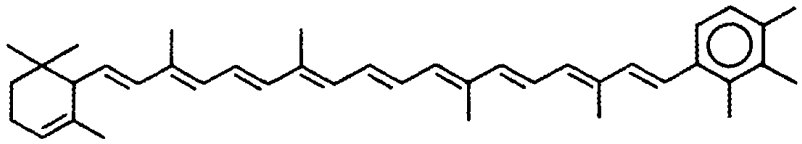
3.3. The Greek-letter prefixes are cited in alphabetical order; the first is separated from the second by a comma, and the second is connected to the stem name by a hyphen.

Note: The Greek-letter alphabetical order is β (beta), γ (gamma), ε (epsilon), κ (kappa), φ (phi), χ (chi), ψ (psi).

Examples:



ε,ε-Carotene



ε,χ-Carotene

Notes: (i) The Greek-letter prefixes are derived: β and ε from the symmetrical carotenoids with the trivial names 'β-carotene' and 'ε-carotene', κ from the symmetrical capsorubin, γ and ψ from γ- and ψ-ionone, φ for phenyl, and χ, the next Greek letter after φ. (ii) α and δ, from the trivial names α- and δ-carotene, are not used.

3.4. When, in a modified or degraded carotenoid, an end group can be derived from more than one specific end group, the end group chosen as the basis of the name is that occurring earliest in the alphabetical order (see Rule Carotenoid 3.3).

Example:



is a derivative of the β end group, not the ε end group.

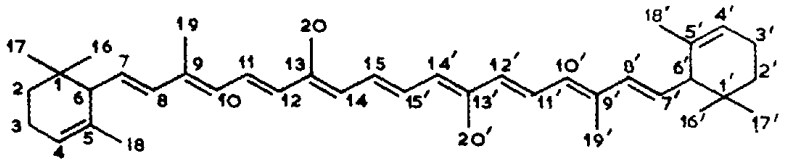
Rule Carotenoid 4. Numbering of carotenoid hydrocarbons

The basic system of numbering is that shown in structure II of Rule Carotenoid 2; the end groups are numbered as indicated in Rule Carotenoid 3. If the two end groups are dissimilar, lower (unprimed) numbers are given to that end of the molecule which is associated with the Greek-letter prefix cited first in the name. (All unprimed locants are cited before primed locants[5].)

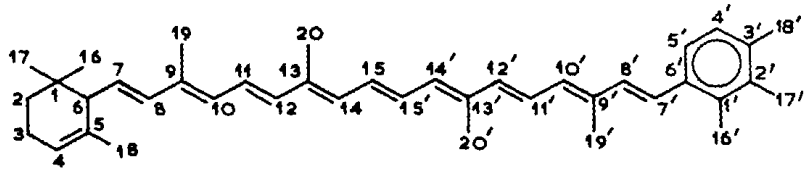
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[5] IUPAC Nomenclature of Organic Chemistry (*Pure Appl. Chem.* **11**, Nos. 1 and 2 (1965); Sections A, B and C published by Butterworths, London, 1971) indicates that, in ranking locants for priority, a primed numeral ranks immediately after the same numeral unprimed. In general organic nomenclature the common practice is therefore to cite locants in the order $x,x',(x+n),(x+n)'$. The established sequence in the carotenoid field is, however, to cite all unprimed numerals before any primed numerals, and this practice is followed in these rules.

Examples:



ε,ε-Carotene



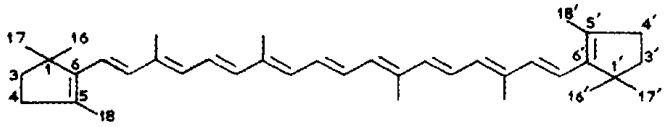
ε,χ-Carotene

Note: It is recommended that formulae be drawn so that unprimed numbers are on the left-hand side.

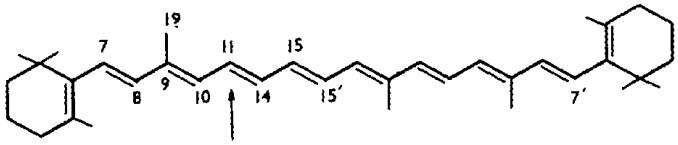
Rule Carotenoid 5. Nor carotenoids and seco carotenoids

5.1. *Nor Carotenoids*

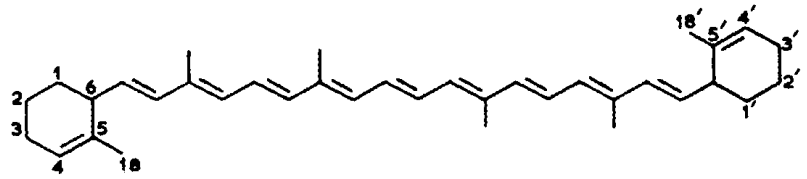
Elimination of a CH_3, CH_2, or CH group from a carotenoid is indicated by the prefix "nor", which in all cases is preceded by the locant of the carbon atom that has been eliminated. The prefix is nondetachable. When alternatives are possible, the locant attached to nor is the lowest possible[6]. The basic numbering of the carotenoid is retained in the nor carotenoid.
Examples:



2,2'-Dinor-β,β-carotene



(12,13,20 formally 'removed' at this point)
12,13,20-Trinor-β,β-carotene



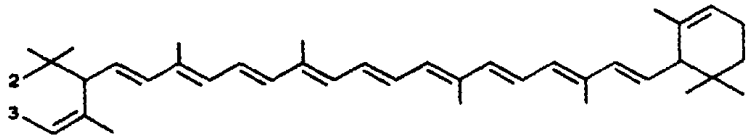
16.17.16',17'-Tetranor-ε,ε-carotene

[6] The contrast with steroid usage [IUPAC–IUB 1971 Definitive Rules for Steroid Nomenclature, *Pure Appl. Chem.* **31**, Nos. 1–2 (1972)] Rule 2S-6, where the prefix 'nor' is associated with the highest permissible number, is to be noted.

5.2. *Seco Carotenoids*

Fission of the bond between two adjacent carbon atoms (other than carbon atoms 1 and 6 of a cyclic end group) with addition of one or more hydrogen atoms at each terminal group thus created, is indicated by the prefix "seco," the original carotenoid numbering being retained.

Example:



2,3-Seco-ε,ε-carotene

Rule Carotenoid 6. Changes in hydrogenation level

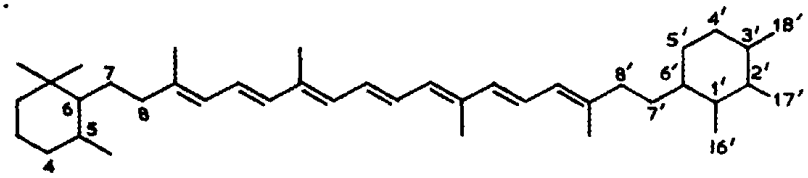
Carotenoid hydrocarbons, including carotenoid acetylenes and allenes, that differ in hydrogenation level from the corresponding carotenoid hydrocarbon defined by Rule Carotenoid 3, are named from the latter by use of the prefixes "hydro" and "dehydro" together with the locants specifying the carbon atoms at which hydrogen atoms have been added or removed.

These prefixes are nondetachable[7] and immediately precede the Greek-letter prefixes denoting the end groups, and, if both occur in one name, are cited in the order: dehydro *before* hydro (multipliers do not affect the order).

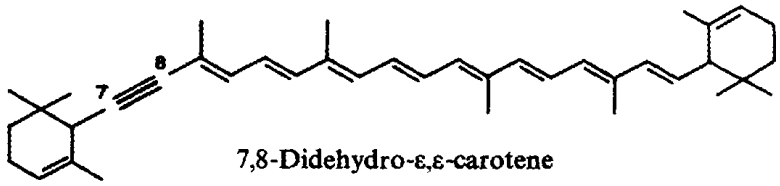
Example: tetradehydrodihydro

Note: Since, to maintain valency requirements, hydrogen atoms are, formally, always added or removed in pairs these prefixes will always be used with an even-number multiplier, e.g. tetrahydro, didehydro.

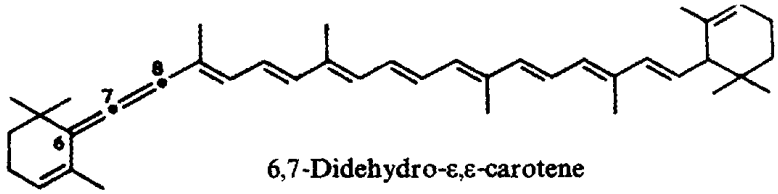
Examples:



5,6,7,8,1',2',3',4',5',6',7',8'-Dodecahydro-β,χ-carotene



7,8-Didehydro-ε,ε-carotene



6,7-Didehydro-ε,ε-carotene

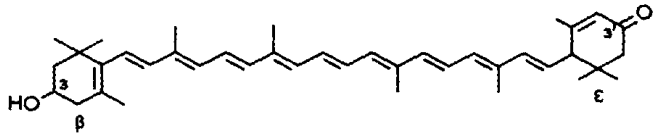
[7] IUPAC Nomenclature of Organic Chemistry (reference in footnote 5), Rule C-16.1. allows the prefix 'hydro' to be detachable or nondetachable and the former has become the established usage in general organic chemistry. However, the common practice in carotenoid names is now to use this prefix as nondetachable, a practice that is followed in this set of rules.

Rule Carotenoid 7. Oxygenated derivatives

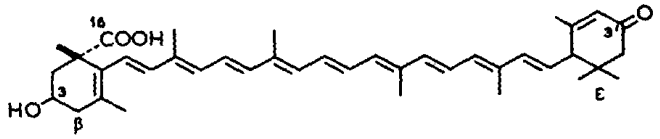
7.1. Oxygenated (and other) derivatives of carotenoid hydrocarbons are named by use of suffixes and prefixes according to the rules of general organic chemical nomenclature[8].

Of the oxygen-containing characteristic groups present, that occurring earliest in the sequence carboxylic acid, ester of carotenoid acid, aldehyde, ketone, alcohol, ester of carotenoid alcohol, is chosen as principal group (following IUPAC Rule C-10.3) and is cited by use of a suffix; all other groups are cited as prefixes.

Examples:

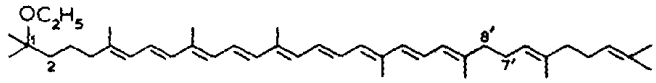


3-Hydroxy-β,ε-caroten-3′-one



3-Hydroxy-3′-oxo-β,ε-caroten-16-oic acid

7.2. A nonbridging ether group is named by use of the appropriate alkoxy or aryloxy prefix (Rule C-211.2).

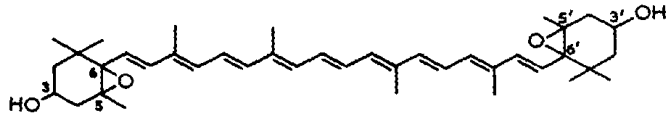


1-Ethoxy-1,2,7′,8′-tetrahydro-ψ,ψ-carotene

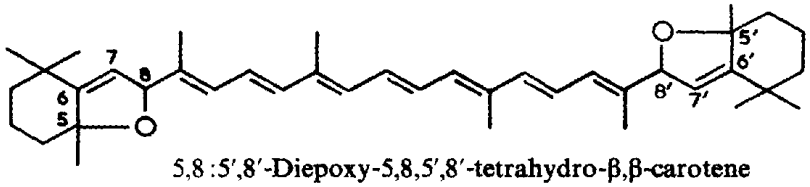
7.3. Oxygen bridges are indicated by use of the prefix 'epoxy'; this prefix is preceded by the locants of the two carbon atoms that form the bridgeheads of the oxygen bridge.

Note: The prefix 'epoxy' denotes replacement, by an oxygen bridge, of a hydrogen atom at each of two carbon atoms already otherwise connected to one another. An epoxide, notionally formed by adding an oxygen atom to a double bond, is therefore an epoxydihydro derivative of the original compound.

Examples:



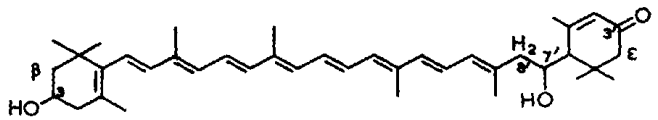
5,6:5′,6′-Diepoxy-5,6,5′,6′-tetrahydro-β,β-carotene-3,3′-diol



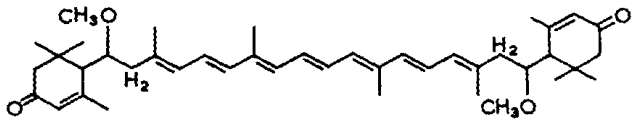
5,8:5′,8′-Diepoxy-5,8,5′,8′-tetrahydro-β,β-carotene

[8] IUPAC Rules, Nomenclature of Organic Chemistry (reference in footnote 5), Subsections C-2 to C-4.

7.4. Compounds that may be formally derived from a carotenoid hydrocarbon by the addition of the elements of water (H, OH) or of methanol (H, OCH_3) to a double bond are named as 'hydroxydihydro' or 'methoxydihydro' derivatives.
Examples:



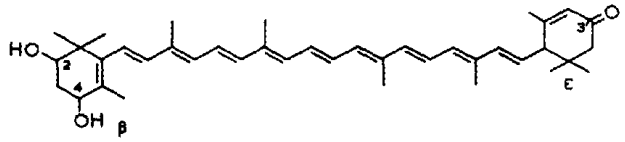
3,7′-Dihydroxy-7′,8′-dihydro-β,ε-caroten-3′-one



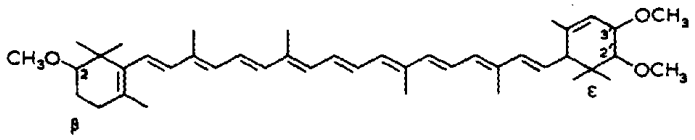
7,7′-Dimethoxy-7,8,7′,8′-tetrahydro-ε,ε-carotene-3,3′-dione

Rule Carotenoid 8. Numbering of oxygenated derivatives

8.1. If the two C_9 end groups of the parent carotenoid hydrocarbon are dissimilar, their oxygenated derivatives are numbered according to Rule Carotenoid 4, i.e. the end group designated by the Greek letter occurring earlier in the Greek alphabet receives unprimed locants.
Examples:



2,4-Dihydroxy-β,ε-caroten-3′-one



2,2′,3′-Trimethoxy-β,ε-carotene

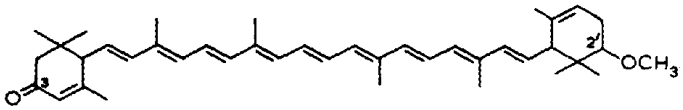
8.2. (a) If the two C_9 end groups of the parent carotenoid hydrocarbon are identical, then the lowest* locant possible is assigned to the principal group, cited as suffix.

(b) If more than one of the group chosen to be cited as suffix is present, the numbering is determined by the principle of lowest locants** applied to the suffixes.

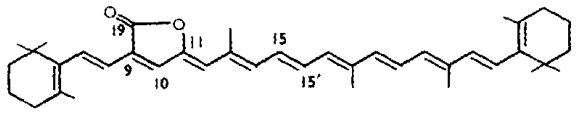
(c) If no group qualifies to be cited as suffix, then the numbering is determined by the principle of lowest locants* for all groups cited as prefixes.

Examples:

(a)



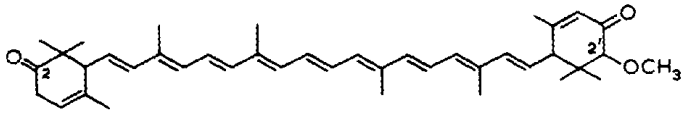
2′-Methoxy-ε,ε-caroten-3-one (not 2-Methoxy-ε,ε-caroten-3′-one)



β,β-Caroten-19,11-olide

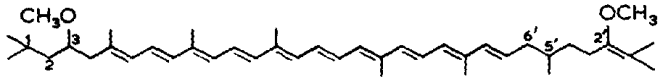
(The position of the lactone group is indicated following the principles of Rule C-472.2)

(b)



2′-Methoxy-ε,ε-carotene-2,3′-dione [not 2-Methoxy-ε,ε-carotene-3,2′-dione; see para (b)]

(c)



3,2′-Dimethoxy-1,2,5′,6′-tetrahydro-ψ,ψ-carotene [not 2,3′-Dimethoxy-1′,2′,5,6-tetrahydro-ψ,ψ-carotene, 1,2,3,2′, 5′, 6′ having priority over 2,5,6,1′,2′,3′; see para (c)]

Notes: * In the carotenoid series *all* unprimed numbers are cited *before* primed numbers and the former are therefore considered as 'lower than' primed numbers, e.g. 2,6,6,1′,2′,6′, etc. ** When series of locants containing the same number of terms are compared term by term, that series is 'lowest' that contains the lowest number on the occasion of the first difference [IUPAC Rule C-13.11(e), footnote].

Rule Carotenoid 9. *retro* Nomenclature

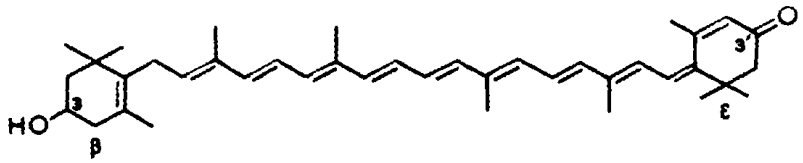
9.1. The prefix '*retro*' (printed in italics) and a pair of locants are used to indicate a shift, by one position, of *all* single and double bonds of the conjugated polyene system delineated by the pair of locants.

9.2. The pair of locants precedes the prefix *retro*. The first locant is that of the carbon atom that has lost a proton, the second that of the carbon atom that has gained one.

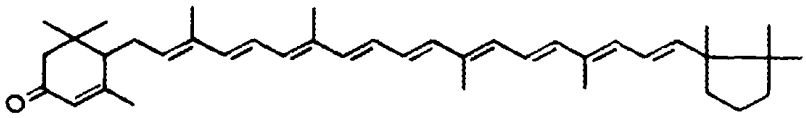
9.3. The prefix and its accompanying locants are placed immediately before, and hyphenated to, the Greek-letter prefixes of the name defined according to Rule Carotenoid 3.

9.4. The prefix and its associated locants are not detachable from the names defined according to Rule Carotenoid 3.

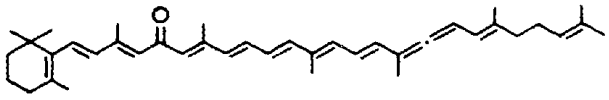
Examples:



3-Hydroxy-6',7-*retro*-β,ε-caroten-3'-one



6',7-*retro*-ε,κ-Caroten-3-one



8',11-*retro*-β,ψ-Caroten-11-one

Rule Carotenoid 10. Apo nomenclature

It is often necessary to designate derivatives in which the carbon skeleton has been shortened by the formal removal of fragments from one or both ends of a carotenoid.

10.1. The unitalicized prefix 'apo', preceded by a locant, is used to indicate that all of the molecule beyond the carbon atom corresponding to that locant has been replaced by hydrogen atoms. A side-chain methyl group is not considered to be 'beyond' the carbon atom to which it is attached.

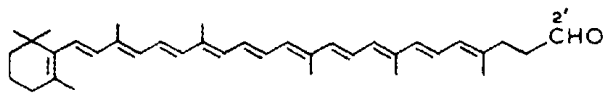
10.2. The prefix and its locant immediately precede the specific name (Rule Carotenoid 3) unless the locant associated with the prefix 'apo' is greater than 5, in which case there is no need to give a Greek-letter end-group designation for that end of the molecule.

10.3. For purposes of numbering, etc., an end that has been shortened by 5 or less skeletal carbon atoms is considered a ψ (acyclic) end group.

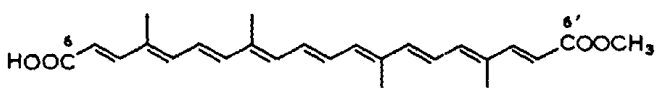
10.4. The prefix diapo, preceded by two locants, is used to indicate removal of fragments from both ends of the molecule.

10.5. If, in a diapo compound, the two ends of the carotenoid skeleton have been shortened unequally, the lower locant associated with the prefix 'diapo' is unprimed.

Examples:



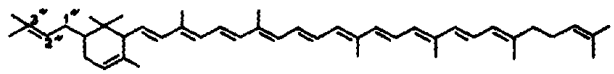
2'-Apo-β,ψ-caroten-2'-al



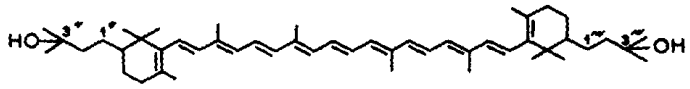
Methyl hydrogen 6,6'-diapocarotene-6,6'-dioate (*trans*-Bixin)

Rule Carotenoid 11. Higher carotenoids

The higher carotenoids are a class of hydrocarbons and their oxygenated derivatives consisting of *more than* eight isoprenoid units joined in a manner similar to that of the C_{40} carotenoids. They are named as mono- or disubstituted C_{40} carotenoids. The numbering of the normal carotenoid is retained. Examples:



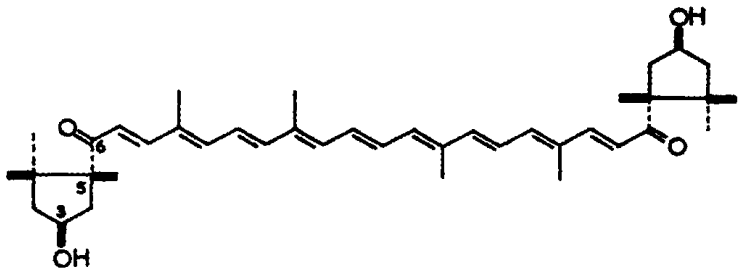
2-(3-Methyl-2-butenyl)-ε,ψ-carotene



2,2′-Bis(3-hydroxy-3-methylbutyl)-β,β-carotene
or
2,2′-Bis(3-methylbutyl)-β,β-carotene-3″,3‴-diol

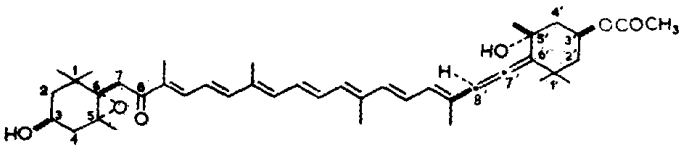
Rule Carotenoid 12. Stereochemistry

12.1. *Absolute Configuration at Chiral Centers.* The absolute configuration at chiral centers is designated by use of the *RS* convention[9], the symbols being placed, with the corresponding locants, before the carotenoid name. Example:



(3*S*,5*R*,3′*S*,5′*R*)-3,3′-Dihydroxy-κ,κ-carotene-6,6′-dione (Capsorubin)

12.2. *Absolute Configuration of Allenic Compounds.* The absolute configuration around allene groups will be similarly designated, when known.

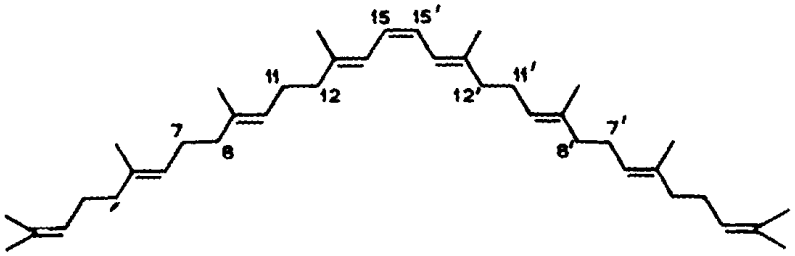


(3′*S*,5′*R*,6′*R*)-3′-Acetoxy-5,6-epoxy-3,5′-dihydroxy-6′,7′-didehydro-5,6,7,8,5′,6′-hexahydro-β,β-caroten-8-one (Fucoxanthin)

12.3. *Geometrical Configuration around Double Bonds.* The stem name 'carotene' implies *trans* configuration about all double bonds unless the contrary is indicated. Following the designation of absolute configuration

[9] For a discussion on the *RS* convention and the use of thickened lines, broken lines, wavy lines, and wedges in displayed formulae, see IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E, Fundamental Stereochemistry, IUPAC *Information Bulletin No. 35*, p 68.

(if any), geometrical configuration is indicated by citing the double bond or bonds with a *cis* configuration.
Example:



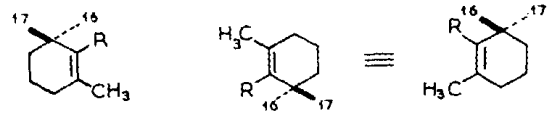
Natural phytoene = 15-*cis*-7,8,11,12,7',8',11',12'-octahydro-ψ,ψ-carotene

At trisubstituted double bonds, the term *cis* refers to the relative position of the two substituents forming parts of the main chain of carbon atoms.
Example: natural bixin = methyl hydrogen 9'-*cis*-6,6'-diapocarotene-6, 6'-dioate.

In the absence of definite information on geometrical configuration, *cis* isomers may be distinguished by prefixes such as neo A, neo U, etc. (cf. Zechmeister, "Cis–Trans Isomeric Carotenoids, Vitamins A and Aryl-polyenes," Springer-Verlag, Vienna, 1962).

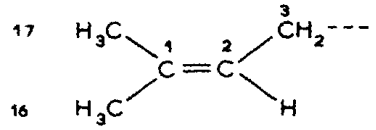
The stereochemical prefixes *E* and *Z* (see footnote to Rule Carotenoid 12.1 and *J. Amer. Chem. Soc.* **90**, 509 (1968)) may be used, especially when the prefixes *cis* and *trans* might lead to ambiguity.

12.4. *Numbering of gem-Dimethyl Groups at* C-1. In an end group of β, γ, κ or ε type, the two methyl groups attached to C-1 are distinguished as follows: when the potential chirality is as shown in formula A, i.e. with the polyene chain (R) to the right of C-1, the methyl groups *below* and *above* the plane of the paper are numbered 16 and 17, respectively; if, with the polyene chain (R) to the left, the end group is as shown in B^1, then these designations are unaltered; if the end group is as shown in B^2, then they are reversed.



(A) (B¹) (B²)

In an acyclic end group, the methyl group that is *trans* to the main skeletal chain is numbered 16 and the methyl group that is *cis* is numbered 17, as shown in C.



(C)

Rule Carotenoid 13. Trivial names

The preceding rules are designed to define precisely the structure of a given carotenoid by its name. Use of the semisystematic names derived from these rules will greatly assist communication between scientists and enable work to be more readily retrieved from the literature.

The appendix contains a list of some trivial names currently in use for naturally occurring carotenoids; it also gives their semisystematic names and structures. These trivial names will be of value in natural-product and biochemical work, but their use in systematic organic work should be restricted. If trivial names are used in a paper, the semisystematic names should always be clearly indicated.

While the need to coin a new trivial name must occasionally arise (e.g. because the structure of the compound is unknown), the list in the appendix should not be unnecessarily enlarged. Simple derivatives of known carotenoids should not be given new trivial names; they may, however, be named by modification of existing trivial names (c.f. Steroid Rule 2S–4.2, Note)[10], but the full semisystematic name according to these Rules should be given for each compound at the first mention in each paper.

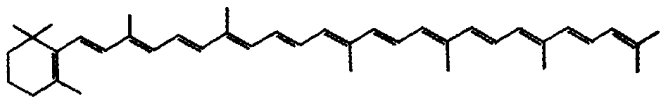
[10] For reference to the Definitive Rules for Steroid Nomenclature, see footnote 6.

APPENDIX

Some Naturally Occurring Carotenoids Having Trivial Names. (The examples in this appendix are based on an exhaustive list of naturally occurring carotenoids prepared by Dr O. Straub, which forms Chapter XII of a book "Carotenoids," O. Isler, Ed., Birkhäuser, Basel and Stuttgart, 1971. The two commissions are greatly indebted to Dr Isler, Dr Straub, and their colleagues of F. Hoffmann-La Roche Co. Ltd., Basel, for providing this list of compounds. The list includes a few compounds whose natural occurrence or structure is doubtful, but whose systematic names illustrate particular points of nomenclature.)

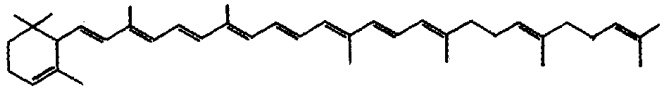
Hydrocarbons

3′,4′-Didehydro-β,ψ-carotene



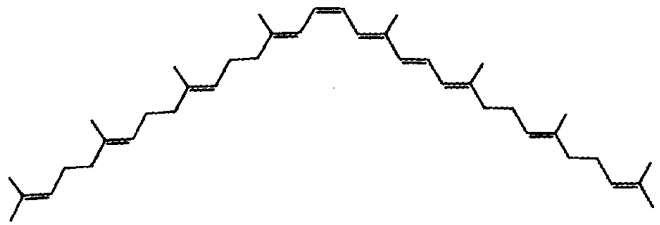
Torulene

7′,8′-Dihydro-ε,ψ-carotene



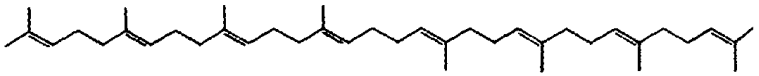
α-Zeacarotene

15-*cis*-7,8,11,12,7′,8′-Hexahydro-ψ,ψ-carotene



Phytofluene
Hexahydrolycopene

7,8,11,12,15,7′,8′,11′,12′,15′-Decahydro-ψ,ψ-carotene



Lycopersene

Alcohols

(3*R*)-5′-*cis*-β,ψ-caroten-3-ol

1′,2′-Dihydro-ϕ,ψ-caroten-1′-ol

1,2-Dihydro-ψ,ψ-caroten-1-ol

ψ,ψ-Caroten-16-ol

3′,4′-Didehydro-1′,2′-dihydro-β,ψ-carotene-3,1′-diol

13-*cis*-1,2-Dihydro-ψ,ψ-carotene-1,20-diol

(3R,3′R)-7,8,7′,8′-Tetradehydro-β,β-carotene-3,3′-diol
Alloxanthin
Cynthiaxanthin
Pectenoxanthin
Cryptomonaxanthin
β,β-Carotene-3,4,3′,4′-tetrol
Crustaxanthin
β,ε-Carotene-3,19,3′-triol
Loroxanthin
Glycosides
1′-(β-D-Glucopyranosyloxy)-3′,4′-didehydro-1′,2′-dihydro-β,ψ-caroten-2′-ol
Phleixanthophyll
2,2′-Bis(β-L-rhamnopyranosyloxy)-3,4,3′,4′-tetradehydro-1,2,1′,2′-tetrahydro-ψ,ψ-carotene-1,1′-diol
Oscillaxanthin
Ethers
1-Methoxy-3,4-didehydro-1,2,7′,8′-tetrahydro-ψ,ψ-carotene
Spheroidene
1′-Methoxy-3′,4′-didehydro-1,2,1′,2′-tetrahydro-ψ,ψ-caroten-1-ol
Rhodovibrin

Epoxides

5,6-Epoxy-7′,8′-didehydro-5,6-dihydro-β,β-carotene-3,3′-diol

Diadinoxanthin

5′,6′-Epoxy-6,7-didehydro-5,6,5′,6′-tetrahydro-β,β-carotene-3,5,19,3′-tetrol

Vaucheriaxanthin

5,8-Epoxy-5,8-dihydro-β,β-carotene-3,3′-diol

Mutatoxanthin
Citroxanthin
Zeaxanthin furanoxide

5′,8′-Epoxy-6,7-didehydro-5,6,5′,8′-tetrahydro-β,β-carotene-3,5,3′-triol

Neochrome
Foliachrome
Trollichrome

5,6:5′,8′-Diepoxy-5,6,5′,8′-tetrahydro-β,β-carotene-3,3′-diol

Luteoxanthin

Aldehydes

3′,4′-Didehydro-β,ψ-caroten-16′-al

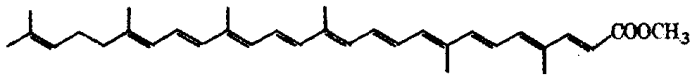
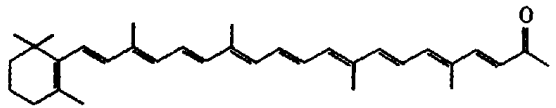
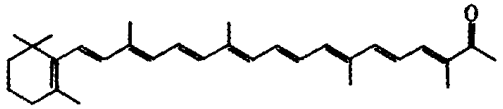
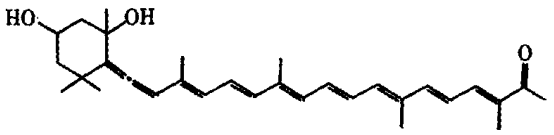
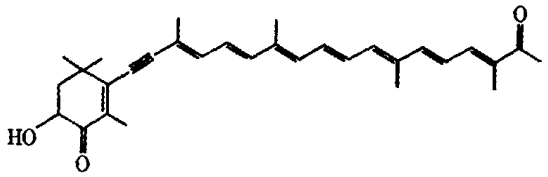
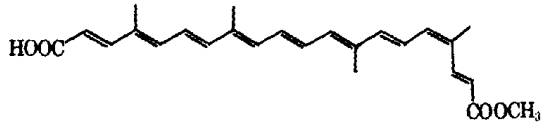
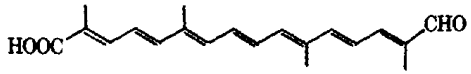
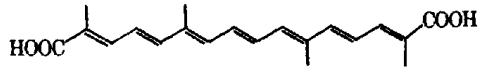
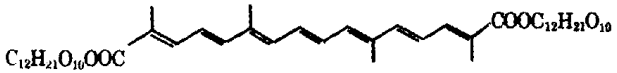
Torularhodinaldehyde

Rhodopinal
Warmingone
Torularhodin
Torularhodin methyl ester
Phoenicopterone
Canthaxanthin
Aphanicin
Chlorellaxanthin
Rubixanthone
Acids and Acid Esters
Ketones
13-cis-1-Hydroxy-1,2-dihydro-ψ,ψ-caroten-20-al
3',4'-Didehydro-β,ψ-caroten-16'-oic acid
Methyl 3',4'-didehydro-β,ψ-caroten-16'-oate
β,ε-Caroten-4-one
β,β-Carotene-4,4'-dione
3-Hydroxy-β,ψ-caroten-4'-one
CHO
HO
COOH
COOCH3
O
O
O
HO

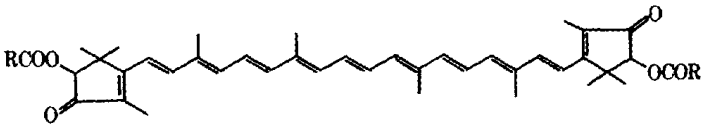
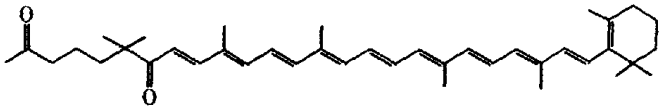
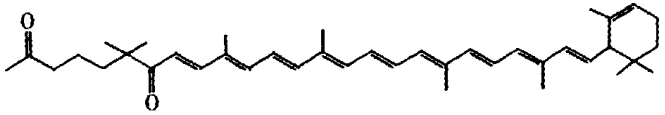
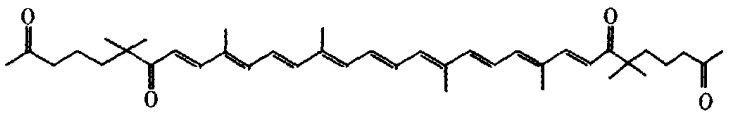
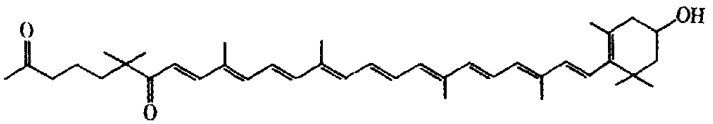
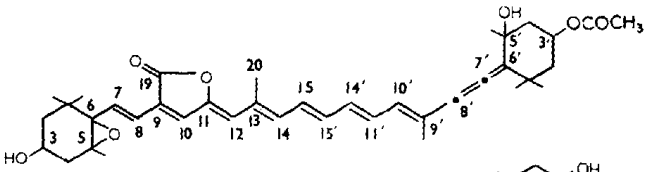
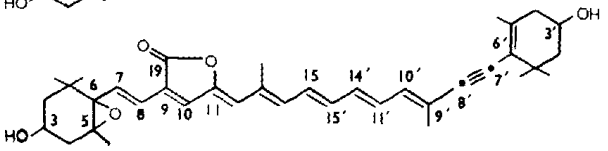
Okenone
Hydroxyspheroidenone
2,2′-Diketospirilloxanthin
Siphonaxanthin
Flexixanthin
Cryptocapsin
Capsanthin
1′-Methoxy-1′,2′-dihydro-χ,ψ-caroten-4′-one
1′-Hydroxy-1-methoxy-3,4-didehydro-1,2,-1′,2′,7′,8′-hexahydro-ψ,ψ-caroten-2-one
1,1′-Dimethoxy-3,4,3′,4′-tetradehydro-1,2,1′,2′-tetrahydro-ψ,ψ-carotene-2,2′-dione
3,19,3′-Trihydroxy-7,8-dihydro-β,ε-caroten-8-one
3,1′-Dihydroxy-3′,4′-didehydro-1′,2′-dihydro-β,ψ-caroten-4-one
(3′S,5′R)-3′-Hydroxy-β,κ-caroten-6′-one
(3R,3′S,5′R)-3,3′-Dihydroxy-β,κ-caroten-6′-one

Capsorubin
Pectenolone
Adonirubin
Phoenicoxanthin
3-OH-Canthaxanthin
Phoeniconone
Dehydroadonirubin
Esters of Alcohols
Zeaxanthin
dipalmitate
Physalien
(3S,5R,3'S,5'R)-3,3'-Dihydroxy-κ,κ-carotene-6,6'-dione
3,3'-Dihydroxy-7',8'-didehydro-β,β-caroten-4-one
3-Hydroxy-β,β-carotene-4,4'-dione
3-Hydroxy-2,3-didehydro-β,β-carotene-4,4'-dione
(3R,3'R)-3,3'-Bispalmitoyloxy-β,β-carotene or (3R,3'R)-β,β-carotene-3,3'-diol dipalmitate

3,3′-Bispalmitoyloxy-2,3,2′,3′-tetradehydro-β,β-carotene-4,4′-dione or 3,3′-dihydroxy-2,3,2′,3′-tetradehydro-β,β-carotene-4,4′-dione dipalmitate
Astacein
3,3′-Dihydroxy-19-lauroyloxy-7,8-dihydro-β,ε-caroten-8-one or 3,19,3′-trihydroxy-7,8-dihydro- β,ε-caroten-8-one 19-laurate
Siphonein
3′-Acetoxy-3,5,5′-trihydroxy-6′,7′-didehydro-5,8,5′,6′-tetrahydro-β,β-caroten-8-one
Isofucoxanthin
3′-Acetoxy-5,6-epoxy-3,5′-dihydroxy-6′,7′-didehydro-5,6,7,8,5′,6′-hexahydro-β,β-caroten-8-one
Fucoxanthin
Apo Carotenoids
3′,4′-Didehydro-2′-apo-β-caroten-2′-al
β-Apo-2′-carotenal
5,6-Dihydroxy-5,6-dihydro-10′-apo-β-caroten-10′-al
Azafrinaldehyde
6′-Apo-ψ-caroten-6′-al
Apo-2-lycopenal
Apo-6′-lycopenal

Methyl 6′-apo-ψ-caroten-6′-oate		Methyl apo-6′-lycopenoate
5′6′-Dihydro-5′-apo-18′-nor-β-caroten-6′-one or 6′-methyl-6′-apo-β-caroten-6′-one		Citranaxanthin
7′,8′-Dihydro-7′-apo-β-caroten-8′-one or 8′-methyl-8′-apo-β-caroten-8′-one		Sintaxanthin
3,5-Dihydroxy-6,7-didehydro-5,6,7′,8′-tetrahydro-7′-apo-β-caroten-8′-one or 3,5-dihydroxy-8′-methyl-6,7-didehydro-5,6-dihydro-8′-apo-β-caroten-8′-one		Paracentrone
3-Hydroxy-7,8-didehydro-7′,8′-dihydro-7′-apo-β-carotene-4,8′-dione or 3-hydroxy-8′-methyl-7,8-didehydro-8′-apo-β-carotene-4,8′-dione		Hopkinsiaxanthin
6′-Methyl hydrogen 9′-*cis*-6,6′-diapocarotene-6,6′-dioate		Bixin
8′-Oxo-8,8′-diapo caroten-8-oic acid		Crocetinsemialdehyde
8,8′-Diapocarotene-8,8′-dioic acid		Crocetin
Digentiobiosyl 8,8′-diapocarotene-8,8′-dioate		Crocin

Nor and Seco Carotenoids

3,3′-Bisacyloxy-2,2′-dinor-β,β-carotene-4,4′-dione		Actinioerythrin
5,6-Seco-β,β-carotene-5,6-dione		Semi-β-carotenone
5,6-Seco-β,ε-carotene-5,6-dione		Semi-α-carotenone
5,6:5′,6′-Diseco-β,β-carotene-5,6,5′,6′-tetrone		β-Carotenone
3′-Hydroxy-5,6-seco-β,β-carotene-5,6-dione		Triphasiaxanthin 3-Hydroxysemi-β-carotenone
3′-Acetoxy-5,6-epoxy-3,5′-dihydroxy-6′,7′-didehydro-5,6,5′,6′-tetrahydro-12′,13′,20′-trinor-β,β-caroten-19,11-olide		Peridinin
5,6-Epoxy-3,3′-dihydroxy-7′,8′-didehydro-5,6-dihydro-12′,13′,20′-trinor-β,β-caroten-19,11-olide		Pyrrhoxanthininol

retro Carotenoids and *retro* Apo Carotenoids

4′,5′-Didehydro-4,5′-*retro*-β,β-carotene-3,3′-diol		Eschscholtzxanthin
3′-Hydroxy-4′,5′-didehydro-4,5′-*retro*-β,β-caroten-3-one		Eschscholtzxanthone
4′,5′-Didehydro-4,5′-*retro*-β,β-carotene-3,3′-dione		Rhodoxanthin
7,8-Dihydro-8,7′-*retro*-β,β-carotene or 7,7′-dihydro-β,β-carotene		No trivial name
3-Hydroxy-5′-methyl-4,5′-*retro*-5′-apo-β-caroten-5′-one or 3-hydroxy-4,5′-*retro*-5′-apo-β-caroten-5′-one		Tangeraxanthin

Higher Carotenoids

2-(4-Hydroxy-3-methyl-2-butenyl)-7′,8′,11′,12′-tetrahydro-ε,ψ-carotene		Nonaprenoxanthin
2,2′-Bis(4-hydroxy-3-methyl-2-butenyl)-ε,ε-carotene		Decaprenoxanthin

C.p. 450

2-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-2′-(3-methyl-2-butenyl)-β,β-carotene

C.p. 473

2′-(4-Hydroxy-3-methyl-2-butenyl)-2-(3-methyl-2-butenyl)-3′,4′-didehydro-1′,2′-dihydro-β,ψ-caroten-1′-ol

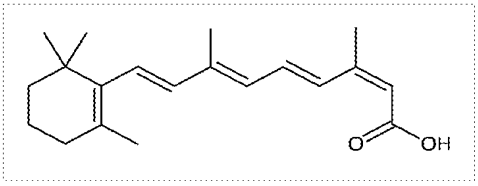
Bacterioruberin

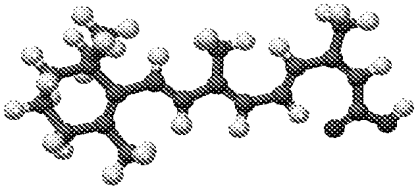
2,2′-Bis(3-hydroxy-3-methylbutyl)-3,4,3′,4′-tetradehydro-1,2,1′,2′-tetrahydro-ψ,ψ-carotene-1,1′-diol

EXHIBIT D

Isotretinoin

Isotretinoin





Systematic (IUPAC) name	
(13*cis*)-retinoic acid	
Clinical data	
Trade names	Accutane
AHFS/Drugs.com	monograph [1]
MedlinePlus	a681043 [2]
Licence data	US FDA:link [3]
Pregnancy cat.	X (AU) X (US)
Legal status	Prescription Only (S4) (AU) POM (UK) ℞-only (US)
Routes	Oral, topical
Pharmacokinetic data	
Bioavailability	Variable
Protein binding	99.9%
Metabolism	Hepatic
Half-life	10–20 hours
Excretion	Renal and fecal
Identifiers	
CAS number	4759-48-2 [4] ✓
ATC code	D10AD04 [5]
PubChem	CID 5282379 [6]
DrugBank	DB00982 [7]
ChemSpider	4445539 [8] ✓
UNII	EH28UP18IF [9] ✓

KEGG	D00348 [10] ✓
ChEBI	CHEBI:6067 [11] ✓
ChEMBL	CHEMBL547 [12] ✓
Chemical data	
Formula	$C_{20}H_{28}O_2$
Mol. mass	300.44 g/mol
✓ **(what is this?) (verify)** [13]	

Isotretinoin, INN, /ˌaɪsoʊtriˈtɪnoʊ.ɨn/,[14] first marketed as **Accutane** by Hoffmann-La Roche, is a medication primarily to cure cystic acne. Rarely, it is also used to prevent certain skin cancers (squamous-cell carcinoma), and can be used in the treatment of brain,[15] pancreatic and other cancers. It is used to treat harlequin-type ichthyosis, a usually lethal skin disease, and lamellar ichthyosis. It is a retinoid, meaning it is related to vitamin A, and is found in small quantities naturally in the body.

Isotretinoin is currently the standard of care for treatment of severe, scarring cystic acne. The most common adverse effects are a transient worsening of acne (lasting 2–3 weeks), dry lips (cheilitis), dry skin, and a propensity to sunburn easily. Other side effects are rare but do include: muscle aches and pains (myalgias), headaches. Isotretinoin is known to cause birth defects due to in utero exposure because of the molecule's close resemblance to retinoic acid, a natural vitamin A derivative which controls normal embryonic development.

In the United States a special procedure is required to obtain the pharmaceutical. In most other countries a consent form is required which explains these risks. Women taking isotretinoin must not get pregnant during, and for 1 month after isotretinoin therapy. Sexual abstinence, or effective contraception is mandatory during this period. Barrier methods by themselves (such as condoms) are not considered adequate due to the unacceptable failure rates of approximately 3%. Women who fall pregnant whilst on isotretinoin therapy are generally counselled to have a termination. Isotretionin has no effect on male reproduction.

There is little evidence in the medical literature linking isotretinoin use with depression and suicide. Despite this, there exists a popular misconception amongst the public that isotretinoin use commonly causes depression.

In 2009, Roche decided to remove Accutane from the US market after juries had awarded millions of dollars in damages to former Accutane users over inflammatory bowel disease claims. Other common brands are **Roaccutane** (Hoffman-La Roche, known as **Accutane** in the United States before July 2009), **Amnesteem** (Mylan), **Claravis** (Barr), **Isotroin** (Cipla) or **Sotret** (Ranbaxy).[*citation needed*]

Medical uses

Isotretinoin is used primarily for severe cystic acne and acne that has not responded to other treatments. Acne treatment usually begins with topical retinoids (e.g.tretinoin, adapalene), in combination with topical antibiotics (e.g. clindamycin, erythromycin) or antiseptics (e.g. benzoyl peroxide-containing preparations), followed by oral antibiotics (e.g. doxycycline or minocycline). In women a cyproterone-containing contraceptive pill can be useful if there are no contraindications.

In cases of hormonal acne, such as in women in their 20s and 30s with cyclical acne, often a course of isotretinoin can permanently improve acne obviating the need for lifelong hormonal manipulation.[*medical citation needed*]

Failure to adequately treat severe acne in a timely manner may lead to permanent scarring. Isotretinoin is the only treatment that effectively cures acne. All other treatments simply control the disease, but do not treat the underlying causes of acne.[*medical citation needed*]

Indications

Isotretinoin's main indication is for the treatment of severe cystic acne vulgaris.[16] Many dermatologists also support its use for treatment of lesser degrees of acne that prove resistant to other treatments, or that produce physical or psychological scarring.

It is also somewhat effective for hidradenitis suppurativa and some cases of severe acne rosacea. It can also be used to help treat harlequin ichthyosis, lamellar ichthyosis and is used in xeroderma pigmentosum cases to relieve keratoses. Isotretinoin has been used to treat the extremely rare condition fibrodysplasia ossificans progressiva. It is also used for treatment of neuroblastoma, a form of nerve cancer.

Isotretinoin therapy has furthermore proven effective against genital warts in experimental use, but is rarely used for this indication as there are more effective treatments. Isotretinoin may represent an efficacious and safe alternative systemic form of therapy for RCA of the cervix. In most countries this therapy is currently unapproved and only used if other therapies failed.

Prescribing restrictions

In the United Kingdom, this drug may be prescribed only by or under the supervision of a consultant dermatologist.[17] Because severe cystic acne has the potential to cause permanent scarring over a short period, restrictions on its more immediate availability have proved contentious. Similar restrictions are common in most Australian states – in New South Wales and Victoria, for instance, the prescriber must be a Fellow of the Australasian College of Dermatologists (FACD).[18] In New Zealand, isotretinoin can be prescribed by any doctor, but is subsidized only if prescribed by a vocationally registered general practitioner or dermatologist.

Since 1 March 2006, the dispensing of isotretinoin in the United States has been controlled by an FDA-mandated website called iPLEDGE – dermatologists are required to register their patients before prescribing and pharmacists are required to check the website before dispensing the drug. The prescription may not be dispensed until both parties have complied. A physician may not prescribe more than a 30-day supply. A new prescription may not be written for at least 30 days. Pharmacies are also under similar restriction. There is also a seven-day window between the time the prescription is written and the time the medication must be picked up at the pharmacy. If the original prescription is lost, or pick-up window is missed, the patient must re-qualify to have another prescription written. Doctors and pharmacists must also verify written prescriptions in an online system before patients may fill the prescription. Due to its teratogenic effects, women with the potential to bear children must commit to the use of two forms of contraception simultaneously for the duration of isotretinoin therapy, as well as for the month immediately preceding and the month immediately following therapy.

In Mexico, Colombia and Brazil use of the drug is restricted and an official identification and patient signature is required by the pharmacies.

Dosage

The dose of isotretinoin patients receive is dependent on their weight and the severity of the condition. High-dose treatments are administered between 0.5 mg/kg/day to 2 mg/kg/day (usually at 0.5 to 1 mg/kg/day,[19] given as a single dose with food). Usually a course will last 8–10 months. A second course may be required. Efficacy appears to be related to the cumulative dose of isotretinoin taken, with a total cumulative dose over each course of 120–150 mg/kg used as a guideline.



10 mg capsule

Nearly all patients achieve initial clearing of acne during a normal course of isotretinoin therapy. 90% of patients achieve excellent clearance of their acne after a cumulative dose of 150 mg/kg.

Lower-dosage treatments, such as 10–20 mg/day (approximately half the high dosage treatments above), can also be effective, with greatly diminished side effects. However, such lower dosage courses may be associated with higher relapse rates, requiring additional courses, especially if not taken for sufficient time.

Usually, a starting dose of 20 mg is taken with the largest meal of the day. After a few months, the dose is increased, e.g. to 40 mg/d. If side-effects permit, a higher dose such as 60 mg/d can be prescribed although daily dose rarely exceeds 60 mg. If 20 mg capsules are supplied, patients may take (for example) 20 mg one day, then 40 mg the next to provide an average daily dose of 30 mg/d.

Very rarely, some patients' acne will respond to a course, but then recur, necessitating multiple courses of treatment. Such isotretinoin 'resistance' most likely has a genetic basis as it is often seen in the same members of one family.[*medical citation needed*]

Preparations

Isotretinoin is marketed under many brand names by various manufacturers. Some brands of oral isotretinoin include: *Accure* (Alphapharm), *Accutane* and *Roaccutane* (Roche), *Aknenormin* (Hermal), *Amnesteem* (Mylan), *Ciscutan* (Pelpharma), *Claravis* (Barr), *Clarus* (Prepharm), *Isohexal* (Hexal Australia), *Istretinoin-A* (Pharmathen), *Isosupra* (SMB Laboratories), *Isotane* (Pacific Pharmaceuticals), *Isotroin* (Cipla), *Oratane* (Douglas Pharmaceuticals), *Atretin* (Lafrancol), *Nimegen* (Medica Korea), *Acnotin* (Mega Lifesciences), *Ruatine* (United Pharmaceutical)and *Sotret* (Ranbaxy), Ausret (Auskin).

It is also available as a 0.05% topical preparation, marketed by Stiefel under the trade name *Isotrex* or *Isotrexin* (with erythromycin), Sotret Gel from Ranbaxy and Isotroin Gel from Cipla. In Russia Ретиноевая мазь 0.05% and 0.1%.

Adverse effects

Increasingly higher dosages will result in higher toxicity, resembling vitamin A toxicity. The following are adverse drug reactions from Roche's UK product information for Roaccutane as of October 2010:

Type of disorders	Very common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Rare (≥ 1/10 000,< 1/1000)	Very rare (≤ 1/10 000)
Infections				• Gram positive (mucocutaneous) bacterial infection
Blood and lymphatic system	• Anemia • Increased red blood cell sedimentation rate • Thrombocytopenia • Thrombocytosis	• Neutropenia		• Lymphadenopathy
Immune system			• Allergic skin reaction • Anaphylactic reactions • Hypersensitivity	
Metabolism				• Diabetes mellitus • Hyperuricaemia
Psychiatric			• Depression • Aggravated depression • Aggressive tendencies • Anxiety • Mood alterations	• Abnormal behaviour • Psychotic disorder • Suicidal ideation • Suicide attempt • Suicide
Nervous system		• Headache		• Benign intracranial hypertension • Convulsions • Drowsiness • Dizziness
Eye	• Blepharitis • Conjunctivitis • Dry eyes • Eye irritation			• Blurred vision • Cataract • Colour blindness • Contact lens intolerance • Corneal opacity • Decreased night vision • Keratitis • Papilloedema • Photophobia • Visual disturbances
Ear				• Impaired hearing
Vascular				• Vasculitis (i.e. Wegener's granulomatosis, allergic vasculitis)
Respiratory, thoracic and mediastinal		• Epistaxis • Nasal dryness • Nasopharyngitis		• Bronchospasm (particularly in patients with asthma) • Hoarseness

Gastrointestinal				• Colitis • Ileitis • Dry throat • Gastrointestinal haemorrhage • Haemorrhagic diarrhoea • Inflammatory bowel disease • Nausea • Pancreatitis
Hepatobiliary	• Increased transaminase			• Hepatitis
Skin and subcutaneous tissues	• Cheilitis • Dermatitis • Dry skin • Localised exfoliation • Pruritus • Rash • Erythematous • Skin fragility		• Alopecia	• Acne fulminans • Aggravated acne (acne flare) • Erythema (facial) • Exanthema • Hair disorders • Hirsutism • Nail dystrophy • Paronychia • Photosensitivity reaction • Pyogenic granuloma • Skin hyperpigmentation • Increased sweating
Musculo-skeletal and connective tissue	• Arthralgia • Myalgia • Back pain			• Arthritis • Calcinosis (calcification of ligaments and tendons) • Premature epiphyseal fusion • Exostosis • Hyperostosis • Osteopenia • Tendonitis
Renal and urinary				• Glomerulonephritis
General				• Increased formation of granulation tissue • Malaise
Investigation	• Increased triglycerides • Decreased HDL	• Increased blood cholesterol • Increased blood glucose • Haematuria • Proteinuria		• Increased creatine phosphokinase

Skin

The most common side effects are muco-cutaneous: dry lips and skin. Regular lip balm and moisturizer is recommended. Sometimes, however, the dose needs to be decreased to reduce these side effects. The skin becomes more fragile -especially to frictional forces- and may not heal as quickly as normal. For this reason: waxing of hair, tattooing, tattoo removal, piercings, dermabrasion, exfoliation etc. are not recommended. Treatment of acne scars (e.g. with fractional laser such as "Fraxel") is generally deferred until 12 months after completion of a course of isotretinoin.

Acne usually flares up 2–3 weeks into the treatment and is usually mild and tolerable. Occasionally this flareup is severe, necessitating oral antiobiotics such as erythromycin. A short course of oral prednisolone may be required.

Some dermatologists favour a few weeks pre-treatment with oral antibiotics before commencing isotretinoin to reduce the chance of a severe flare.

Elevated lipids

It is expected that most patients will experience a modest elevation in cholesterol and triglyceride levels during treatment that returns to baseline soon after ceasing.

Headaches

Isotretinoin is known to very rarely induce headaches due to increased intracranial pressure (Benign Intracranial Hypertension, or Pseudotumor Cerebri). This adverse effect can also be seen with tetracycline antibiotics (Minocycline, Doxycycline) and therefore these medications should not be taken with isotretinoin. Patients who have experienced headaches from these antibiotics should be treated very cautiously with isotretinoin. Neurology and ophthalmology referral is usually indicated. Isotretinoin does not increase the risk or severity of migraine headaches (unlike the combined contraceptive pill).[*medical citation needed*]

Teratogenicity (birth defects)

Isotretinoin is a teratogen and is highly likely to cause birth defects if taken by women during pregnancy or even a short time before conception. A few of the more common birth defects this drug can cause are hearing and visual impairment, missing or malformed earlobes, facial dysmorphism, and mental retardation. Isotretinoin is classified as FDA Pregnancy Category X and ADEC Category X, and use is contraindicated in pregnancy.

The manufacturer recommends pregnancy be excluded in female patients two weeks prior to commencement of isotretinoin, and they should use two simultaneous forms of effective contraception at least one month prior to commencement, during, and for at least one month following isotretinoin therapy.[20]

In the U.S., more than 2,000 women have become pregnant while taking the drug between 1982 and 2003, with most pregnancies ending in abortion or miscarriage. About 160 babies with birth defects were born. As a consequence, the iPLEDGE program was introduced by the U.S. FDA on 12 August 2005 in an attempt to ensure female patients receiving isotretinoin do not become pregnant. As of 1 March 2006, only prescribers registered and activated in iPLEDGE are able to prescribe isotretinoin, and only patients registered and qualified in iPLEDGE will be able to have isotretinoin dispensed by a registered pharmacy. All patients, including women not of child-bearing age and men, must register with iPLEDGE. FDA's intent with the iPLEDGE program is to tightly control the distribution and dispensing of isotretinoin and thereby prevent the potential for distribution or sharing of the drug outside of the program to women of child-bearing age. As of 2013, the FDA has yet to provide information or statistics to validate whether the iPLEDGE program has achieved its goal of reducing pregnancies among women patients of child-bearing age.

Patients receiving isotretinoin therapy are not permitted to donate blood during and for at least one month after discontinuation of therapy due to its teratogenicity.[21]

Depression

Since Isotretinoin was introduced a large number of independent clinical trials have been performed to examine the relationship between isotretinoin and mood disorders. In the vast majority of cases, there has been no association found between isotretinoin and depression. Scientific studies are required to ascertain if there is an increased, or decreased rate of depression compared with controls - e.g. a similar age/sex/acne- affected cohort treated with antibiotics.

In a 2012 Turkish study examining 63 patients, there was no increase in depression on psychometric testing- however it was noted that there was 'improved executive function and control of anger'.

In a 2013 study from Spain, in 346 consecutively treated patients, the mean DLQI (quality of life) score improved by approximately 9 points- indicating a very significant improvement. There were significant improvements in "physical function, vitality, social function and mental health". Anxiety was seen to reduce on the HADS scale from 26% to 3.5%, and depression was seen to reduce from 3.5% to 1.7%. All these results were statistically significant.

A 2013 study from the Czech Republic examined depression scores (BDI: Beck's Depression Inventory Version II) and found that isotretinoin significantly improved depression scores. No risk for suicide was found during followup, and there was no occurrence of suicidal ideation.

Chee Hong describes isotretinoin-related depression as "an idiosyncratic side-effect", claiming that anxiety can often bring on acne and depression, thus creating more anxiety. Correspondingly, treatment of severe acne with isotretinoin has been shown to reduce anxiety and depression, for tests have shown acne to be a main depressant in most tested patients' lives.

Studies have shown that patients with acne, the population group eligible to receive isotretinoin therapy, have an increased risk of clinical depression compared with the general population.

An Iranian study from 2013 concluded "Acne vulgaris has significant effects on psychological status. Effective concomitant anti-acne therapy and psychological assessment make significant contributions for the mental health and should be strongly recommended."

A Canadian study in 1988 concluded "The 5.6-7.2% prevalence of active suicidal ideation among the psoriasis and acne patients was higher than the 2.4-3.3% prevalence reported among general medical patients. Our findings highlight the importance of recognizing psychiatric comorbidity, especially depression, among dermatology patients and indicate that in some instances even clinically mild to moderate disease such as non-cystic facial acne can be associated with significant depression and suicidal ideation."

Various case reports of depression, suicidal ideation, suicide attempt, and suicide occurring patients treated with isotretinoin have been reported to the U.S. FDA Adverse Events Reporting System, with 431 cases reported between 1982 and May 2001 – of these, 37 patients had committed suicide.

Rodent studies

In a study in 2006, it was demonstrated for the first time that isotretinoin administration enhances depression-related behaviors in mice. The mechanism by which this occurs was not elucidated, although altered neuronal gene regulation and changes in hippocampal neurogenesis were thought to be involved. This study generated controversy due to its putative linking of observed behaviors in rodents that were deliberately and slowly drowned, with the mental state of human teenagers treated with isotretinoin. The study did not account for the fact that the medication was injected into the peritoneal cavity which may have produced inflammation and pain. The study did not consider alternative hypotheses such as an improvement in memory and learning (subsequently demonstrated in humans) which may have resulted in improved 'learned helplessness' compared with control mice.

In 2004, two studies showed that Accutane in mice significantly reduces cell proliferation in the hippocampus and the subventricular zone, suppresses hippocampal neurogenesis, and severely disrupts the capacity of the mice to learn a spatial radial maze task.

In 2009, it was shown that isotretinoin given to mice alters metabolism in raphe nuclei and disrupts functional connectivity between the raphe nuclei and the hippocampal formation, which the researchers thought may contribute to the observed increase in depression-related behaviors.

In 2010, one in vitro study showed that isotretinoin lead to a decrease of hypothalamic cells and that it may contribute to the increased depression-related behaviors observed in mice given isotretinoin.

In 2008, a study showed that isotretinoin alters the morphology of serotonergic neurons in rats, which are thought to be associated with depressive symptoms.

Human brain studies

In 2005, psychiatrist Dr. Doug Bremner found decreased orbitofrontal cortex function on brain imaging in patients treated with Accutane (isotretinoin). Bremner's study, which used positron emission tomography (PET), found that patients treated with isotretinoin experienced an average 21% decrease in orbitofrontal-lobe brain activity. However, there were no changes in the depressive state of the patients that could be measured with the Hamilton depression scale. Bremner's findings have prompted members of the scientific community to call for more studies regarding isotretinion's links to depression and suicidal behavior.

In 2007, one in vitro study demonstrated that isotretinoin reduced available serotonin in synapses by increasing 5-HT1A receptors and serotonin transporter protein levels.

Permanent side effects

Inflammatory bowel disease

Several scientific studies have posited isotretinoin as a possible cause of Crohn's disease and ulcerative colitis in some individuals. Several trials over inflammatory bowel disease claims have been held in the United States thus far, with many of them resulting in multimillion dollar judgments against the makers of isotretinoin. And in 2009 Roche decided to pull Accutane off the market, claiming at the time that the move was to stem the tide of Accutane lawsuits. As of January 2012, there were an additional 6,000 cases pending.

A study looking at 45,000 patients showed no association between isotretinoin and inflammatory bowel disease (Ulcerative Colitis and Crohn's Disease). The authors concluded "Because inflammatory acne in children and adolescents carries a high psychological burden, clinicians should not be discouraged from prescribing this drug owing to a putative association with IBD."

Eye changes

Dry eyes are common during treatment. It is recommended to limit contact lens wearing. Keratoconjunctivitis sicca (dry eyes) has been reported as a long-term sequelae however this condition is most commonly due to Sjogren's Syndrome.

Extremely rarely, patients notice reduced night vision. This has been reported in cases of underlying cystic fibrosis which causes low vitamin A levels due to poor absorption of fat-soluble vitamins. It was suggested that patients with cystic fibrosis or other conditions associated with fat malabsorption should have adequate vitamin A levels prior to isotretinoin therapy. If a career in aviation or the armed forces is considered, it is recommended that patients check with their local authorities.

Reduced growth in children

Isotretinoin may be used in younger patients.

Advanced bone age, and hyperostosis have been reported. The U.S. Food and Drug Administration's (FDA) medication guide for Accutane states the drug "may stop long bone growth in teenagers who are still growing."[22]

In a retrospective cohort done in 2011, advanced bone age was observed in 29% of children who had received isotretinoin with an accumulative dose of 13440 mg/m² body surface area for treatment of neuroblastoma as compared to none in the group treated without isotretinoin. These effects are seen because isotretinoin like all retinoids (including excessive vitamin a intake) negatively impairs chondrogenesis (formation of new cartilage), with diminishing cartilage in the epiphyseal plate to ossify, growth slows down and subsequently stops when all remaining cartilage has been ossified. Since the age until complete ossification of bones normally varies between individuals (17–20 years for upper limbs, 18–23 years for lower limbs)[23] and since many are prescribed Accutane in their late teens when growth still occurs, but has begun decelerating, there is a risk that deceleration of growth from use of isotretinoin is mistakenly seen as the normal deceleration of growth. It is also worth noting that stunted growth of long bones and other bones with epiphyseal plates that are not affecting an individuals height, for example the clavicles, scapula and sternum is almost impossible to detect since no measurements of these bones are done. The effect of multiple courses of Accutane on epiphyseal closure is unknown.

One study in 2007 also found a significant decrease of growth hormone (GH) levels from 0.9 mU/L to 0.3 mU/L after three months of isotretinoin treatment. And a study in 2010 found that isotretinoin treatment decreases insulin-like growth factor-1 (IGF-1) levels. IGF-1 is produced in the liver as response to growth hormone and is the primary mediator of GH.

A study looking at bone metabolism in 36 patients showed no sign of osteoporosis, or altered bone turnover.

Other issues

In a study from 2011, twenty male patients all developed heart hypertrophy and hypovolemia after 10 weeks of isotretinoin treatment with 0.5 mg/kg/day.

During a prospective study in Mexico that evaluated the efficacy and safety of isotretinoin in acne, six male patients reported difficulties in maintaining adequate penile erection, in addition to depression, suggesting a potential link between isotretinoin and risk of erectile dysfunction.

Research suggests vitamin E supplementation in the form of alpha-tocopherol reduces the toxicity of isotretinoin treatment in subjects with cancer and myelodysplastic syndrome. In contrast, a randomized study in 82 subjects taking isotretinoin (1 mg/kg/day) for acne vulgaris found no difference in the incidence or severity of side effects in the group taking an additional 800 IU/day of vitamin E in the form of d-l-alphatocopherol.

One study noted that keloid formation may be induced by isotretinoin therapy.

Mechanism of action

Isotretinoin itself has low affinity for retinoic acid receptors (RAR) and retinoid X receptors (RXR), however it may be converted intracellularly to metabolites that act as agonists of RAR and RXR nuclear receptors.

Isotretinoin's exact mechanism of action is unknown but several studies have shown that isotretinoin induces apoptosis (cell death) in various cells in the body such as cells in meibomian glands, hypothalamic cells, hippocampus cells and important for treatment of acne, in sebaceous gland cells.

One study found that isotretinoin significantly changed the expression of hundreds of genes in skin after 8 weeks of therapy.

Isotretinoin is also one of several drugs discussed in a recent study examining epigenetic side effects (for example DNA methylation) of common pharmaceuticals that leads to silencing of genes.[*citation needed*]

One study suggests the drug amplifies production of neutrophil-gelatinase-associated lipocalin (NGAL) in the skin, which has been shown to reduce sebum production by inducing apoptosis in sebaceous gland cells, while exhibiting an antimicrobial effect on *Propionibacterium acnes*.[24] The drug decreases the size and sebum output of the sebaceous glands. Isotretinoin's combined impact on several of acne's contributory factors distinguishes it from alternative remedies, such as antibiotics, and accounts for its greater efficacy in severe, nodulocystic cases.[*citation needed*]

The effect on sebum production can be temporary and remission of the disease can be "complete and prolonged."

Isotretinoin has been speculated to down-regulate the telomerase enzyme and hTERT, inhibiting "cellular immortalization and tumorigenesis."

Isotretinoin has also been proved, according to a 2007 study, to inhibit the action of the metalloprotease MMP-9 (gelatinase) in sebum, without any influence in the action of TIMP1 and TIMP2 (tissue inhibitors of metalloproteases). It is already known that metalloprotases play an important role in the pathogenesis of acne, thus the inhibition of their action by isotretinoin is an additional mechanism of action that contributes to the efficacy of Isotretinoin.

Pharmacokinetics

Isotretinoin, when administered orally, is best absorbed when taken after a high-fat meal, as it has a high level of lipophilicity. In a crossover study, the peak plasma concentration was found to be more than doubled when taken after a high-fat meal versus a fasted condition. Isotretinoin is primarily (99.9%) bound to plasma proteins, mostly albumin. At least three metabolites have been detected in human plasma after oral administration: 4-oxo-isotretinoin, retinoic acid, and 4-oxo-retinoic acid. Isotretinoin also oxidizes, irreversibly, to 4-oxo-isotretinoin. The metabolites of isotretinoin are excreted through both urine and feces. The mean elimination half-life is 21 hours, with a standard deviation from this mean of 8.2 hours.

History

An early treatment of acne first used during the 1930s was high doses of the fat-soluble vitamin A (retinoic acid).[*citation needed*] At these dosage levels (sometimes 500,000 IU per day), sebum production is notably reduced, thwarting acne, but overly dry hair is a negative side effect, and such high doses can lead to vitamin A toxicity. Use of animal-based vitamin A at nutritive levels (where the upper limit dosage is 10,000 IU daily), taken over the course of a year, has also been shown to reduce acne.[*citation needed*]

Building on the discovery that vitamin A can inhibit sebum production at toxic dosages, the retinoic acid derivative isotretinoin (13-*cis*-retinoic acid) was developed in 1982 by Hoffmann-La Roche. Dr. Gary Peck is credited with discovering its use for the treatment of cystic acne, as well as disorders of keratinization, such as lamellar ichthyosis, Darier's disease, and pityriasis rubra pilaris. In addition, he demonstrated its chemopreventive properties in patients with basal cell nevus syndrome, also known as nevoid basal cell carcinoma syndrome and Gorlin's syndrome. In fact, within one year of attaining the U.S. patent for discovering the use of isotretinoin in the treatment of acne, he received the Inventor's Award from the US Department of Commerce and a Meritorious Service Medal from the US Public Health Services in 1983. In 2003, he was honored with The Discovery Award by the Dermatology Foundation in "recognition of extraordinary scientific accomplishments that have had a profound influence on the specialty of dermatology and have gained the respect and admiration of the world scientific community".

Dosage requirements of isotretinoin have been disputed. After a 1984 study funded by Roche, relatively high dosages of isotretinoin became mainstream in treatment in the United States. Lower dosages were found to be effective in treatment by independent research (see dosage section).

From the time of its introduction, the drug was known to have teratogenic potential, and pregnancies with the drug were strongly discouraged. When they occurred, they were found to have approximately 30% rates of congenital

malformation, versus a 3–5% baseline risk. Beginning in 1998, prescriptions of the drug came under scrutiny, as fewer than half of prescribers were testing for pregnancy, usually relying on less-sensitive urine tests. On the grounds that pregnancies by women taking the drug had been underreported by the manufacturer between 1982 and 2000, and that, once generic manufacturers entered the market risk management was no longer centralized, the FDA instituted restrictions on prescribing and dispensing the drug, first with the "System to Manage Accutane Related Teratogenicity" (SMART) in 2000, and subsequently the iPLEDGE program in 2006. A retrospective cohort study recently found that pregnancy rates were quite high during the period (one per 30 women per year), and 84% of pregnancies were ended by induced abortion.

In February 2002, Roche's patents for isotretinoin expired, and there are now many other companies selling cheaper generic versions of the drug. On June 29, 2009, Roche Pharmaceuticals, the original creator and distributor of isotretinoin, officially discontinued both the manufacture and distribution of their **Accutane** brand in the United States due to what the company described as business reasons related to low market share (below 5%), coupled with the high cost of defending personal-injury lawsuits brought by some patients prescribed the drug. Generic isotretinoin will remain available in the United States through various manufacturers. Roche USA continues to defend Accutane and claims to have treated over 13 million patients since its introduction in 1982. F. Hoffmann-La Roche Ltd. apparently will continue to manufacture and distribute **Roaccutane** outside of the United States.

Among others, actor James Marshall sued Roche over Accutane-related disease that resulted in removal of his colon. The jury, however, decided that James Marshall had a pre-existing bowel disease.

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- DermNet *treatments/isotretinoin* (http://dermnetnz.org/treatments/isotretinoin.html)

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Electronic Acknowledgement Receipt

EFS ID:	16865425
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
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:	13533/541US
Receipt Date:	16-SEP-2013
Filing Date:	14-OCT-2010
Time Stamp:	16:39:39
Application Type:	U.S. National Stage under 35 USC 371

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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	13533_541US_Response-to-OA_9-16-2013.pdf	605847 0692e5f86736b0156e176f7ef9aef8eaf61e9aa8	no	27

Warnings:	
Information:	

2	Amendment/Req. Reconsideration-After Non-Final Reject	Exhibit-A_Nomenclature-of-retinoids.pdf	1060532 d6ad8c6ff3c9e0fdf899c995487d46338b04a137	no	7
Warnings:					
Information:					
3	Amendment/Req. Reconsideration-After Non-Final Reject	Exhibit-B-Reduction-in-Serum.pdf	907729 ffd5f164605e0179d2c08b385349d7edad6766db	no	10
Warnings:					
Information:					
4	Amendment/Req. Reconsideration-After Non-Final Reject	Exhibit-C_Nomenclature-of-carotenoids.pdf	3140289 df1acbac83c546db94d5f4fb642784e52362408c	no	27
Warnings:					
Information:					
5	Amendment/Req. Reconsideration-After Non-Final Reject	Exhibit-D-Isotretinoin.pdf	13197822 c09d58b19f61273d9cfae159ddcda40c64e9b2cb	no	15
Warnings:					
Information:					
		Total Files Size (in bytes):	18912219		

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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.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/733,631	Filing Date 10/14/2010	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) 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

AMENDMENT **09/16/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 65	Minus	** 65	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 5	Minus	***6	= 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

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
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
/VANESSA BARBER/

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.**
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	13533/541US	4180

26646 7590 06/14/2013

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1629	

MAIL DATE	DELIVERY MODE
06/14/2013	PAPER

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.

Office Action Summary	Application No. 12/733,631	Applicant(s) WASHINGTON, ILYAS	
	Examiner ZOHREH FAY	Art Unit 1629	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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *20 February 2013*.

☐ 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) *50-114* is/are pending in the application.

5a) Of the above claim(s) *50-60,67-74,82 and 108-114* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *61-66,75-81 and 83-107* 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.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/10/2010, 9/5/2012, 2/26/2013*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Claims 50-114 are pending in the instant application.

Claims 61-66 and 75-81 and 84-107 are presented for examination.

Claims 50-60, 67-74 and 108-114 are withdrawn from the consideration.

Applicant's arguments regarding the restriction requirement has been noted. As the claims are amended the shared technical feature between the groups ids C20-D1-3 retinoid. WO 95/04018 teaches C20-D1-3 in a composition. Therefore, the shared technical feature does not contribute to the state of the art. Thus, restriction for examination purpose is considered to be proper and is made final.

Claim Rejections - 35 USC § 112

The following is a quotation 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 35 U.S.C. 112 (pre-AIA), first paragraph:
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 61-66, 75-81 and 84-107 are 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 claims are directed to "A method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in the retina" using a "substituted C20-D1-3 retinoid" and a pharmaceutically acceptable carrier. The specification discloses examples of structures of some 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 C20-D1-3 retinoid and any others that might be found using the claimed method. Structural identifying characteristics of group of substituted C20-D1-3 retinoid 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. The claims also fail to comply with the written description requirement for lacking an adequate description for "A method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in the retina". The specification discloses a few disorders within the scope of what is claimed. However, in the absence of understanding the disorders to be treated the artisan would not have accepted that applicant was in possession of the claimed method of use.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 61-66, 75-81 and 84-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radu et al. in view of WO 95/04018 (Boehm) and further in view of WO 2005/065669 (Lang) and Widder (US 2007/0015827).

Radu teaches the use of isotretinoin, a C20-retinoid for inhibition of lipofuscin pigment in a retina. Such reference suggests that the treatment with isotretinoin may inhibit lipofuscin accumulation and thus delay the onset of visual loss in Stargardt's patient. See the entire article. Radu also teaches that lipofuscin pigment is A2E. See page 4742. Radu differs from the claimed invention in using substituted C20-D1-3 and the use of the secondary components. Boehm discloses a substituted C20 retinoid. Tritium labeled is taught in page 5, line 13-19, formula V, and deuterium labeled is taught on page 6, lines 15-37. It would have been obvious to a person skilled in the art to use the labeled retinoid instead of retinoid for the inhibition of lipofuscin and treat a

disease, such as, stargardt's characterized by lipofuscin accumulation and to improve efficacy of treatment, motivated by Boehm, which teaches the advantage of radio labeled retinoid in bind to the retinoid receptors. Lang teaches a composition for retarding the formation of a lipofuscin pigment in the retina comprising retinoid and a pharmaceutically acceptable carrier. See page 8, line 9-10, 21-23; page 9, line 1-3. The dosage form and the vitamins and supplements are taught on page 11. The concentration of Zinc is taught on page 13. The concentration of Vitamin E is taught on page 12, page 27 and example 3A. The concentration of Vitamin D is taught on page 30, 31 and example 4A. The use of antioxidants is taught on page 7. The use of minerals is taught on page 14. The use of carotenoids, such as zeaxanthin and lutein is taught on page 17. Widder teaches the use of phospholipids in combination with retinoid for the treatment of ophthalmic conditions, such as Stargardt's disease. See Para [0024], [0214], and claim 4. It would have been obvious to a person skilled in the art to add the secondary components to the composition of Radu and Boehm, motivated by the teachings of Lang and Widder, which teach the addition of such agents to retinoid as old and well known. Applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention, and as such, claims est61-66, 75-81 and 84-107 are properly rejected under 35 U.S.C. 103 (a).

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
/Zohreh A Fay/
Primary Examiner, Art Unit 1629

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12/733,631
Filing Date	March 10, 2010
First Named Inventor	Ilyas WASHINGTON
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	C035795/0307366

U.S.PATENTS						
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.	5,310,764		5/10/1994	Baranowitz, et al.	
	2.	6,660,297		12/9/2003	Bartels, et al.	
	3.	7,566,808		7/28/2009	Rando	
If you wish to add additional U.S. Published Application citation information please click the Add button.						

U.S.PATENT APPLICATION PUBLICATIONS						
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
	4.	2002/0012966		1/31/2002	Shi, et al.	
	5.	2003/0032078		2/13/2003	Travis	
	6.	2003/0149997		8/7/2003	Hageman	
	7.	2004/0009907		1/15/2004	Alsobrook, et al.	
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	10.	2005/0059010		3/17/2005	Stone, et al.	
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	12.	2005/0176662		8/11/2005	Inana, et al.	
	13.	2005/0220768		10/6/2005	McVey, et al.	
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	15.	2006/0094063		5/4/2006	Mata, et al.	
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	17.	2006/0135460		6/22/2006	Widder, et al.	
	18.	2006/0292099		12/28/2006	Milburn, et al.	
	19.	2007/0135481		6/14/2007	Jordan, et al.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12/733,631
Filing Date	March 10, 2010
First Named Inventor	Ilyas WASHINGTON
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	C035795/0307366

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1.	JP 2004-526725			9/2/2004	Eli Lilly & Co. et al.		Abstract
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	3.	WO 07/19503			2/15/2007	President and Fellows of Harvard College		

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U. S. PATENT DOCUMENTS

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	A1	US- 2006/0089411	04/27/2006	Gierhart	
	A2	US- 2007/0015827	01/18/2007	Widder, et al.	
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	B1	WO 1995/004018	02/09/1995	Ligand Pharmaceuticals		
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	C1	Radu, et al. "Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt's Macular Degeneration," PNAS 100(8): 4742-4747 (2003)	
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12733631	WASHINGTON, ILYAS
	Examiner	Art Unit
	ZOHREH FAY	1629

CPC- SEARCHED		
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CPC COMBINATION SETS - SEARCHED		
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Filing Date	2010-10-14
First Named Inventor	Ilyas Washington
Art Unit	1627
Examiner Name	Fay, Zohreh A.
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	1	8124646	B2	2012-02-28	Liu	
	2	8263601	B2	2012-09-11	Tung	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12733631
	Filing Date	2010-10-14
	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	"What is Deuterium?" [retrieved on 2/11/2013], <URL: http://www.innovateus.net/print/science/what-deuterium>. 4 pages.	☐
	2	BAILLIE, Thomas A., "The Use of Stable Isotopes in Pharmacological Research", Pharmacological Reviews, Vol. 33, No. 2, pp. 81-132, 1981.	☐
	3	FOSTER, Allan, "Deuterium Isotope Effects in Studies of Drug Metabolism," TIPS-- December 1984.	☐
	4	HANDELMAN et al., "An Improved Protocol for Determining Ratios of Retinol-d4 to Retinol Isolated from Human Plasma", Anal. Chem., 65, 2024-2028, 1993.	☐
	5	HASKINS, N.J., "The Application of Stable Isotopes in Biomedical Research", Biomedical Mass Spectrometry, Vol. 9, No. 7, pp. 269-277, 1982.	☐
	6	KUSHNER et al., "Pharmacological uses and perspectives of heavy water and deuterated compounds," Can. J. Physiol. Pharmacol. 77: 79-88 (1999).	☐
	7	PARK, et al. "Metabolism of Fluorine-Containing Drugs," Annu. Rev. Pharmacol. Toxicol. (41) 443-70 (2001).	☐
	8	TANG, G. et al., "Deuterium enrichment of retinol in humans determined by gas chromatography electron capture negative chemical ionization mass spectrometry", J. Nutr. Biochem, 9:408-414, 1998.	☐
	9	TUNG, Office action for US Patent Application 12/874,783, Dated 08/16/2011.	☐
	10	WOLEN, Robert L., "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence", The Journal of Clinical Pharm., Vol.26, pp. 419-424, 1986.	☐

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	Application Number	12733631
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	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

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EXAMINER SIGNATURE			
Examiner Signature	/Zohreh Fay/ (06/11/2013)	Date Considered	

*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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12733631
	Filing Date	2010-10-14
	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

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)	2013-02-26
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.**

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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 record s.

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.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/733,631	10/14/2010	Ilyas Washington	13533/541US

CONFIRMATION NO. 4180

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

POA ACCEPTANCE LETTER

OC000000060107105

Date Mailed: 04/05/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/21/2013.

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.

/ddinh/

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

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/733,631	10/14/2010	Ilyas Washington	C035795/0307366

CONFIRMATION NO. 4180

POWER OF ATTORNEY NOTICE

83369
BRYAN CAVE LLP
1290 AVENUE OF THE AMERICAS
NEW YORK, NY 10104

OC000000060107069

Date Mailed: 04/05/2013

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/21/2013.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/ddinh/

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

IR 2207
KK 13733.541

PTO/SB/81 (01-09)
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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	12/733,631
Filing Date	October 14, 2010
First Named Inventor	Ilyas Washington
Title	Compositions and Methods for Treating Macul
Art Unit	1627
Examiner Name	Zohreh A. Fay
Attorney Docket Number	13533/541US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

26646

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

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Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature	Gonzalo Merino, Ph.D., J.D.	Date	3/13/2013
Name	Associate General Counsel	Telephone	212-854-0284
Title and Company	The Trustees of Columbia University in the City of New York Columbia University		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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.**

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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: The Trustees of Columbia University in the City of New York

Application No./Patent No.: 12/733,631 Filed/Issue Date: October 14, 2010

Titled: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

The Trustees of Columbia University in the City of, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 025141, Frame 0787, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

_____ 3/13/2013

Signature Date

Gonzalo Merino, Ph.D., J.D. Associate General Counsel Columbia University

Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). 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 1.11 and 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.**

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Electronic Acknowledgement Receipt

EFS ID:	15322628
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	83369
Filer:	Joseph A. Coppola/Loretta E. Charles
Filer Authorized By:	Joseph A. Coppola
Attorney Docket Number:	C035795/0307366
Receipt Date:	21-MAR-2013
Filing Date:	14-OCT-2010
Time Stamp:	15:42:00
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13533-541US_Transmittal-Power-of-Attorney.pdf	281921 db1361fb6a6960f61d96025435c2c1ccf94b8728	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	1
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	Assignee showing of ownership per 37 CFR 3.73.	3	3
Warnings:			
Information:			
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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.

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE			
TRANSMITTAL LETTER FOR POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST		Docket Number: **13533/541US**	
Application Number **12/733,631**	Filing Date **October 14, 2010**	Examiner **Fay, Zohreh A**	Art Unit **1627**
Invention Title **COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**		Inventor(s) **Ilyas Washington**	

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 *March 21, 2013.*

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

MADAME:

Transmitted herewith for entry in the above-identified patent application are a Revocation of Prior Power of Attorney and Appointment of New Power of Attorney and Change of Correspondence Address, and a Statement under 37 C.F.R. § 3.73(b).

Please change the Attorney Docket Number for the above-identified patent application to "13533/541US".

Respectfully submitted,

Dated: March 21, 2013

By: /Joseph A Coppola/
Joseph A. Coppola
(Reg. No. 38,413)

KENYON & KENYON LLP
One Broadway
New York, New York 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)
CUSTOMER NO. 26646

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12733631
Filing Date	2010-10-14
First Named Inventor	Ilyas Washington
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	13533/541US

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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	8124646	B2	2012-02-28	Liu	
	2	8263601	B2	2012-09-11	Tung	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	"What is Deuterium?" [retrieved on 2/11/2013], <URL: http://www.innovateus.net/print/science/what-deuterium>. 4 pages.	☐
	2	BAILLIE, Thomas A., "The Use of Stable Isotopes in Pharmacological Research", Pharmacological Reviews, Vol. 33, No. 2, pp. 81-132, 1981.	☐
	3	FOSTER, Allan, "Deuterium Isotope Effects in Studies of Drug Metabolism," TIPS-- December 1984.	☐
	4	HANDELMAN et al., "An Improved Protocol for Determining Ratios of Retinol-d4 to Retinol Isolated from Human Plasma", Anal. Chem., 65, 2024-2028, 1993.	☐
	5	HASKINS, N.J., "The Application of Stable Isotopes in Biomedical Research", Biomedical Mass Spectrometry, Vol. 9, No. 7, pp. 269-277, 1982.	☐
	6	KUSHNER et al., "Pharmacological uses and perspectives of heavy water and deuterated compounds," Can. J. Physiol. Pharmacol. 77: 79-88 (1999).	☐
	7	PARK, et al. "Metabolism of Fluorine-Containing Drugs," Annu. Rev. Pharmacol. Toxicol. (41) 443-70 (2001).	☐
	8	TANG, G. et al., "Deuterium enrichment of retinol in humans determined by gas chromatography electron capture negative chemical ionization mass spectrometry", J. Nutr. Biochem, 9:408-414, 1998.	☐
	9	TUNG, Office action for US Patent Application 12/874,783, Dated 08/16/2011.	☐
	10	WOLEN, Robert L., "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence", The Journal of Clinical Pharm., Vol.26, pp. 419-424, 1986.	☐

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	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

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Examiner Signature		Date Considered	

*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	12733631
	Filing Date	2010-10-14
	First Named Inventor	Ilyas Washington
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	13533/541US

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)	2013-02-26
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 record s.

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.

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE			
REQUEST FOR REFUND - SMALL ENTITY ASSERTION		Docket No. **13533/541US**	Confirmation No. **4180**
Serial No. **12/733631**	Filing Date **October 14, 2010**	Examiner **Fay, Zohreh A.**	Art Unit **1627**
Invention Title **COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**		Inventors **Ilyas Washington**	

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 **February 26, 2013.**

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

SIR:

Pursuant to 37 C.F.R. 1.27 and 1.28, Applicant asserts that it qualified as a small entity at the time of the filing of the subject application. Applicant further asserts that it continues to qualify as a small entity and requests a refund in the amount of **$1,141.00.**

The refund amounts to *$645.00* excess Extension of Time fees and *$496.00* excess claims fees paid in the subject application on February 20, 2013 via the United States Patent and Trademark Office electronic filing system. A copy of Electronic Acknowledgement Receipt dated February 20, 2013 is attached.

The large entity fee was paid in error.

The refund in the amount of **$1,141.00** should be credited to Kenyon & Kenyon LLP Deposit Account No.: **11-0600.**

Future Patent Office fees will be paid at the small entity rate as already established.

Respectfully submitted,

Dated: February 26, 2013

By: /Joseph A. Coppola/
Joseph A. Coppola
(Reg. No.38,413)
KENYON & KENYON LLP
One Broadway
New York, N.Y. 10004
(212) 425-7200
Customer No. 26646

NY01 2519125 v1

Electronic Acknowledgement Receipt

EFS ID:	15008284
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	83369
Filer:	Joseph A. Coppola/Loretta E. Charles
Filer Authorized By:	Joseph A. Coppola
Attorney Docket Number:	C035795/0307366
Receipt Date:	20-FEB-2013
Filing Date:	14-OCT-2010
Time Stamp:	18:30:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2282
RAM confirmation Number	9167
Deposit Account	110600
Authorized User	
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	Response to Election / Restriction Filed	Response-to-RR_2-20-2013.pdf	262774 ddcdfd1500876a6c4a8bbad2c6cb15bf90fd27a9	no	15
Warnings:					
Information:					
2	Extension of Time	Petition-for-Extension-of-Time.pdf	83395 7a92ab05d63f12f3bd5bf7ab5f1b15b4033bd9a0	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32273 5dafb3de01e8e0b29b40ebcab89b0f5b416cbfdf	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	378442		

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.

Electronic Acknowledgement Receipt

EFS ID:	15056573
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	83369
Filer:	Joseph A. Coppola/Loretta E. Charles
Filer Authorized By:	Joseph A. Coppola
Attorney Docket Number:	C035795/0307366
Receipt Date:	26-FEB-2013
Filing Date:	14-OCT-2010
Time Stamp:	17:02:19
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	13533-541US_Supp-IDS-Transmittal-Letter.pdf	114825 6e98293237075a6e7bff325465951b295623895e	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	13533-541US_Supplemental-IDS.pdf	613326 90d4d2235ca9492d9cfb40a3b08711b4b7a1da3f	no	5
Warnings:					
Information:					
3	Non Patent Literature	Baille_1981.pdf	12795674 bd7fc6991f7f0fc32eac1077deed5859e54e9f39	no	52
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Information:					
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Information:					
5	Non Patent Literature	Handelman_1993.pdf	10697006 d30501e9d6d4fd99636b8a0cee9fbd3cc3474774	no	5
Warnings:					
Information:					
6	Non Patent Literature	Haskins_1982.pdf	19920437 3f7cfe18571102fc0dd43acb383f3cd8f299fa79	no	9
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
7	Non Patent Literature	Kushner_1999.pdf	1786410 e006a158c499b39a6dd414d67082ca229aa96cdc	no	10
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8	Non Patent Literature	Park_2001.pdf	462724 2ba0941402a9ca2298c9dfc7189a7cb162373aef	no	30
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9	Non Patent Literature	Tang_1998.pdf	219128 aeb59bd2ee40510032efb3179853f3f7d9c42974	no	7
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10	Non Patent Literature	Tung_OA-12874783.pdf	7367084 2fd6e866c7ebcae0a2d2a88e96c9c08461555a23	no	9

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Information:					
12	Non Patent Literature	What-is-Deuterium.pdf	58998 8151acb824ac5f4bc64feb4a157aca3051ea4914	no	4
Warnings:					
Information:					
13	Refund Request	13533-541US_Refund-Request.pdf	137813 83a47676df6b39d5a03f724f546fbad1f56ccfee	no	3
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
			Total Files Size (in bytes):	75105418	

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

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application No.: 12/733,631 | Confirmation No.: 4180

Filed: October 14, 2010 | Art Unit: 1627

For: Compositions and Methods for Treating Macular Degeneration | Examiner: Fay, Zohreh A.

Via EFS-Web
MS: Amendment
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 **February 26, 2013.**

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir/Madam:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 CFR 1.97(b)(3)).

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 11-0600.

Dated: February 26, 2013

Respectfully submitted,

/Joseph A. Coppola/
Joseph A. Coppola
Registration No.: 38,413

KENYON AND KENYON LLP
One Broadway
New York, New York 10004-1050
(212) 425-7200
Customer No. 26646

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ilyas Washington

Application No.: 12/733,631 | Confirmation No.: 4180

Filed: October 14, 2010 | Art Unit: 1627

For: Compositions and Methods for Treating Macular Degeneration | Examiner: Fay, Zohreh A.

VIA EFS-Web
MS: Amendment
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 ***February 20, 2013.***

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

RESPONSE TO RESTRICTION REQUIREMENT

Dear Sir/Madam:

This Paper is in response to the Restriction Requirement mailed November 7, 2012. Applicant requests that the time period for reply be extended to March 7, 2013. A Petition for Extension of Time is being filed concurrently herewith. Authorization is hereby granted to charge the extension fee, the excess claim fees and any additional fees which may be required regarding this application, or credit any overpayment, to Deposit Account No. 11-0600.

Please amend the subject application as follows:

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1-49. (Cancelled)

50. (Withdrawn-New) A pharmaceutical composition comprising a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

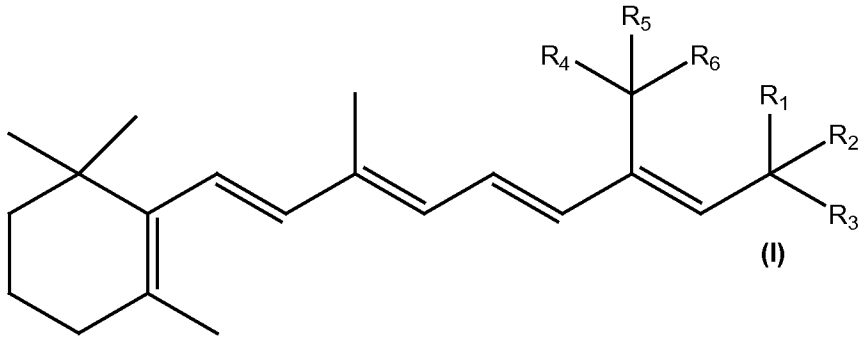
51. (Withdrawn-New) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is a C_{20}-D_3-retinoid.

52. (Withdrawn-New) The pharmaceutical composition according to Claim 51 in a unit dosage form.

53. (Withdrawn-New) The pharmaceutical composition according to Claim 51, which is a vitamin supplement.

54. (Withdrawn-New) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

55. (Withdrawn-New) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is according to formula I :



(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 H or D, wherein R_4, R_5, and R_6 are not each H.

56. (Withdrawn-New) The pharmaceutical composition according to Claim 50, wherein the substituted C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal or a C_{20}-D_3-carotenoid.

57. (Withdrawn-New) The pharmaceutical composition according to Claim 50, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

58. (Withdrawn-New) The pharmaceutical composition according to Claim 57, wherein the C_{20}-D_3-retinol acetate inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinol acetate.

59. (Withdrawn-New) The pharmaceutical composition according to Claim 57, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

60. (Withdrawn-New) The pharmaceutical composition according to Claim 50, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

61. (New) A method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

62. (New) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinoid.

63. (New) The method according to Claim 61, wherein the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

64. (New) The method according to Claim 61, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

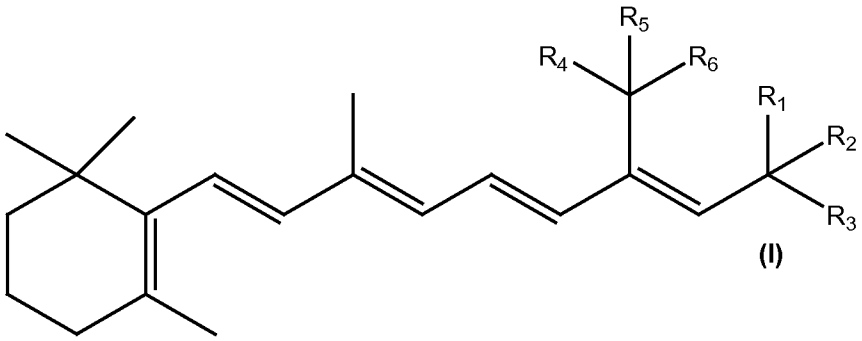
65. (New) The method according to Claim 61, wherein the pharmaceutical composition is administered as a unit dosage form.

66. (New) The method according to Claim 61, wherein the disease is a macular degeneration.

67. (Withdrawn-New) The method according to Claim 66, wherein the macular degeneration is age-related macular degeneration.

68. (Withdrawn-New) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

69. (Withdrawn-New) The method according to Claim 67, wherein the substituted C_{20}-D_{1-3}-retinoid is according to formula I :



(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 H or D, wherein R_4, R_5, and R_6 are not each H.

70. (Withdrawn-New) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-carotenoid.

71. (Withdrawn-New) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

72. (Withdrawn-New) The method according to Claim 71, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

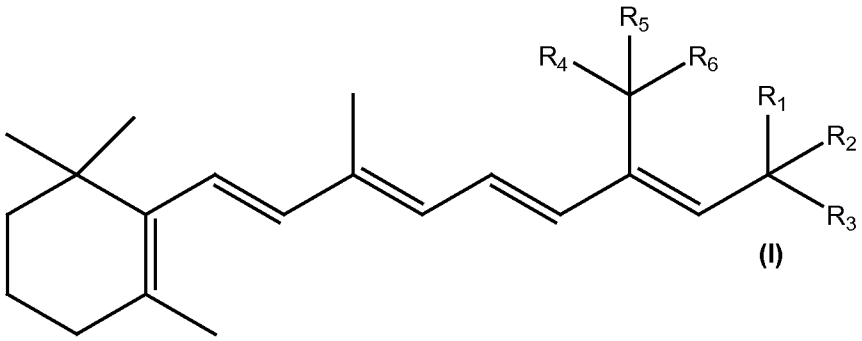
73. (Withdrawn-New) The method according to Claim 67, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

74. (Withdrawn-New) The method according to Claim 67, wherein the disease is dry (non-neovascular) age-related macular degeneration.

75. (New) The method according to Claim 61, wherein the disease is Stargardt disease.

76. (New) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

77. (New) The method according to Claim 75, wherein the substituted C_{20}-D_{1-3}-retinoid is according to formula I :



(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 H or D, wherein R_4, R_5, and R_6 are not each H.

78. (New) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-carotenoid.

79. (New) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

80. (New) The method according to Claim 79, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

81. (New) The method according to Claim 75, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

82. (Withdrawn-New) The method according to Claim 61, wherein the disease is selected from the group consisting of Vitelliform or Best disease, Sorsby's fundus dystrophy, retinitis pigmentosa, and Malattia Leventinese.

83. (New) The method according to Claim 61, wherein the disease is characterized by one or more mutation(s) in the ABCA4 gene.

84. (New) The method according to Claim 61 further comprising administering to the patient 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.

85. (New) The method according to Claim 84, wherein the visual cycle antagonist is selected from the group consisting of TDH, TDT, 13-cis-retinoic acid, ret-NH_2, and combinations thereof.

86. (New) The method according to Claim 84, wherein the molecule that inhibits influx of a retinoid into an eye is fenretinide.

87. (New) The method according to Claim 84 further comprising one or more additives.

88. (New) The method according to Claim 87, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.

89. (New) The method according to Claim 88, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 80 mg.

90. (New) The method according to Claim 88, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 10 mg.

91. (New) The method according to Claim 88, wherein the zinc is present in the pharmaceutical composition at between about 10 to about 80 mg.

92. (New) The method according to Claim 88, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 3,000 mg.

93. (New) The method according to Claim 88, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 15 mg.

94. (New) The method according to Claim 88, wherein the vitamin E is present in the pharmaceutical composition at between about 15 to about 3,000 mg.

95. (New) The method according to Claim 88, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.1 mg.

96. (New) The method according to Claim 88, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.015 mg.

97. (New) The method according to Claim 88, wherein the vitamin D is present in the pharmaceutical composition at between about 0.015 to about 0.1 mg.

98. (New) The method according to Claim 61, wherein the substituted C_{20}-D_{1-3}-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.

99. (New) The method according to Claim 61 further comprising an additional active.

100. (New) The method according to Claim 99, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

101. (New) The method according to Claim 100, 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.

102. (New) The method according to Claim 100, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

103. (New) The method according to Claim 100, wherein the negatively charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

104. (New) The method according to Claim 100, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

105. (New) The method according to Claim 61, wherein the C_{20}-D_{1-3}-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

106. (New) The method according to Claim 61, wherein the C_{20}-D_3-retinaldehyde, corresponding to the aldehyde of the C_{20}-D_3-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinaldehyde.

107. (New) The method according to Claim 61, wherein the pharmaceutical composition is administered directly to the eye.

108. (Withdrawn-New) A method of retarding formation of a lipofuscin pigment in a retina comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

109. (Withdrawn-New) The method according to Claim 108, wherein the C_{20}-D_{1-3}-retinoid is a C_{20}-D_3-retinoid.

110. (Withdrawn-New) The method according to Claim 108, wherein the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

111. (Withdrawn-New) The method according to Claim 108, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

112. (Withdrawn-New) The method according to Claim 108, wherein the pharmaceutical composition is administered as a unit dosage form.

113. (Withdrawn-New) A method of retarding formation of a lipofuscin pigment selected from the group consisting of A2E, ATR-dimer, and combinations thereof, the method comprising replacing a retinoid with a pharmaceutical composition comprising a C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier, under conditions sufficient to impede formation of A2E, ATR-dimer, or both A2E and ATR-dimer.

114. (Withdrawn-New) A method of retarding formation of A2E in a retina comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

REMARKS

Claim Amendments

Claims 1-49 have been cancelled.

The new set of Claims consists in Claims 50-114 that are either new or amended from the original Claims:

- **Group I (original Claims 1-5) corresponds to new Claims 108-112** that have been amended from the original claims to recite a method of retarding lipofuscin formation in the retina using a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier;
- **Group II (original Claims 6-13) corresponds to new Claims 61-107** that have been amended from the original claims to recite a method of retarding lipofuscin formation in the retina using a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier;
- **Group III (original Claims 14-18) corresponds to new Claims 50-60** that have been amended from the original claims to recite a pharmaceutical composition comprising a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier;
- **Group IV is identical to Group III;**
- **Group V (original Claim 19) corresponds to new Claim 113** that has been amended from the original claim to recite a method of retarding the formation of a lipofuscin pigment using a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier;
- **Group VI (original Claims 20-46):** the original claims have been amended so that they now dependent on either new claim 50 (Group III) or on new claim 61 and dependent claims (Group II). As such, Group VI does not exist anymore;
- **Group VII (original Claims 47-49) corresponds to new Claim 114** that has been amended to recite a method of retarding A2E formation using a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

Composition Claims have been changed to pharmaceutical compositions; and method Claims have been amended to recite pharmaceutical compositions. All new claims now require a pharmaceutical composition comprising a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier.

Explanation and support for the new set of claims is detailed in table below:

New claim number (independent claims underlined)	**Original claim number (when applicable)**	**Major Amendment(s) and Support (when necessary)**
<u>50</u>	14	Now recites a pharmaceutical composition. Restricts broad substitution at C20 to substitution by 1 to 3 deuterium atoms (D1-3). Support found in paragraphs 0045 and 0046. Phrase "for retarding formation of a lipofuscin pigment in the retina" has been deleted.
51	15	Deleted references to C20-T3-retinoid and C20-F3-retinoid.
52	16	
53	17	
54	20	Now dependent from Claim 50. Amended to replace the chemical structure with chemical names found in paragraph 0057.
55	20	Now dependent from Claim 50. Amended to restrict choice of substitution to deuterium only as found in paragraph 0060.
56	22	Replaces tritium (^{3}H or T) with deuterium D. Replaces chemical structure with chemical name as found in paragraph 0060.
57		Recites C20-D3-retinol acetate as found in paragraph 0057.
58		Recites C20-D3-retinol acetate inhibits formation of A2E and/or ATR dimers compared to non substituted (non deuterium enriched) retinol acetate as found in paragraphs 0045 and 0061.
59		Recites that the corresponding aldehyde of the substituted retinoid can inhibit formation of A2E by about 7 times as found in paragraphs 0045, 0035 and 0088.
60		Recites C20-D1-3-retinoid inhibits formation of A2E/ATR-

		dimers compared to non-substituted retinoids as found in paragraphs 0045 and 0061.
61	6	Restricts substitution at C20 to substitution by 1 to 3 deuterium atoms (D1-3). Support found in paragraphs 0045 and 0046. Deleted "in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina". Added expression "an effective amount".
62	7	
63	8	
64	9	Added the expression "composition is suitable for use as".
65	10	
66	11	Disease is generally defined as "a" macular degeneration . Macular degeneration is composed of various degenerative diseases of the retina (Stargardt disease being one of them), as found in paragraph 0004.
67		Disease is age-related macular degeneration as found in 0004.
68		Restriction to C_{20}-D_{1-3}-retinol and -retinol ester as found in 0057.
69	20	Now recited as a method Claim. Now dependent from Claim 67. Amended to restrict choice of substitution to deuterium only as found in paragraph 0060.
70		Restriction to C_{20}-D_3-retinol, -a retinol ester, -retinal or – carotenoid. Support found in paragraph 0060.
71		Restriction to C_{20}-D_3-retinol acetate. Support in paragraph 0057.
72		Similar to claim 59.
73		Similar to claim 58.
74		Age-related macular degeneration restricted to its dry form, as found in 0005.
75	12	Restricted the Claim to only Stargardt disease (as found in

		paragraph 0004)
76		Restriction to C_{20}-D_{1-3}-retinol and -retinol ester as found in 0057.
77	20	Now recited as a method Claim. Now dependent from Claim 75. Amended to restrict choice of substitution to deuterium only as found in paragraph 0060.
78		Restriction to C_{20}-D_3-retinol, -a retinol ester, -retinal or – carotenoid, as found in paragraph 0060.
79		Restriction to C_{20}-D_3-retinol acetate, as found in paragraph 0057.
80		Similar to claim 59
81		Similar to claim 58.
82	12	Deleted “age-related macular degeneration” and “Stargardt”
83		Restriction to diseases (Stargardt disease being one of them) characterized by mutation(s) in ABCA4 gene as found in paragraph 0008.
84-104	26-46	Similar as original claims, but changed to method claims. Now dependent from claim 61.
105		Similar to claim 58.
106		Similar to claim 59.
107	49	Now dependent from Claim 61. Direct application to the eye as found in paragraph 0056.
108	1	Restricts substitution at C20 to substitution with 1 to 3 deuterium atoms. Support found in paragraphs 0045 and 0046.
109	2	

110	3	
111	4	
112	5	
113	19	Recites C20-D1-3 instead of C20-D3 as found in 0045 and 0046. Replaces "ATR substrate" by "retinoid substrate".
114	47	Deleted "replacing an all-trans-retinal substrate". Added "administering an effective amount of a pharmaceutical composition". Replaced C_{20}-D_3-retinoid with C_{20}-D_{1-3}-retinoid as found in 0045 and 0046.

Response to the Restriction Requirement and Requirement for Election of Species

In response to the restriction requirement, Applicant hereby elect the invention of Group II, now corresponding to new Claims 61-107 (Original Claims 6-13). Claims 84-104 (Original Claims 26-46), originally belonging to group VI, have been amended to method of treatment claims and now ultimately depend from Claim 61, and as such now also belong to Group II. Claim 107 (original Claim 49) originally from group VII has been amended to a method of treatment claim depending from Claim 61, and as such now belongs to Group II. Claims 69 and 77 (original Claim 20) have been amended to recite a method of treatment claim ultimately depending from Claim 61, and as such now belongs to Group II.

The Examiner asserts that restriction among the seven groups is proper because unity of invention is lacking among these seven groups. Specifically, the Examiner asserts that there is no technical relationship among the inventions involving one or more of the same or corresponding technical features. Applicant respectfully traverses the restriction with respect to groups I through VII.

The unity of invention standard for restriction in a U.S. National Stage is set forth in 37 C.F.R. 1.475(a):

> An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is

> claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Applicant asserts that there is a special technical feature present in all of the claims, as amended, that distinguishes over the prior art. Specifically, all of the claims require a pharmaceutical composition comprising a substituted C_{20}-D_{1-3}-retinoid and a pharmaceutically acceptable carrier; and this feature distinguishes the claimed subject matter over the prior art and is therefore a special technical feature. No prior art of record has been identified to the contrary. Unless the Examiner can identify prior art which disclose or render obvious this pharmaceutical composition, unity of invention exists and the restriction requirement is improper. Withdrawal is requested of the restrictions between groups I through VII.

Applicant also notes that Group III (original Claims 14-18 corresponding to new Claims 50-53) appears to be a duplicate of Group IV. If this is not the case, clarification is requested from the Examiner. Otherwise, Applicant requests that the restriction requirement between Groups III and IV be withdrawn.

Applicant also traverses the restriction requirement with respect to Group III (new Claims 50-60) and Group VI (original Claims 20-46, corresponding to new Claims 54, 55, 69, 77 and 84-104) on other grounds. New Claim 54 and 55 have been amended to depend from Claim 50. New Claim 69 has been amended to depend from Claim 67. New Claim 77 has been amended to depend from Claim 75. New Claims 84-104 have been amended to depend from Claim 61. The subject matter of Claims 50 and 54-55, of Claims 69 and 67, of Claims 77 and 75 are therefore related as genus/subgenus, and so is the subject matter of Claims 84-104. MPEP 806.04 provides that restriction between a generic claim and a reasonable number of species should not be made. As such, withdrawal of the restriction requirement between Groups III and VI is requested.

Applicant reserves the right to prosecute the non-elected claims in a divisional or continuation application.

In response to the requirement for election of species with respect to compounds, Applicant hereby elects C_{20}-D_3-retinoid. All of the claims read on the elected species; and within the elected group, Group II, all of the claims, 61-107, read on the elected species.

In response to the requirement for election of species with respect to diseases, Applicant hereby elects Stargardt disease. Within the elected group, Group II, claims 61-66, 73-81 and 83-104 read on the elected species.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The time for responding to the Office Action was set for December 7, 2012. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response. Please charge any corresponding fees for the Petition to Kenyon & Kenyon LLP's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Commissioner is authorized to charge Kenyon & Kenyon LLP's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: February 20, 2013

By: /Joseph A. Coppola /
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PTO/SB/22 (10-12)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 13533/541US

Application Number: 12/733,631

Filed: October 14, 2010

For: Compositions and Methods for Treating Macular Degeneration

Art Unit: 1627

Examiner: Fay, Zohreh A.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$150	$75	$
☐ Two months (37 CFR 1.17(a)(2))	$570	$285	$
■ Three months (37 CFR 1.17(a)(3))	$1,290	$645	$ 1,290
☐ Four months (37 CFR 1.17(a)(4))	$2,010	$1,005	$
☐ Five months (37 CFR 1.17(a)(5))	$2,730	$1,365	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

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

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____.

■ Payment made via EFS-Web.

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.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☐ attorney or agent of record. Registration number _____.

■ attorney or agent acting under 37 CFR 1.34. Registration number 38,413

/Joseph A. Coppola/ — Signature

February 20, 2013 — Date

Joseph A. Coppola — Typed or printed name

212 425 7200 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 1.11 and 1.14. This collection is estimated to take 6 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: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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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.

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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.

Electronic Patent Application Fee Transmittal

Application Number:	12733631
Filing Date:	14-Oct-2010
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:	C035795/0307366

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1615	16	62	992
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1290	1290
Miscellaneous:				
			Total in USD ($)	**2282**

Electronic Acknowledgement Receipt

EFS ID:	15008284
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	83369
Filer:	Joseph A. Coppola/Loretta E. Charles
Filer Authorized By:	Joseph A. Coppola
Attorney Docket Number:	C035795/0307366
Receipt Date:	20-FEB-2013
Filing Date:	14-OCT-2010
Time Stamp:	18:30:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2282
RAM confirmation Number	9167
Deposit Account	110600
Authorized User	
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	Response to Election / Restriction Filed	Response-to-RR_2-20-2013.pdf	262774 ddcdfd1500876a6c4a8bbad2c6cb15bf90fd27a9	no	15
Warnings:					
Information:					
2	Extension of Time	Petition-for-Extension-of-Time.pdf	83395 7a92ab05d63f12f3bd5bf7ab5f1b15b4033bd9a0	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32273 5dafb3de01e8e0b29b40ebcab89b0f5b416cbfdf	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	378442		

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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.

PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/733,631	10/14/2010	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 02/20/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 65	Minus	** 49	= 16	X $31 =	496	OR	X $ =	
Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $125 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	496	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	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))									
☐ 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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TERRY MALLOY/

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.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/733,631	10/14/2010	Ilyas Washington	C035795/0307366	4180

83369 7590 11/07/2012

BRYAN CAVE LLP
1290 AVENUE OF THE AMERICAS
NEW YORK, NY 10104

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
11/07/2012	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	12/733,631	WASHINGTON, ILYAS	
	Examiner	Art Unit	
	ZOHREH FAY	1627	

-- 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 *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 _____.

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) *1-49* 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) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-49* 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).

a)☐ All b)☐ Some * c)☐ None of:

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)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-5 are, drawn to a method of retarding formation of lipofuscin pigment in the retina using a substituted C20-retinoid.

Group II, claim(s) 6-13 are, drawn to 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 C20-retinoid.

Group III, claim(s) 14-18 are, drawn to a composition for retarding formation of a lipofuscin pigment using a substituted C20-retinoid.

Group IV, claim(s) 14-18 are, drawn to a composition for retarding formation of lipofuscin pigment in the retina comprising a substituted C-20 retinoid.

Group V, claim(s) 19 is , drawn to a method comprising replacing an all-trans-retinla (ATR) substrate with a C20-D3-retinoid substrate under conditions sufficient to impede the formation of A2E, ATR dimer or both A2E and ATR dimer.

Group VI, claim(s) 20-46 are, drawn to a composition of Formula I.

Group VII, claim(s) 47-49 are, drawn to a method of retarding the formation of A2E in a patient comprising replacing an all-trans –retinal (ATR) substrate with a substituated C20-D3-retinoid substrate in a patient under conditions sufficient to impede the formation of A2E.

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

C20-D3-retinoid, C20-T3-retinoid, C20-F3-retinoid and the diseases of macular degeneration, stargardt, vitelliform or Best (VMD), Sorsby's fundus Dystrophy, age related macular degeneration and Malattia Leventinese.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an allowed generic claim. Currently, the following claim(s) are generic: 1, 6, 14, 19, 20 and 47.

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of

the same or corresponding special technical features. The expression “special technical features” shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

WHEN CLAIMS ARE DIRECTED TO MULTIPLE CATEGORIES OF INVENTIONS

As provided in 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475(c).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention or species.

Should applicant traverse on the ground that the inventions have unity of invention (37 CFR 1.475(a)), applicant must provide reasons in support thereof. Applicant may submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. Where such evidence or admission is provided by applicant, if the examiner finds one of

the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

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
/Zohreh A Fay/
Primary Examiner, Art Unit 1627

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12/733,631
Filing Date	March 10, 2010
First Named Inventor	Ilyas WASHINGTON
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	C035795/0307366

U.S.PATENTS

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.	5,310,764		5/10/1994	Baranowitz, et al.	
	2.	6,660,297		12/9/2003	Bartels, et al.	
	3.	7,566,808		7/28/2009	Rando	

If you wish to add additional U.S. Published Application citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

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
	4.	2002/0012966		1/31/2002	Shi, et al.	
	5.	2003/0032078		2/13/2003	Travis	
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FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1.	JP 2004-526725			9/2/2004	Eli Lilly & Co. et al.		Abstract
	2.	WO 05/087210			9/22/2005	Lars Michael Larsen		
	3.	WO 07/19503			2/15/2007	President and Fellows of Harvard College		
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Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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	Application Number	12/733,631
	Filing Date	March 10, 2010
	First Named Inventor	Ilyas WASHINGTON
	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned
	Attorney Docket Number	C035795/0307366

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	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12/733,631
	Filing Date	March 10, 2010
	First Named Inventor	Ilyas WASHINGTON
	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned
	Attorney Docket Number	C035795/0307366

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).

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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	Jihong Zang	Date (YYYY-MM-DD)	2012-09-05
Name/Print	/Jihong Zang/	Registration Number	56,606

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.**

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Application Number:	12733631
Filing Date:	14-Oct-2010
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Filer:	Jihong Zang/Teresa Rodriguez
Attorney Docket Number:	C035795/0307366

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
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Miscellaneous-Filing:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	13662346
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	83369
Filer:	Jihong Zang
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Receipt Date:	05-SEP-2012
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Time Stamp:	16:06:00
Application Type:	U.S. National Stage under 35 USC 371

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Payment Type	Deposit Account
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Docket No.: IR 2207 (C035795/0307366)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
Ilyas WASHINGTON	)	
	)	Examiner: Not Yet Assigned
Serial No.: 12/733,631	)	
	)	Art Unit: Not Yet Assigned
Filed: March 10, 2010	)	
	)	
For: **COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**	)	

New York, NY
September 5, 2012

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

Sir:

Pursuant to 37 C.F.R. § 1.56 and in accordance with 37 C.F.R. §§ 1.97-1.98, applicants wish to bring the following documents to the Examiner's attention.

U.S. PATENT DOCUMENTS

	Patent No.	Date	Name
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2.	2003/0032078	2/13/2003	Travis
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	Patent No.	Date	Name
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We note that a copy of document #71 above was submitted in the previous information disclosure statement dated March 10, 2010, but is relisted here in a format that conforms with the electronic citation requirements of the USPTO.

The Examiner's independent consideration of all of these documents and their relevance before issuance of the first official action is respectfully requested. The Examiner is also requested to initial and return a copy of the accompanying forms PTO/SB/08 to evidence such consideration.

Copies of all documents identified above, other than the U.S. patent documents, are provided. See MPEP § 609(III)(A)(2)(A) (8th Ed., Rev. 2, May 2004, p. 600-128).; See also 1276 OG 55 (August 5, 2003) (Waiving the requirement under Rule 98(a)(2)(1) to provide a copy of each cited U.S. patent document for any application filed after June 30, 2003).

The filing of this statement is not to be construed as an admission that the information cited herein is, or is considered to be, material to the patentability of the invention claimed in the instant application, and that it qualifies as prior art against any or all of the current claims.

This Information Disclosure Statement is being filed in accordance with the provisions under 37 C.F.R. §1.97(b)(3), before the mailing of a first Office Action on the merits. Accordingly, no fee is believed to be due. If, however, a fee is due, please charge the same to Deposit Account No. 02-4467.

If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

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Electronic Acknowledgement Receipt

EFS ID:	13662647
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	Ilyas Washington
Customer Number:	83369
Filer:	Jihong Zang
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/733,631	10/14/2010	Ilyas Washington	C035795/0307366

CONFIRMATION NO. 4180

83369
BRYAN CAVE LLP
1290 AVENUE OF THE AMERICAS
NEW YORK, NY 10104

PUBLICATION NOTICE

OC000000045936704

Title:COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

Publication No.US-2011-0034554-A1
Publication Date:02/10/2011

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
12/733,631	Ilyas Washington	C035795/0307366

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INTERNATIONAL APPLICATION NO.	
PCT/US2008/010676	
I.A. FILING DATE	PRIORITY DATE
09/12/2008	09/12/2007

CONFIRMATION NO. 4180
371 ACCEPTANCE LETTER

OC000000044261126

Date Mailed: 11/02/2010

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

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10/14/2010	10/14/2010
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 03/10/2010
- Copy of the International Search Report filed on 03/10/2010
- Preliminary Amendments filed on 03/10/2010
- Information Disclosure Statements filed on 03/10/2010
- Oath or Declaration filed on 10/14/2010
- U.S. Basic National Fees filed on 03/10/2010
- Assignment filed on 10/14/2010
- Priority Documents filed on 03/10/2010
- Specification filed on 03/10/2010
- Claims filed on 03/10/2010
- Abstracts filed on 03/10/2010
- Drawings filed on 03/10/2010
- Authorization to Permit Access filed on 10/14/2010

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VONDA M WALLACE

Telephone: (571) 272-3734

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12/733,631	10/14/2010		1474	C035795/0307366	49	6

CONFIRMATION NO. 4180

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NEW YORK, NY 10104

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OC000000044261125

Date Mailed: 11/02/2010

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**

Applicant(s)

Ilyas Washington, New York, NY;

Power of Attorney: The patent practitioners associated with Customer Number 83369

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US2008/010676 09/12/2008
which claims benefit of 60/993,379 09/12/2007

Foreign Applications

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Projected Publication Date: 02/10/2011

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****

Title

COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

Preliminary Class

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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).

Docket No.: IR 2207 (C035795/0307366)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
Ilyas WASHINGTON	)	Examiner: Not Yet Assigned
Serial No.: 12/733,631	)	Art Unit: Not Yet Assigned
Filed: March 10, 2010	)	
For: **COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**	)	

New York, NY
October 14, 2010

RESPONSE TO NOTIFICATION OF MISSING REQUIREMENTS AND PETITION FOR EXTENSION OF TIME

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

Sir:

The shortened statutory period of time for response to the Notification Of Missing Requirements Under 35 U.S.C. 371 mailed April 5, 2010 expired on June 5, 2010. A five-month extension of time is hereby requested. Accordingly, this Response is timely filed with an executed certificate of transmission on or before November 5, 2010. *See* 37 C.F.R. §1.136. Please charge the amount of $1,175.00 to cover the fee for the petition for extension of time for five months to Deposit Account No. 02-4467. *See* 37 C.F.R. §1.17(a).

Applicants submit herewith a properly signed Declaration and Power of Attorney in compliance with 37 C.F.R. § 1.497(a) and (b).

Docket No.: IR 2207 (C035795/0307366)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
Ilyas WASHINGTON	)	Examiner: Not Yet Assigned
Serial No.: 12/733,631	)	Art Unit: Not Yet Assigned
Filed: March 10, 2010	)	
For: **COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**	)	

New York, NY
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Applicants submit herewith a properly signed Declaration and Power of Attorney in compliance with 37 C.F.R. § 1.497(a) and (b).

Please charge our Deposit Account No. 02-4467 in the amount of $65.00 to cover the fee for the surcharge (small entity). 37 C.F.R. § 1.16(f). A duplicate copy of this sheet is enclosed.

Please charge any required fee not otherwise covered or credit any overpayment to our Deposit Account No. 02-4467. As noted above, a duplicate copy of this sheet is enclosed.

I hereby certify that this correspondence is being transmitted in accordance with 37 CFR §§1.6(a)(4) and 1.8 via the U.S. Patent and Trademark Office (USPTO) electronic filing system (EFS-Web) to: Mail Stop Missing Parts, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on October 14, 2010.

Kevin C. Hooper, Reg. No. 40,402

Respectfully submitted,

By: _____

Kevin C. Hooper
Registration No. 40,402
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300
Tel.: (212) 541-2000
Fax: (212) 541-4630

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

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
12/733,631		C035795/0307366

Kevin C. Hooper, Esq.
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104

C35795 | 307366
(12 2007)
Cahuenga U -
Docket -
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INTERNATIONAL APPLICATION NO.	
PCT/US2008/010676	
I.A. FILING DATE	PRIORITY DATE
09/12/2008	09/12/2007

CONFIRMATION NO. 4180
371 FORMALITIES LETTER

OC000000040964989

Date Mailed: 04/05/2010

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as a Designated Office (37 CFR 1.494):

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 03/10/2010
- Copy of the International Search Report filed on 03/10/2010
- Preliminary Amendments filed on 03/10/2010
- Information Disclosure Statements filed on 03/10/2010
- U.S. Basic National Fees filed on 03/10/2010
- Priority Documents filed on 03/10/2010
- Specification filed on 03/10/2010
- Claims filed on 03/10/2010
- Abstracts filed on 03/10/2010
- Drawings filed on 03/10/2010

The applicant needs to satisfy supplemental fees problems indicated below.

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.492(h) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fees required for this application is **$65** for a Small Entity:

- **$65** Surcharge.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
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.

VONDA M WALLACE

Telephone: (703) 756-1425

DECLARATION FOR UTILITY OR DESIGN PATENT APPPLICATION (37 CFR 1.63)		
	Attorney Docket Number	IR 2207 (C035795/0307366)
	First Named Inventor	Ilyas WASHINGTON
	COMPLETE IF KNOWN	
	Application Number	12/733,631
	Filing Date	March 10, 2010
	Art Unit	Not yet assigned
	Examiner Name	Not yet assigned

☐ Declaration Submitted With Initial Filing OR ☒ Declaration Submitted After Initial Filing (surcharge (37 CFR 1.16(f)) required))

As a below named inventor, I hereby declare that: (1) my residence, mailing address, and citizenship are as stated below next to my name; and (2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention titled:

COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

(Title of the Invention)

the application of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 03/10/2010 as United States Application Serial Number 12/733,631 and was amended on (MM/DD/YYYY) 03/10/2010 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Authorization To Permit Access To Application by Participating Offices

☒ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to

which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

National Stage

The present application is a U.S. National Stage entry from the PCT under 35 U.S.C. §371. ☒ Yes ☐ No

If the present application is a U.S. National Stage application, it enters the U.S. National Stage from International Application No. PCT/US08/010676, filed September 12, 2008.

Claim of Foreign Priority Benefits

Prior Foreign/PCT Application(s) Filed Within 12 Months (6 Months for Design) Prior to this Application and any Priority Claims Under 35 U.S.C. § 119(a)-(d))

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed	
(Foreign Application Number)	(Country or PCT)	(MM/DD/YYYY)	☐ Yes	☐ No
(Foreign Application Number)	(Country or PCT)	(MM/DD/YYYY)	☐ Yes	☐ No

DECLARATION – Utility or Design Patent Application

Claim of U.S. Priority Benefit Under 35 U.S.C. § 119(e)

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States Provisional application(s) listed below:

60/993,379 (U.S. Application Serial No.)	September 12, 2007 (Filing Date)	expired (Status) (pending, expired)
(U.S. Application Serial No.)	(Filing Date)	(Status) (pending, expired)

Claim of Domestic Benefit Under 35 U.S.C. § 120 or § 365(c)

I hereby claim the benefit under Title 35, United States Code, § 120 and § 365(c) of any United States application(s) or PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information material to patentability of this application as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

PCT/US08/10676 (Application Serial No.)	PCT (US or PCT)	09/12/2008 (Filing Date)	abandoned (Status) (patented, pending, abandoned)
(Application Serial No.)	(US or PCT)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(US or PCT)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(US or PCT)	(Filing Date)	(Status) (patented, pending, abandoned)

DECLARATION – Utility or Design Patent Application

Direct all correspondence to:	☒	The address associated with Customer Number:	83369	OR ☐	Correspondence address below

Name			
Address			
City		State	Zip
Country	Telephone	E-Mail	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Ilyas	Washington

Inventor's Signature	Date
I. W	10/14/2010

Residence: City	State	Country	Citizenship
New York	NY	US	US

Mailing Address

~~601 West 113th Street~~ 29 West 119th st Apt. 61

City	State	Zip	Country
New York	NY	~~10025~~ 10026	US

I.W 10/14/2010

I.W 10/14/2010

Electronic Patent Application Fee Transmittal

Application Number:	12733631
Filing Date:	
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	
Filer:	Kevin C. Hooper/Teresa Rodriguez
Attorney Docket Number:	C035795/0307366

Filed as Small Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Oath/decl > 30 mo. from priority date	2617	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 5 months with $0 paid	2255	1	1175	1175
Miscellaneous:				
			Total in USD ($)	**1240**

Electronic Acknowledgement Receipt

EFS ID:	8629839
Application Number:	12733631
International Application Number:	
Confirmation Number:	4180
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
First Named Inventor/Applicant Name:	
Correspondence Address:	Kevin C. Hooper, Esq. BRYAN CAVE LLP 1290 Avenue of the Americas - New York NY 10104 US - -
Filer:	Kevin C. Hooper/Teresa Rodriguez
Filer Authorized By:	Kevin C. Hooper
Attorney Docket Number:	C035795/0307366
Receipt Date:	14-OCT-2010
Filing Date:	
Time Stamp:	17:31:34
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1240

RAM confirmation Number	4093
Deposit Account	024467
Authorized User	

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. 1.492 (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)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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	Transmittal Letter	0307366_response.PDF	178854 7a768b003a45c316f2e3e2013636e0c86db28140	no	5
Warnings:					
Information:					
2	Oath or Declaration filed	0307366_declaration.pdf	219448 3eb415fcbd4c39c744e4bab971bde4ad45617b2c	no	4
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	32206 a4013a98942a079426964b148c4ea2d051dd5c34	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	430508		

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.

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

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
12/733,631		C035795/0307366

Kevin C. Hooper, Esq.
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104

INTERNATIONAL APPLICATION NO.	
PCT/US2008/010676	
I.A. FILING DATE	PRIORITY DATE
09/12/2008	09/12/2007

CONFIRMATION NO. 4180
371 FORMALITIES LETTER



Date Mailed: 04/05/2010

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

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- Copy of the International Application filed on 03/10/2010
- Copy of the International Search Report filed on 03/10/2010
- Preliminary Amendments filed on 03/10/2010
- Information Disclosure Statements filed on 03/10/2010
- U.S. Basic National Fees filed on 03/10/2010
- Priority Documents filed on 03/10/2010
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- Claims filed on 03/10/2010
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- $**65** Surcharge.

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

VONDA M WALLACE

Telephone: (703) 756-1425

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 12/733631

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
U.S. NATIONAL STAGE FEES		
BASIC FEE	SMALL ENT. = $ 150	LARGE ENT. = $ 300
EXAMINATION FEE	Satisfies PCT-Article 33(1)-(4) = $ 50 / $ 100	All other situations = $ 100 / $ 200
SEARCH FEE	U.S. is ISA = $ 50 / $ 100 ALL other countries = $ 200 / $ 400	All other situations = $ 250 / $ 500
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =
TOTAL CHARGEABLE CLAIMS	49 minus 20 =	* 29
INDEPENDENT CLAIMS	6 minus 3 =	* 3
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐ OR OTHER THAN SMALL ENTITY

RATE	FEE	OR	RATE	FEE
BASIC FEE	165	OR	BASIC FEE	
EXAM. FEE	110		EXAM. FEE	
SEARCH FEE	50		SEARCH FEE	
X $ 125 =			X $ 250 =	
X $ 25 =	754	OR	X $ 50 =	
X $ 100 =	330	OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL	1409	OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY OR OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. 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.

FORM PTO-875 (Rev. 02/2005)
Patent and Trademark Office - U.S. DEPARTMENT OF COMMERCE

MULTIPLE DEPENDENT CLAIM
FEE CALCULATION SHEET
(FOR USE WITH FORM PTO-875)

SERIAL NO. 12/733,631

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	/					
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TOTAL IND.	6	↓		↓		↓
TOTAL DEP.	43	←		←		←
TOTAL CLAIMS	49					

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
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TOTAL IND.		↓		↓		↓
TOTAL DEP.		←		←		←
TOTAL CLAIMS						

PTO-1360 (REV. 11/04)

U.S. DEPARTMENT of COMMERCE
Patent and Trademark Office

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PTO-1390 (Rev. 09-08)
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
C035795/0307366	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	12773631

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US2008/010676	12 September 2008	12 September 2007 (earliest)

TITLE OF INVENTION
Compositions and Methods for Treating Macular Degeneration

APPLICANT(S) FOR DO/EO/US
Ilyas WASHINGTON

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☑ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
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7. ☑ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
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   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821- 1.825.
18. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. 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 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering information, preparing, and submitting the completed 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: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
12/733631	PCT/US2008/010676	C035795/0307366

20. Other items or information:

Certificate of Express Mailing (2 pages); Form PTO/SB/08a; Return postcard
Copy of International Search Report; Form PTO/SB/08b;
Copy of Written Opinion; Five cited documents;

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. ☑ Basic national fee (37 CFR 1.492(a)) **$330**	$ 330.00	
22. ☑ Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** All other situations **$220**	$ 220.00	
23. ☑ Search fee (37 CFR 1.492(b)) If the written opinion of the ISA/US or the International preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$100** International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB ..... **$430** All other situations **$540**	$ 100.00	
TOTAL OF 21, 22 and 23 =	$ 650.00	
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). The fee is **$270** for each additional 50 sheets of paper or fraction thereof.		

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE	
- 100 =	/50 =		x $270	$

Surcharge of **$130.00** for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	49 - 20 =	29	x $ 52	$ 1,508.00	
Independent claims	6 - 3 =	3	x $220	$ 660.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $390	$	
			TOTAL OF ABOVE CALCULATIONS =	$ 2,818	
☑ Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.					
			SUBTOTAL =	$ 1,409	
Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). +				$	
			TOTAL NATIONAL FEE =	$ 1,409	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$ 1,409	
			Amount to be refunded:	$	
			Amount to be charged	$ 1,409	

IAP01Rec'd PCT 10 MAR 2010

PTO-1390 (Rev. 09-08)
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a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 02-4467 in the amount of $ 1,409.00 to cover the above fees.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4467.

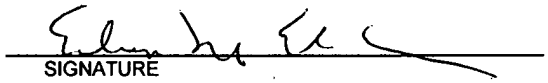
d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

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NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

SEND ALL CORRESPONDENCE TO:

Kevin C. Hooper, Esq.
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, New York 10104
Phone: (212) 541-2000
Fax: (212) 541-4630


SIGNATURE

Eileen M. Ebel
NAME

37,316
REGISTRATION NUMBER

Express Mail Label No.: EB 687787695 US

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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER C035795/0307366
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 12733631
INTERNATIONAL APPLICATION NO. PCT/US2008/010676	INTERNATIONAL FILING DATE 12 September 2008	PRIORITY DATE CLAIMED 12 September 2007 (earliest)
TITLE OF INVENTION Compositions and Methods for Treating Macular Degeneration		
APPLICANT(S) FOR DO/EO/US Ilyas WASHINGTON		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

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Total Sheets: - 100 = / Extra Sheets: /50 = / Number of each additional 50 or fraction thereof (round up to a whole number): / RATE: x **$270**	$	
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CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	49 - 20 =	29	x **$ 52**	$ 1,508.00	
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MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$390**	$	
			TOTAL OF ABOVE CALCULATIONS =	$ 2,818	
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12/733631

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 02-4467 in the amount of $ 1,409.00 to cover the above fees.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4467.

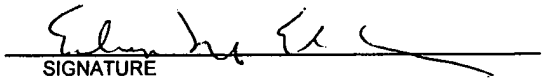
d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

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NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

SEND ALL CORRESPONDENCE TO:

Kevin C. Hooper, Esq.
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, New York 10104
Phone: (212) 541-2000
Fax: (212) 541-4630



SIGNATURE

Eileen M. Ebel

NAME

37,316

REGISTRATION NUMBER

IAP01Rec'd PCT 10 MAR 2010

Express Mail Label No.: EB 687787695 US
Docket No.: C035795/0307366
12/733631

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE ACTING AS THE DESIGNATED/ELECTED OFFICE (DO/EO/US) UNDER THE PATENT COOPERATION TREATY CONCERNING A FILING UNDER 35 U.S.C. § 371

In re Application of:		Examiner:	Not Yet Assigned
Ilyas WASHINGTON			
Based on International Appln. No.:	PCT/US2008/010676		
International Filing Date:	12 September 2008	Art Unit:	Not Yet Assigned
Filed:	Herewith		
For:	**COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**		

New York, NY
March 10, 2010

CERTIFICATE OF EXPRESS MAILING

"Express Mail" Mailing Label No.: **EB 687787695 US**
Date of Deposit: March 10, 2010

I hereby certify that the following:

1. This Certificate of Express Mailing (2 pages);
2. Transmittal Letter To The United States Designated/Elected Office (DO/EO/US) Concerning A Submission Under 35 U.S.C. 371 (3 pages) in duplicate;
3. Preliminary Amendment (5 pages including duplicate page 1);
4. Information Disclosure Statement (4 pages including duplicate page 3); Forms PTO/SB/08a and b (2 pages) with International Search Report (3 pages); Written Opinion (6 pages); and 5 cited documents
5. Return postcard

IAP01Rec'd PCT 10 MAR 2010

are being deposited with the United States Postal Service "Express Mail Post Office To Addressee" service under 37 C.F.R. §1.10 on the Date of Deposit indicated above in an envelope addressed to Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104

C Londono
Christina Londono

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12/733631

Express Mail Label No.: EB 687787695 US
Docket No.: C035795/0307366

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE ACTING AS THE DESIGNATED/ELECTED OFFICE (DO/EO/US) UNDER THE PATENT COOPERATION TREATY CONCERNING A FILING UNDER 35 U.S.C. § 371

In re Application of:			
Ilyas WASHINGTON		Examiner:	Not Yet Assigned
Based on International Appln. No.:	PCT/US2008/010676		
International Filing Date:	12 September 2008	Art Unit:	Not Yet Assigned
Filed:	Herewith		
For:	**COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**		

New York, NY
March 10, 2010

PRELIMINARY AMENDMENT

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

Sir:

Prior to examination on the merits, please enter the amendments set forth below. Because this Preliminary Amendment is being filed concurrently with the above-identified application, no fee is believed due. If, however, a fee is due, please charge the same to Deposit Account No. 02-4467. A duplicate copy of this sheet is enclosed.

Express Mail Label No.: EB 687787695 US
Docket No.: C035795/0307366

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE ACTING AS THE DESIGNATED/ELECTED OFFICE (DO/EO/US) UNDER THE PATENT COOPERATION TREATY CONCERNING A FILING UNDER 35 U.S.C. § 371

In re Application of:		)	
		)	
Ilyas WASHINGTON		)	Examiner: Not Yet Assigned
		)	
Based on International Appln. No.:	PCT/US2008/010676	)	
		)	
International Filing Date:	12 September 2008	)	Art Unit: Not Yet Assigned
		)	
Filed:	Herewith	)	
		)	
For: **COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**		)	

New York, NY
March 10, 2010

PRELIMINARY AMENDMENT

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

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Prior to examination on the merits, please enter the amendments set forth below. Because this Preliminary Amendment is being filed concurrently with the above-identified application, no fee is believed due. If, however, a fee is due, please charge the same to Deposit Account No. 02-4467. A duplicate copy of this sheet is enclosed.

Please amend the application as follows:

AMENDMENTS TO THE SPECIFICATION begin on page 3 of this paper.

REMARKS begin on page 4 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please amend the specification as follows:

Please delete paragraph 2 on page 1, and replace it with the following as paragraph 2:

--This application 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.--

REMARKS

The specification has been amended to update the Cross-Reference to Related Applications section, by deleting paragraph 2 and replacing it with a paragraph stating that the present application 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.

Approval and entry of this Preliminary Amendment prior to Examination on the merits, and allowance of all the claims, respectfully, are requested. If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

Respectfully submitted,

By: _____

Eileen M. Ebel
Registration No. 37,316
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104
Phone: (212) 541-2000
Fax: (212) 541-4630

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In re Application of:			
Ilyas WASHINGTON		Examiner:	Not Yet Assigned
Based on International Appln. No.:	PCT/US2008/010676		
International Filing Date:	12 September 2008	Art Unit:	Not Yet Assigned
Filed:	Herewith		
For:	**COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**		

New York, NY
March 10, 2010

INFORMATION DISCLOSURE STATEMENT

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

Sir:

Applicant wishes to make of record the following documents. Forms PTO/SB/08a and PTO/SB/08b listing the documents are enclosed. The following documents were cited in the International Search Report (mailed December 12, 2008) in the International application corresponding to the above-captioned case.

IAP01Rec'd PCT 10 MAR 2010
12/733631

U.S. PATENT DOCUMENTS

	Patent No.	Date	Name
A1	2006/0089411	04/27/2006	Gierhart
A2	2007/0015827	01/18/2007	Widder, et al.

FOREIGN PATENT DOCUMENTS

	Document No.	Date	Country
B1	WO 1995/004018	02/1995	WO
B2	WO 2002/072528	09/2002	WO
B3	WO 2005/065669	07/2005	WO

OTHER DOCUMENTS

C1 Radu, et al. "Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt's Macular Degeneration," *PNAS* 100(8): 4742-4747 (2003)

C2 Walker, "New/Old Findings on Unique Vitamin E," retrieved from the Internet: http://www.enerex.ca/articles/new_old_findings_on_unique_vitamin_e.htm (01 Dec 2008)

A copy of the International Search Report and Written Opinion are enclosed herewith.

All documents cited in these reports are identified herein and copies of all documents, other than the U.S. patent documents, are provided. See MPEP § 609(III)(A)(2)(A) (8th Ed., Rev. 2, May 2004, p. 600-128).; See also 1276 OG 55 (August 5, 2003) (Waiving the requirement under Rule 98(a)(2)(1) to provide a copy of each cited U.S. patent document for any application filed after June 30, 2003).

The Examiner's independent consideration of all of these documents and their relevance before issuance of the first official action is respectfully requested. The Examiner is also requested to initial and return a copy of the accompanying forms PTO/SB/08a and PTO/SB/08b to evidence such consideration.

This Information Disclosure Statement is being filed in accordance with the provisions under 37 C.F.R. §1.97(b)(2), within three months of the date of entry of the national stage of the international application. Accordingly, no fee is believed to be due. If, however, a fee is due, please charge the same to Deposit Account No. 02-4467. A duplicate copy of this sheet is enclosed.

If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

Respectfully submitted,

By: _____

Eileen M. Ebel
Registration No. 37,316
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300
Phone: (212) 541-2000
Fax: (212) 541-4630

IAP01Rec'd PCT 10 MAR 2010
12/733631

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Express Mail Label No.: EB 687787695 US

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PTO-1390 (Rev. 09-08)
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: C035795/0307366

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 12/733631

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US2008/010676	12 September 2008	12 September 2007 (earliest)

TITLE OF INVENTION: Compositions and Methods for Treating Macular Degeneration

APPLICANT(S) FOR DO/EO/US: Ilyas WASHINGTON

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
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4. ☑ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
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   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
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   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
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This collection of information is required by 37 CFR 1.414 and 1.491-1.492. 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 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering information, preparing, and submitting the completed 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: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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12/733631	PCT/US2008/010676	C035795/0307366

20. Other items or information:

Certificate of Express Mailing (2 pages); Form PTO/SB/08a; Return postcard
Copy of International Search Report; Form PTO/SB/08b;
Copy of Written Opinion; Five cited documents;

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. ☑ Basic national fee (37 CFR 1.492(a)) **$330**	$ 330.00	
22. ☑ Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** All other situations **$220**	$ 220.00	
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TOTAL OF 21, 22 and 23 =	$ 650.00	
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). The fee is **$270** for each additional 50 sheets of paper or fraction thereof.		

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE	
- 100 =	/50 =		x $270	$

Surcharge of **$130.00** for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	49 - 20 =	29	x $ 52	$ 1,508.00	
Independent claims	6 - 3 =	3	x $220	$ 660.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $390	$	
			TOTAL OF ABOVE CALCULATIONS =	$ 2,818	
☑ Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.					
			SUBTOTAL =	$ 1,409	
Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). +				$	
			TOTAL NATIONAL FEE =	$ 1,409	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$ 1,409	
			Amount to be refunded:	$	
			Amount to be charged	$ 1,409	

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b. ☑ Please charge my Deposit Account No. 02-4467 in the amount of $ 1,409.00 to cover the above fees.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4467.

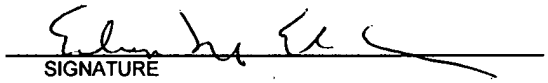
d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

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NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

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SIGNATURE

Eileen M. Ebel
NAME

37,316
REGISTRATION NUMBER

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		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 12733631
INTERNATIONAL APPLICATION NO. PCT/US2008/010676	INTERNATIONAL FILING DATE 12 September 2008	PRIORITY DATE CLAIMED 12 September 2007 (earliest)
TITLE OF INVENTION Compositions and Methods for Treating Macular Degeneration		
APPLICANT(S) FOR DO/EO/US Ilyas WASHINGTON		

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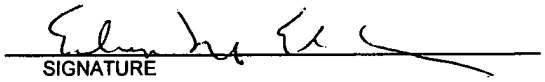
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SIGNATURE

Eileen M. Ebel

NAME

37,316

REGISTRATION NUMBER

IAP01Rec'd PCT 10 MAR 2010

Express Mail Label No.: EB 687787695 US
Docket No.: C035795/0307366
12/733631

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE ACTING AS THE DESIGNATED/ELECTED OFFICE (DO/EO/US) UNDER THE PATENT COOPERATION TREATY CONCERNING A FILING UNDER 35 U.S.C. § 371

In re Application of:		Examiner:	Not Yet Assigned
Ilyas WASHINGTON			
Based on International Appln. No.:	PCT/US2008/010676		
International Filing Date:	12 September 2008	Art Unit:	Not Yet Assigned
Filed:	Herewith		
For:	**COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION**		

New York, NY
March 10, 2010

CERTIFICATE OF EXPRESS MAILING

"Express Mail" Mailing Label No.: **EB 687787695 US**
Date of Deposit: March 10, 2010

I hereby certify that the following:

1. This Certificate of Express Mailing (2 pages);
2. Transmittal Letter To The United States Designated/Elected Office (DO/EO/US) Concerning A Submission Under 35 U.S.C. 371 (3 pages) in duplicate;
3. Preliminary Amendment (5 pages including duplicate page 1);
4. Information Disclosure Statement (4 pages including duplicate page 3); Forms PTO/SB/08a and b (2 pages) with International Search Report (3 pages); Written Opinion (6 pages); and 5 cited documents
5. Return postcard

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BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104

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Christina Londono

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	Not yet assigned
Filing Date	Herewith
First Named Inventor	Ilyas Washington
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	C035795/0307366

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	US- 2006/0089411	04/27/2006	Gierhart	
	A2	US- 2007/0015827	01/18/2007	Widder, et al.	
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	B1	WO 1995/004018	02/09/1995	Ligand Pharmaceuticals		
	B2	WO 2002/072528	09/19/2002	Eli Lilly and Company		
	B3	WO 2005/065669	07/21/2005	Alcon, Inc.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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 2 hours 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, 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 (1-800-786-9199) and select option 2.

IAP01Rec'd PCT 10 MAR 2010

Express Mail Label No.: EB 687787695 US

12/733631

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	Not yet assigned
Filing Date	Herewith
First Named Inventor	Ilyas Washington
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	C035795/0307366

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	C1	Radu, et al. "Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt's Macular Degeneration," PNAS 100(8): 4742-4747 (2003)	
	C2	Walker, "New/Old Findings on Unique Vitamin E," retrieved from the Internet: http://www.enerex.ca/articles/new_old_findings_on_ unique_vitamin_e.htm (01 Dec 2008)	

Examiner Signature		Date Considered	

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

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 2 hours 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, 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 (1-800-786-9199) and select option 2.

Express Mail Label No.: EB 687787695 US

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
KEVIN C. HOOPER
BRYAN CAVE LLP
1290 AVENUE OF THE AMERICAS
33RD FLOOR
NEW YORK, NY 10104

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 12 DEC 2008
Applicant's or agent's file reference C035795/0220068	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 08/10676	International filing date *(day/month/year)* 12 September 2008 (12.09.2008)
Applicant TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C035795/0220068	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 08/10676	International filing date *(day/month/year)* 12 September 2008 (12.09.2008)	(Earliest) Priority Date *(day/month/year)* 12 September 2007 (12.09.2007)
Applicant TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/10676

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/135 (2008.04)
USPC - 514/646
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 514/646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 426/611; 514/171; 514/613; 435/326; 546/341; 546/347

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST, Google Scholar: lipofuscin, accumulation, method, C20 retinoid, C20-D3-retinoid, C20-T3-retinoid, C20-F3-retinoid, vitamin A analog or compound, ocular, deuterated, tritium, tritiated, fluorine, flourinated, relacing, administering

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RADU et al. Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargardt's macular degeneration. PNAS, 15 Apr 2003, 100(8):4742-4747; pg 4742, LHS paar 1, RHS para 2; pg 4744, LHS para 2 & RHS paar 2; pg 4745, LHS last para & RHS para 1; pg 4747 RHS paar 1; pg 4743 - B	1-13, 20-46
Y	WO 1995/04018 A1 (BOEHM) 09 Feb 1995 (09. 02.1995); pg 3, ln 1-8; pg 2, ln 6; pg 4, ln 26-28; pg 5, ln 13-19, 34-36, Compounds II-V; pg 7, ln 34-36; pg 6, ln 34-36	1-19, 22, 47-49
Y	WO 2005/065669 A1 (LANG et al) 21 Jul 2005 (21.07.2005); pg 1, ln 8-10; pg 2, ln 6-15; pg 4, ln 1-3, 8-17; pg 5, ln 34-36; pg 7, ln 1-11, 21-23; pg 8, ln 9-10, 21-23; pg 9, ln 1-3; pg 10, ln 18-20; pg 11, ln 1-10; pg 12, ln 3-9, 13-17; pg 13, ln 19-21; pg 14, ln 3-5; pg 15, ln 1-3, 5-10; pg 16, ln 6-8; pg 17, ln 3-10, 19-23; pg 27, Example 3A; pg 30 & 31 - Example 4A	4, 5, 9, 10, 14-18, 20-46
Y	US 2006/0089411 A1 (GIERHART) 27 Apr 2006 (27.04.2006); para [0002], [0012], [0029], [0046]-[0049], [0052], [0067], [0068], [0177], [0178], [0180], [0188], [0195]	13, 18, 19, 47-49
Y	WO 2002/072528 A1 (BELL et al) 19 Sep 2002 (19.09.2002); pg 1, ln 6-15; pg 2, ln 1-4; pg 4, ln 1-4, 15-16; pg 5, ln 8-11	21, 22
Y	US 2007/0015827 A1 (WIDDER et al) 18 Jan 2007 (18.01.2007); para [0002], [0009], [0012], [0024], [0041], [0059], [0064], [0166], [0168]	28, 45, 49
A	Walker. New/Old Findings on Unique Vitamin E. 1992. [Retrieved from the Internet 01 Dec 2008: <http://www.enerex.ca/articles/new_old_findings_on_unique_vitamin_e.htm>]	34-36

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 2008 (19.11.2008)	12 DEC 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

Express Mail Label No.: EB 687787695 US

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
KEVIN C. HOOPER
BRYAN CAVE LLP
1290 AVENUE OF THE AMERICAS
33RD FLOOR
NEW YORK, NY 10104

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* 12 DEC 2008
Applicant's or agent's file reference C035795/0220068	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/10676	12 September 2008 (12.09.2008)	12 September 2007 (12.09.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/135 (2008.04)
USPC - 514/646

Applicant TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	19 November 2008 (19.11.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/10676

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/10676

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-49	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-49	NO
Industrial applicability (IA)	Claims	1-49	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1 -3, 6-8, 11 and 12 lack an inventive step under PCT Article 33 (3) as being obvious over the article entitled "Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargardt's macular degeneration" by RADU et al (hereinafter "RADU") in view of WO 1995/04018 A1 (BOEHM).

Regarding claim 1, RADU teaches a method of retarding formation of a lipofuscin pigment in the retina (pg 4742, LHS para 1) comprising administering to a patient in need thereof a C20-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina (pg 4744, LHS para 2 - mice, injection, isotretinoin; pg 4745, LHS last para & RHS 1st para).
RADU does not teach a substituted C20 retinoid. BOEHM, in the teaching of pharmaceutically acceptable salts (pg 5, ln 34-36; pg 3, ln1-8; pg 2, ln 6 - RAR activity) does disclose a substituted C20 retinoid (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34-36 - deuterium). It would have been obvious to a person skilled in the art at the time of invention to combine RADU and BOEHM by using BOEHM's retinoids viz. labeled retinoids in the method taught by RADU to improve efficacy of the treatment.

Regarding claim 2, BOEHM teaches that the substituted C20-retinoid is selected from the group consisting of a C20-D3-retinoid and C20-T3-retinoid (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34-36 - deuterium).

Regarding claim 3, RADU teaches that the lipofuscin pigment is A2E (pg 4742, LHS para 1).

Regarding claim 6, RADU teaches a method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina (pg 4742, LHS para 1 - Stargardt's) comprising administering to a patient in need thereof a C20-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina (pg 4744, LHS para 2 - mice, injection, isotretinoin; pg 4745, LHS last para & RHS 1st para; pg 4747, RHS para 1).
RADU does not teach the claimed substituted C20 retinoid. This element is taught by BOEHM (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34-36 - deuterium). As BOEHM (pg 5, ln 34-36 - pharmaceutically acceptable salts; pg 3, ln1-8; pg 2, ln 6 - RAR activity) also relates to retinoids that find use as pharmaceuticals, it would have been obvious to a person skilled in the art at the time of invention to combine RADU and BOEHM by using BOEHM's retinoids viz. labeled retinoids in the method taught by RADU so as to obtain a broad spectrum of use of the retinoid and improved efficacy with treatment.

Regarding claim 7, BOEHM teaches that the substituted C20-retinoid is selected from the group consisting of a C20-D3-retinoid and C20-T3-retinoid (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34-36 - deuterium).

Regarding claim 8, RADU teaches that the lipofuscin pigment is A2E (pg 4742, LHS para 1).
Regarding claim 11, RADU teaches that the disease is macular degeneration (pg 4742, LHS para 1).
Regarding claim 12, RADU teaches that the disease is Stargardt (pg 4742, LHS para 1).

Claims 14-17 lack an inventive step under PCT Article 33 (3) as being obvious over WO 2005/065669 A1 to LANG et al (hereinafter "LANG") in view of BOEHM.

Regarding claim 14, LANG teaches a composition for retarding formation of a lipofuscin pigment in the retina comprising a retinoid (pg 1, ln 8-10; pg 2, ln 6-10; pg 7, ln 3-5) and a pharmaceutically acceptable carrier (pg 8, ln 9-10, 21-23; pg 9, ln 1-3 - polymer; pg 11, ln 6-8 - lacquered).
BOEHM teaches a substituted C20-retinoid (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34-36 - deuterium). Both LANG and BOEHM (pg 5, ln 34-36 - pharmaceutically acceptable salts; pg 3, ln1-8; pg 2, ln 6 - RAR activity) relate to retinoids that find use as pharmaceuticals and therefore it would have been obvious to a person skilled in the art at the time of invention to combine BOEHM's specific retinoids viz. labeled retinoids and use them in LANG's composition so as to obtain a specific pharmaceutical use thereof.

Regarding claim 15, BOEHM teaches that the substituted C20-retinoid is selected from the group consisting of a C20-D3-retinoid and C20-T3-retinoid (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34-36 - deuterium).

----------continued in Supplemental Box----------

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
BOX V(2):

Regarding claim 16, LANG teaches a unit dosage form comprising the composition of claim 15 (pg 11, ln 1-8).
Regarding claim 17, LANG teaches a vitamin supplement (pg 11, ln 8-10).

Claims 20, 23-27, 29-44 and 46 lack an inventive step under PCT Article33 (3) as being obvious over RADU, as above, in view of LANG.

Regarding claim 20, RADU teaches the compound of formula I of claim 20 when R4 = R5 = R6 = H1; R1 = oxo; R2 = nothing; R3 = hydroxy (pg 4743- B- compound atRAL).
LANG teaches a composition (pg 1, ln 8-10; pg 7, ln 3-5) comprising a pharmaceutically acceptable carrier (pg 8, ln 9-10, 21-23; pg 9, ln 1-3 - polymer; pg 11, ln 6-8 - lacquered). As both, LANG (pg 2, ln 6-10; pg 7, ln 3-5) and RADU (pg 4742, LHS para 1), relate to retinoids used for retarding accumulation of lipofuscin, it would have been obvious to one skilled in the art at the time of invention to use RADU's specific retinoid in a composition taught by LANG so as to obtain a new composition showing increased efficacy in treating lipofuscin related diseases.

Regarding claims 23 - 25, RADU teaches that R4, R5, and R6 are H (see claim 20 explanation above).

Regarding claims 26 and 27, LANG teaches a supplement (pg 7, ln 21-23 - antioxidant) and RADU teaches the supplement to be a visual cycle antagonist (pg 4742, LHS 1st para and RHS 2nd para - isotretinoin, 13-cis retinoic acid).

Regarding claim 29, LANG teaches one or more additives (pg 11. ln 8-9; pg 12,ln 6-9).
Regarding claim 30, LANG teaches that the additive is vitamin E (pg 11. ln 8-9; pg 12. ln 6-9).

Regarding claims 31-33, LANG teaches 15 mg, 100, mg and 150 mg of zinc (pg 13, ln 19-21), thereby obviating the claimed range of 3-10 mg of zinc.

Regarding claims 34-36, LANG teaches that vitamin E is present in15 - 400 IU (pg 12, ln 15-16; pg 27, Example 3A) and it is well-known in the art that 1 IU of vitamin E = 2/3 mg.

Regarding claims 37-39, LANG teaches that the vitamin D is present in the composition at between about 0.005 to about 0.1 mg, 0.005 to about 0.015 mg and 0.015 to about 0.1 mg (pg 30 and 31, Example 4A) and it is well-known in the art that 1IU of vitamin D = 0.025 micro gram.

Regarding claim 40, RADU teaches that the compound is present in the composition at a level sufficient to deliver about 0.1 to about 90 mg/day to a patient (pg 4744, RHS para 2).

Regarding claims 41 and 42, LANG teaches an additional active like eye antioxidants (pg 7, ln 21), minerals (pg 14, ln 3-5 - zinc oxide; pg 15, ln 1-3 - cupric oxide) and carotenoids (pg 8, ln 1-4; pg 15, ln 5-10 - beta carotene).

Regarding claim 43, LANG teaches that the eye antioxidant is selected from the group consisting of vitamin C (pg 12, ln 3-5), vitamin E (pg 12, ln 13-17), beta carotene (pg 16, ln 6-8).

Regarding claim 44, LANG teaches that the mineral is zinc oxide (pg 14, ln 3-5) and cupric oxide (pg 15, ln 1-3).

Regarding claim 46, LANG teaches that the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof (pg 17, ln 3-10, 19-23).

Claims 19, 47 and 48 lack an inventive step under PCT Article33 (3) as being obvious over BOEHM, as above, in view of US 2006/0089411 A1 (GIERHART).

Regarding claim 19, GIERHART teaches a method of retarding formation of a lipofuscin pigment selected from the group consisting of an A2E, an ATR dimer, and combinations thereof using a C20-retinoid (paras [0079], [0195], [0188]- Accutane; para [0180]).
BOEHM teaches a C20-D3-retinoid (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34-36 - deuterium).
GIERHART further teaches that all-trans retinal causes formation of A2E and further Stargardt's disease (paras [0046]-[0048], [0012]).
It would have been obvious to one of ordinary skill in the art that all-trans retinoid that cause the accumulation of lipofuscin should be removed, and further it would have been obvious that the all-trans retinoid be replaced by the therapeutic retinoid, specifically BOEHM's C20-D3-retinoid as per claim 19.
As GIERHART (para [0002]) like BOEHM teaches compounds that treat diseases characterized by accumulation of lipofuscin, it would have been obvious to a person skilled in the art at the time of invention to combine a method taught by GIERHART using a compound as per BOEHM, so as to obtain improved efficacy with treatment.

----------continued in next Supplemental Box----------

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
BOX V(2):

Regarding claim 47, GIERHART teaches a method of retarding formation of A2E using a C20-retinoid (paras [0079], [0178], [0188]-Accutane), while BOEHM teaches a C20-D3-retinoid (pg 4, ln 26-28 - tritium labeled; pg 5, ln 13-19 - formula V; pg 7, ln 34-36; pg 6, ln 34 -36 - deuterium).
GIERHART further teaches that all-trans retinal causes formation of A2E and therefore Stargardt's disease (paras [0046]-[0048], [0012]).
It would have been obvious that all-trans retinoid which causes the accumulation of A2E should be removed, and further that all-trans retinoid be replaced by the therapeutic retinoid, which may be BOEHM's C20-D3-retinoid as per claim 47.
As GIERHART (para [0002]) like BOEHM teaches compounds that treat diseases characterized by accumulation of lipofuscin/A2E, it would have been obvious to a person skilled in the art at the time of invention to combine GIERHART and BOEHM by using the compound taught by BOEHM in a method taught by GIERHART, so as to obtain improved efficacy with treatment.

Regarding claim 48, GIERHART teaches that the replacing step comprises administering to the patient a substituted C20-D3-retinoid substrate (para [0188]).

Claims 4, 5, 9 and 10 lack an inventive step under PCT Article33 (3) as being obvious over RADU in view of BOEHM, as above, and further in view of LANG.

Regarding claims 4 and 9, LANG teaches that the substituted C20-retinoid is administered as part of a pharmaceutical or a nutraceutical composition (pg 3, ln 21-23; pg 4, ln 1-3, 8-17; pg 7, ln 1-11).

Like RADU and BOEHM, LANG (pg 2, ln 6-15; pg 1, ln 8-10 - macular degeneration; pg 10, ln 18-20) also relates to retinoids that finds use as pharmaceuticals (pg 5, ln 34-36 - pharmaceutically acceptable salts; pg 3, ln1-8; pg 2, ln 6 - RAR activity). Therefore, it would have been obvious to a person skilled in the art at the time of invention to combine BOEHM's retinoids viz. labeled retinoids and use them for a method as per RADU so as to obtain a broad spectrum of use of the retinoid and improved efficacy with treatment.

Regarding claims 5 and 10, LANG teaches that the substituted C20-retinoid is administered as a unit dosage form (pg 11, ln 1-8).

Claim 13 lacks an inventive step under PCT Article33 (3) as being obvious over RADU in view of BOEHM, as above, and further in view of GIERHART.

Regarding claim 13, GIERHART teaches that the dietary source of all-trans retinal which causes Stargardt's disease, is beta carotene (paras [0046]-[0048], [0012]) and therefore large and heavy dosages of beta-carotene, among people who suffer from Stargardt's disease, is ill-advised (para [0049], [0052]).
RADU and BOEHM teach a substituted C20-retinoid is administered to treat a disease the effects of a disease characterized by accumulation of lipofuscin (see claim 6 explanation above).
It would have been obvious that the patient's diet comprises beta carotene which is a source of all-trans retinoid and therefore and that beta carotene or all-trans retinoid should be replaced with a component that removes the all-trans retinoid and treats the disease viz a substituted C20-retinoid; as per claim 13.
As GIERHART (para [0002]), similarly to RADU and BOEHM, teaches compounds that treat diseases characterized by accumulation of lipofuscin, therefore it would have been obvious to a person skilled in the art at the time of invention to combine a method taught by GIERHART and use a compound as per RADU/BOEHM, so as to obtain improved efficacy with treatment.

Claim 18 lacks an inventive step under PCT Article33 (3) as being obvious over LANG in view of BOEHM, as above, and further in view of GIERHART.

Regarding claim 18, GIERHART teaches a pharmaceutical formulation (para [0067]- treating, para [0068] - inhibit; PARA [0177] -human clinical trial).
As GIERHART (para [0002]), similarly to LANG and BOEHM, teaches compounds that treat diseases characterized by accumulation of lipofuscin, and therefore it would have been obvious to a person skilled in the art at the time of invention to use a formulation taught by LANG and BOEHM as a pharmaceutical formulation as per GIERHART so as to achieve best use thereof.

Claim 21 lacks an inventive step under PCT Article33 (3) as being obvious over RADU in view of LANG, as above, and further in view of WO 02/072528 A1 to BELL et al (hereinafter "BELL").

Regarding claim 21, BELL teaches a compound (pg 4, ln 1-4) which is retinoid -like compound (pg 1, ln 6-15; pg 2, ln 1-4 - ATRA, RAR, RXR; pg 5, ln 8-11 - RXR) in which R10 = trifluoromethyl (pg 4, ln 15-16) is the same substituent to claim 21's corresponding R4, R5 and R6.
As BELL, similalry to LANG and RADU, teaches retinoids, it would have been obvious to a person skilled in the art at the time of invention to use BELL's substituent for a retinoid as per RADU and make a composition as per LANG, so as to obtain a new pharmaceutical composition with improved efficacy.

----------continued in next Supplemetal Box----------

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
BOX V(2):

Claims 28 and 45 lack an inventive step under PCT Article33 (3) as being obvious over RADU in view of LANG, as above, and further in view of US 2007/0015827 A1 to WIDDER et al (hereinafter "WIDDER").

Regarding claim 28, WIDDER teaches that the molecule that inhibits influx of a retinoid into an eye is fenretinide (para [0064]). As WIDDER (paras [0002], [0012] - ophthalmic; [0009] - Stargardt; para [0024]- macular degeneration, para [0059] - formula), similarly to RADU and LANG, relates to retinoids for macular degeneration like RADU/LANG, it would have been obvious to a person skilled in the art at the time of invention to combine WIDDER's compound as a supplement in LANG's composition along with RADU's retinoid so as to add synergistic value to the composition.

Regarding claim 45, WIDDER teaches that the negatively charged phospholipid is phosphatidylglycerol (para [0041]). As WIDDER (paras [0002], [0012] - ophthalmic; [0009] - Stargardt; para [0024]- macular degeneration, para [0059] - formula), similarly to RADU and LANG, relates to retinoids for macular degeneration like RADU/LANG, it would have been obvious to a person skilled in the art at the time of invention to combine WIDDER's compound as a supplement in LANG's composition along with RADU's retinoid so as to add synergistic value to the composition.

Claim 49 lacks an inventive step under PCT Article33 (3) as being obvious over GIERHART in view of BOEHM, as above, and further in view of WIDDER.

Regarding claim 49, WIDDER teaches that the substituted C20-03-retinoid substrate is administered directly to the eye (paras [0166], [0168]). As WIDDER (paras [0002], [0012] - ophthalmic; [0009] - Stargardt; para [0024]- macular degeneration, para [0059] - formula), similalrly to GIERHART and BOEHM, relates to retinoids for macular degeneration, it would have been obvious to a person skilled in the art at the time of invention to combine WIDDER's way of administration in a method as per GIERHART so as to obtain more efficacy.

Claim 22 lacks an inventive step under PCT Article33 (3) as being obvious over RADU in view of LANG, as above, and further in view of BELL and BOEHM.

Regarding claim 22, RADU teaches the compound of formula I of claim 20 when R4 = R5 = R6 = H1; R1 = oxo; R2 = nothing; R3 = hydroxy (pg 4743- B- compound at RAL).
LANG teaches a composition (pg 1, ln 8-10; pg 7, ln 3-5) comprising a pharmaceutically acceptable carrier (pg 8, ln 9-10, 21-23; pg 9, ln 1-3 - polymer; pg 11, ln 6-8 - lacquered). As both, LANG (pg 2, ln 6-10; pg 7, ln 3-5) and RADU (pg 4742, LHS para 1), relate to retinoids used for retarding accumulation of lipofuscin, it would have been obvious to one skilled in the art at the time of invention to use RADU's specific retinoid in a composition taught by LANG so as to obtain a new composition showing increased efficacy in treating lipofuscin related diseases.
BOEHM further teaches tritium labeled retinoids (pg 5, compound V) and intermediates (pg 5, compounds II, III and IV). For the rest of the compound of claim 22, see claim 20 explanation above.
As the BOEHM, BELL, LANG and RADU references teach retinoids and therefore it would have been obvious to a person skilled in the art at the time of invention to use BELL's/BOEHM's substituents for a retinoid as per RADU and make a composition as per LANG, so as to obtain a new pharmaceutical composition with improved efficacy.

Claims 1-49 have industrial applicability as defined by PCT Article 33(4) since the subject matter can be made or used in the industry.

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(54) **Title:** COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

(57) **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 C_{20}-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-frans-retinal (ATR) substrate with a C_{20}-D_3-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 C_{20}-retinoid and a pharmaceutically acceptable carrier are also provided.

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 (Doyne 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 A*BCR* (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-NH_2) 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-NH_2 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 Aibipunctatus, 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 dugs 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 trails 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/m^2 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/m^2 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/m^2 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/m^2 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 C_{20}-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

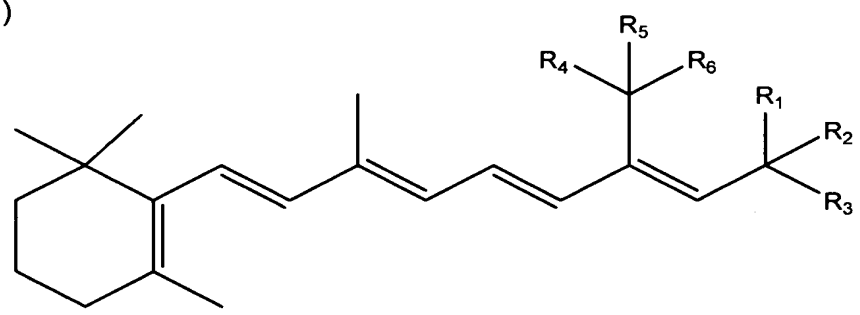
lipofuscin pigment in a retina. This method includes the step of administering to a patient in need thereof a substituted C_{20}-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

[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 C_{20}-D_3-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 C_{20}-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:

(I)



wherein:

R_1 is oxo or H;

R_2 is H or nothing;

R_3 is hydroxy or oxo or CHR_7 where R_7 forms a carotenoid and

R_4, R_5, and R_6 are independently selected from the group consisting of ^1H, ^2H, ^3H, halogen, and C_{1-8}alkyl.

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 C_{20}-D_3-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 C_{20}-D_3-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. C_{20}-D_3-all-*trans*-retinal forms A2E about 7-times slower than all-*trans*-retinal.

[0036] FIG. 4 shows HPLC profiles of reaction mixtures of C_{20}-D_3-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 C_{20}-D_3-all-*trans*-retinal ATR-dimer formation is much slower. FIG. 4C is a plot of ATR-dimer formation over time for the above reactions. C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-all-*trans*-retinol acetate diet. FIG. 5C shows plots of total retinol and retinol ester or D_3-retinol and D_3-retinol ester concentrations in the above mice raised on either the retinol acetate or C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-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, C_{20}-D_3-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 C_{20}-D_3-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-D_3-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 C_{20} hydrogens of all-*trans*-retinoids are replaced by fluorine atoms (F_3), the formation of A2E is eliminated, as measured by monitoring the disappearance of C_{20}-F_3-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 C_{20} (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.*, C_{20}-F_{1-3}-retinal) hampers the reactivity of all-*trans*-retinal, and, thus slows or eliminates the formation of A2E *in vitro*. By replacing hydrogen atoms at C_{20} with fluorine, the [1,5] hydrogen shift step is blocked. Accordingly, C_{20}-F_{1-3}-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 C_{20}

hydrogen bond. Therefore, treatment with a C_{20}-F_{1-3}-retinoid (which may be transformed into C_{20}-F_{1-3}-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] C_{20}-D_{1-3}-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 C_{20} 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 C_{20}-D_{1-3}-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 C_{20}-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C_{20}-retinoid is selected from the group consisting of a C_{20}-D_{1-3}-retinoid and a C_{20}-F_{1-3}-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 C_{20}-retinoid is administered to the patient as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C_{20}-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 C_{20}-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 C_{20}-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 C_{20}-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C_{20}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinoids and C_{20}-F_{1-3}-retinoids. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

[0051] Preferably, the substituted C_{20}-retinoid is administered as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C_{20}-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

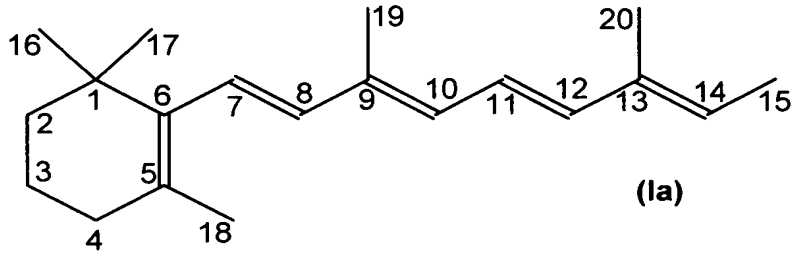
component that contains a substituted C_{20}-retinoid. By "replacing a component of a patient's diet" it is meant that a part of the diet that contains vitamin A or its precursors (including, but not limited to carotenoids) is replaced with a component that contains a substituted C_{20}-retinoid. Preferably, 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 C_{20}-retinoid. The replacement may be through, e.g., administering substituted C_{20}-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 C_{20}-retinoid and a pharmaceutically acceptable carrier. Preferably, the substituted C_{20}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinoid and C_{20}-F_{1-3}-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 C_{20}-D_3-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.

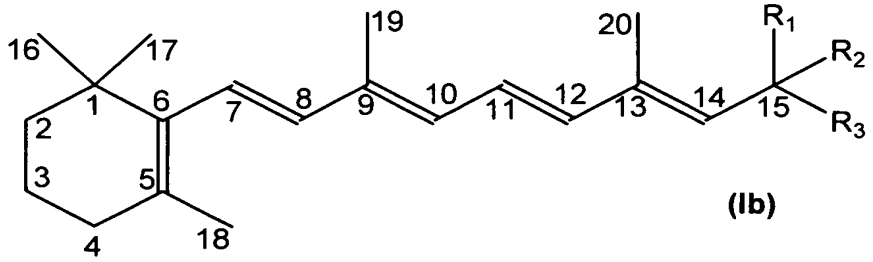
[0056] A further embodiment of the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-*trans*-retinal (ATR) substrate with a C_{20}-D_3-retinoid substrate under conditions sufficient to impede the formation of A2E. The replacing step in the 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 C_{20}-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 Ia for retinoids shall be used:



(Ia)

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



(Ib)

wherein

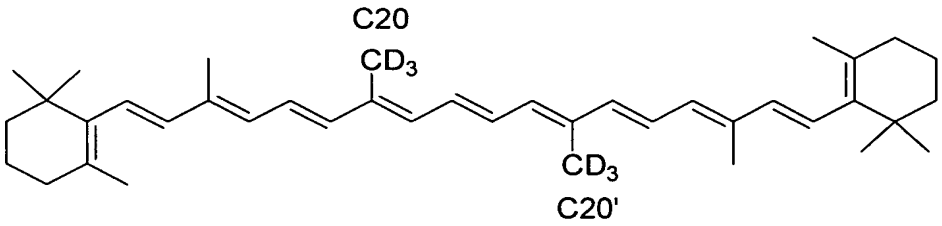
R_1 and R_2 are both H and R_3 is OH (retinol); or

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

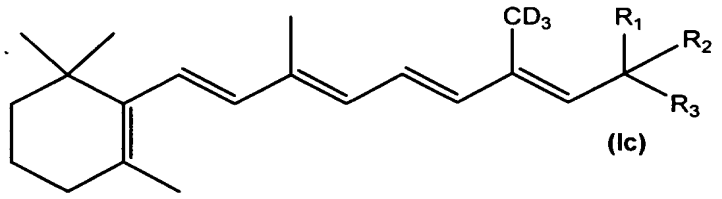
R_1 is =O, R_2 is nothing and R_3 is OH (retinoic acid) or

R_1 is H, R_3 is nothing, and R_2 is $=CH-R_7$, 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:

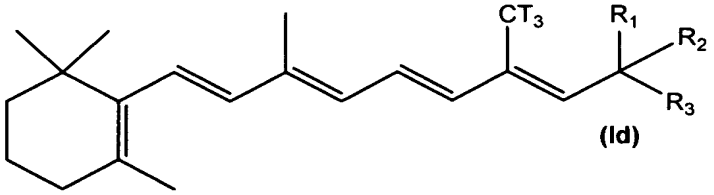


(Ib')

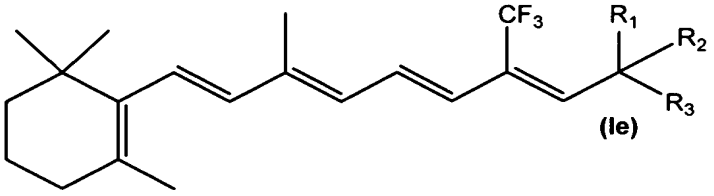
[0058] Exemplary substituted C_{20}-retinoid compounds that may be used in the compositions of the present invention include the following (compounds Ic-Ie):



(Ic)



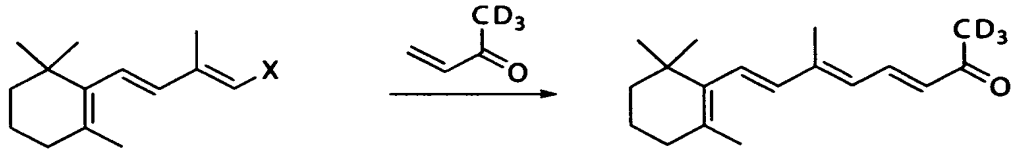
(Id)



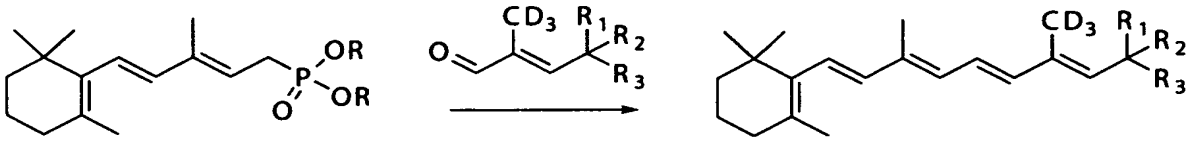
(Ie)

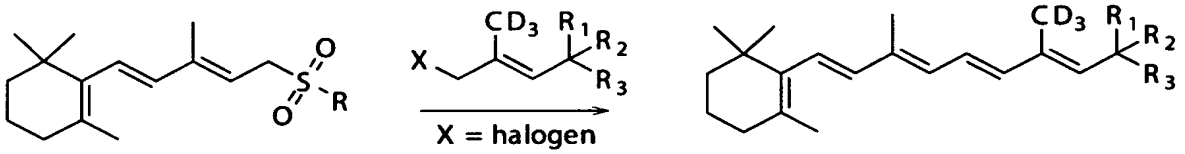
wherein R_1, R_2, and R_3 are as defined in Formula Ib.

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

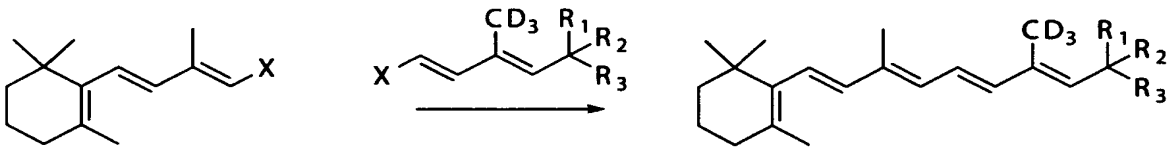


X = halogen

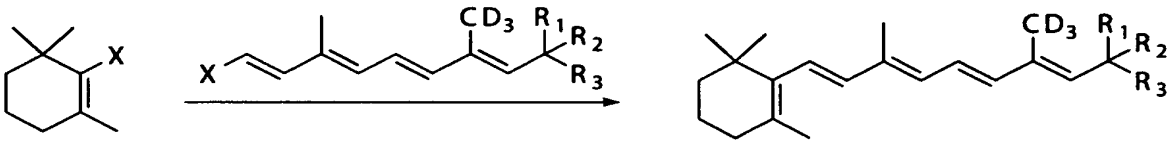




X = halogen

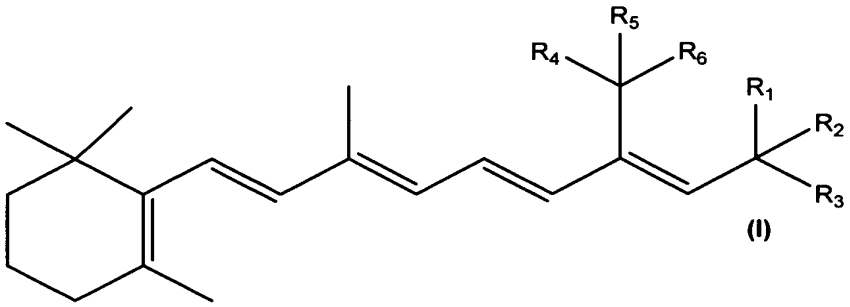


X = halogen, SnR_3 (where r = alkyl), $B(HO)_2$, OTf



X = halogen, SnR_3 (where r = alkyl), $B(HO)_2$, OTf

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



(I)

wherein:

R_1 is oxo or H;

R_2 is H or nothing;

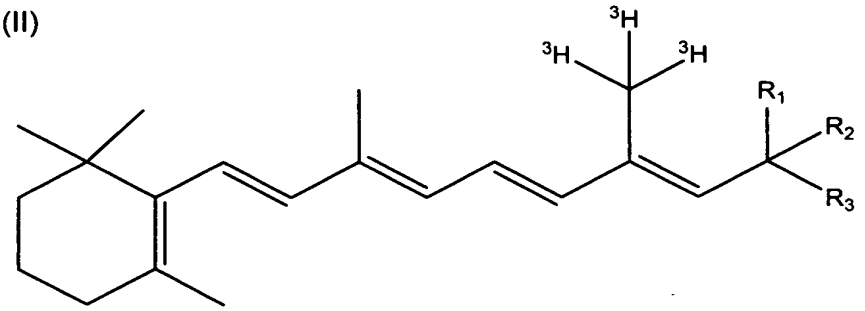
R_3 is hydroxy or oxo or =CH-R_7, where R_7 forms a carotenoid; and

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:

(II)



wherein:

R_1 is oxo or H;

R_2 is H or nothing; and

R_3 is hydroxy or oxo or =CH-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 C_{20}-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-Ie 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-cyrptoxanthin, 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 monosterate; (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 monosterate, 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 C_{20} hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E *in vitro*

[0087] C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-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 C_{20} hydrogens of all-*trans*-retinal with deuteriums slows the formation of ATR-dimer *in vitro*

[0089] C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-all-*trans*-retinal formed ATR-dimer 15 times slower than the unlabeled retinal as shown in FIG. 4C.

EXAMPLE 3

Replacing the C_{20} hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E-lipofuscin in CD-1 (ICR) mice

[0090] C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-all-*trans*-retinal quickly replaces normal vitamin A stores with the C_{20}-D_3-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 patents 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 C_{20}-D_3-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 C_{20} hydrogens of all-*trans*-retinal with deuteriums reduces the formation of A2E in $ABCR^{-/-}$ mice

[0092] C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-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-NH_2, 13-*cis*-retinoic, acid and fenretinide. However, in this example A2E reduction is achieved with doses of C_{20}-D_3-all-*trans*-retinol acetate that are 11- to 40-times less.

EXAMPLE 5

$ABCR^{-/-}$ mice raised exclusively on a C_{20}-D_3-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 where raised either on diets containing C_{20}-D_3-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 where 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 C_{20}-D_3-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 C20D_3-all-*trans*-retinol acetate, eyecups from both groups of mice (2 from each group) were evaluated by electron microscopy. Mice on the C_{20}-D_3-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

C_{20}-D_3-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 C_{20}-D_3-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 C_{20}-D_3-all-*trans*-retinal. Massive dosing with C_{20}-D_3-all-*trans*-retinal quickly replaces normal vitamin A stores

with the C_{20}-D_3-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 $C_{20}D_3$-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.

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[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 C_{20}-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 C_{20}-retinoid is selected from the group consisting of a C_{20}-D_3-retinoid, a C_{20}-T_3-retinoid, and a C_{20}-F_3-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 C_{20}-retinoid is administered as part of a pharmaceutical or a nutraceutical composition.

5. The method according to claim 1, wherein the substituted C_{20}-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 C_{20}-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 C_{20}-retinoid is selected from the group consisting of a C_{20}-D_3-retinoid, a C_{20}-T_3-retinoid, and a C_{20}-F_3-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 C_{20}-retinoid is administered as part of a pharmaceutical nutraceutical composition

10. The method according to claim 6, wherein the substituted C_{20}-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 C_{20}-retinoid.

14. A composition for retarding formation of a lipofuscin pigment in the retina comprising a substituted C_{20}-retinoid and pharmaceutically acceptable carrier.

15. A composition according to claim 14, wherein the substituted C_{20}-retinoid is selected from the group consisting of a C_{20}-D_3-retinoid, a C_{20}-T_3-retinoid, and a C_{20}-F_3-retinoid.

16. A unit dosage form comprising the composition of claim 15.

17. A composition according to claim 15, which is a vitamin supplement.

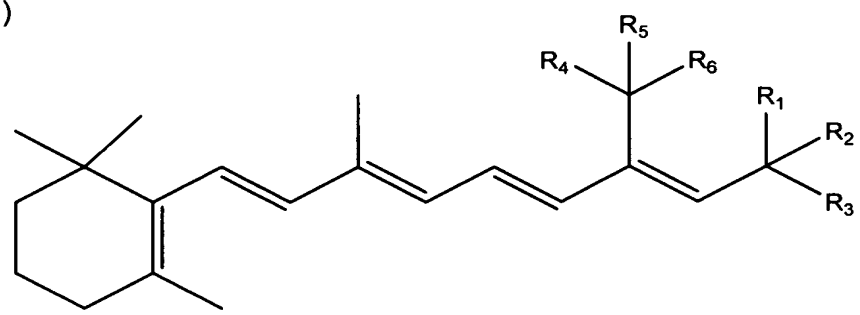
18. A composition according to claim 15, which is a pharmaceutical formulation.

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 C_{20}-D_3-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:

(I)



wherein:

R_1 is oxo or H;

R_2 is H or nothing;

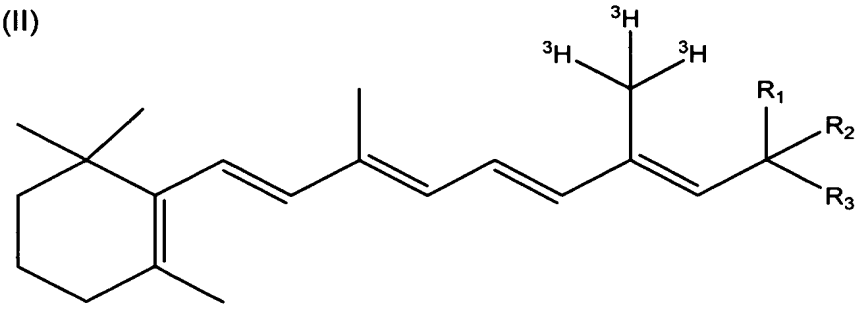
R_3 is hydroxy or oxo or =CH-R_7, where R_7 forms a carotenoid; and

R_4, R_5, and R_6 are independently selected from the group consisting of ^1H, ^2H, ^3H, halogen, and C_{1-8}alkyl.

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:

(II)



wherein:

R_1 is oxo or H;

R_2 is H or nothing; and

R_3 is hydroxy or oxo or =CH-R_7, where R_7 forms a carotenoid.

23. The composition of claim 20, wherein R_4, R_5, and R_6 are independently selected from H or a substituent that slows lipofuscin formation.

24. The composition of claim 20, wherein R_4, R_5, and R_6 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 R_4, R_5, and R_6 are independently selected from H or a substituent that slows hydrogen abstraction or migration at the C_{20} 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-NH_2, 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 C_{20}-D_3-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 C_{20}-D_3-retinoid substrate.

49. The method according to claim 48, wherein the substituted C_{20}-D_3-retinoid substrate is administered directly to the eye.

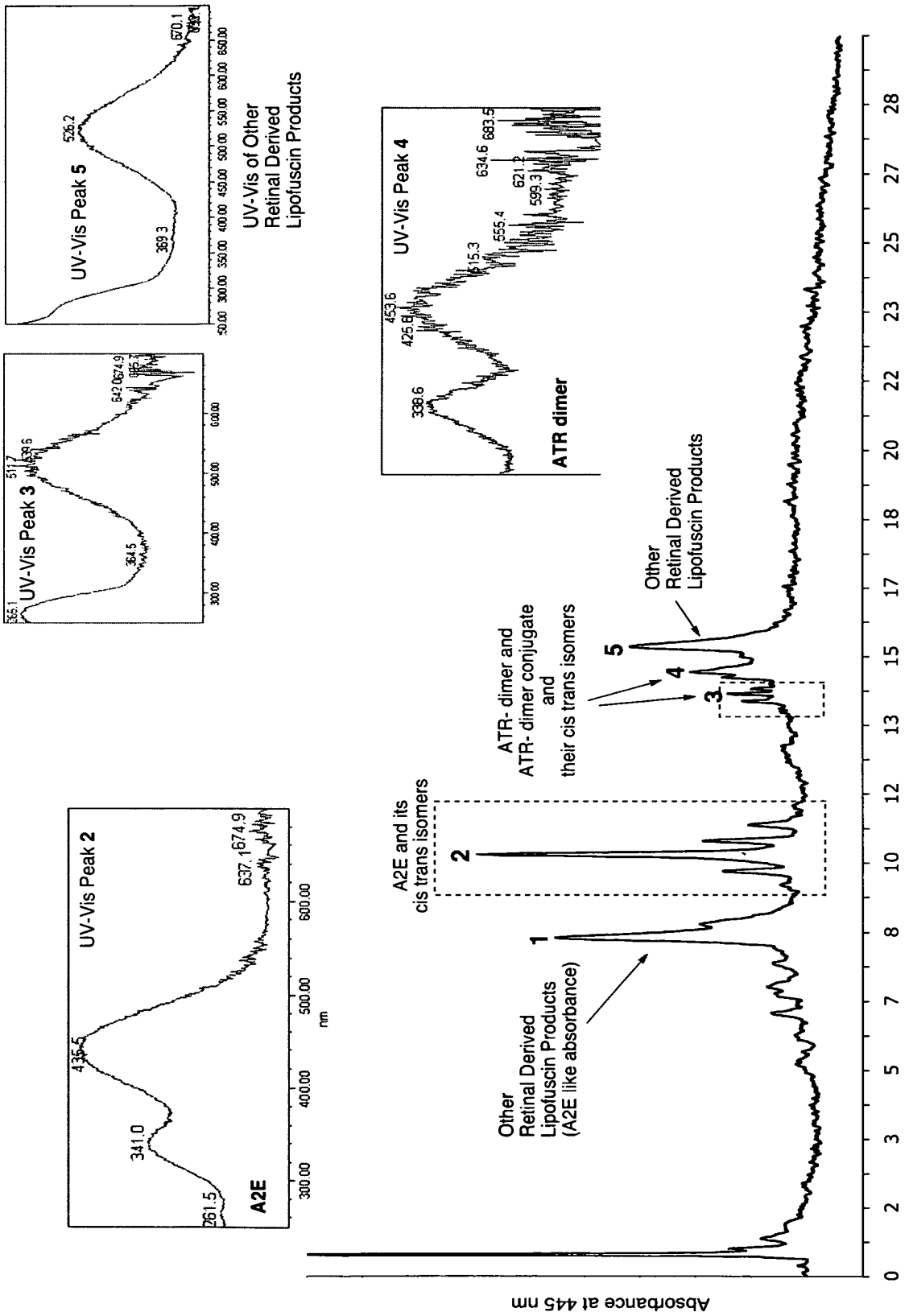

UV-Vis Peak 2
A2E
UV-Vis Peak 3
UV-Vis Peak 5
UV-Vis of Other
Retinal Derived
Lipofuscin Products
UV-Vis Peak 4
ATR dimer
Other
Retinal Derived
Lipofuscin Products
(A2E like absorbance)
A2E and its
cis trans isomers
ATR- dimer and
ATR- dimer conjugate
and
their cis trans isomers
Other
Retinal Derived
Lipofuscin Products
Absorbance at 445 nm
nm

FIG 1.

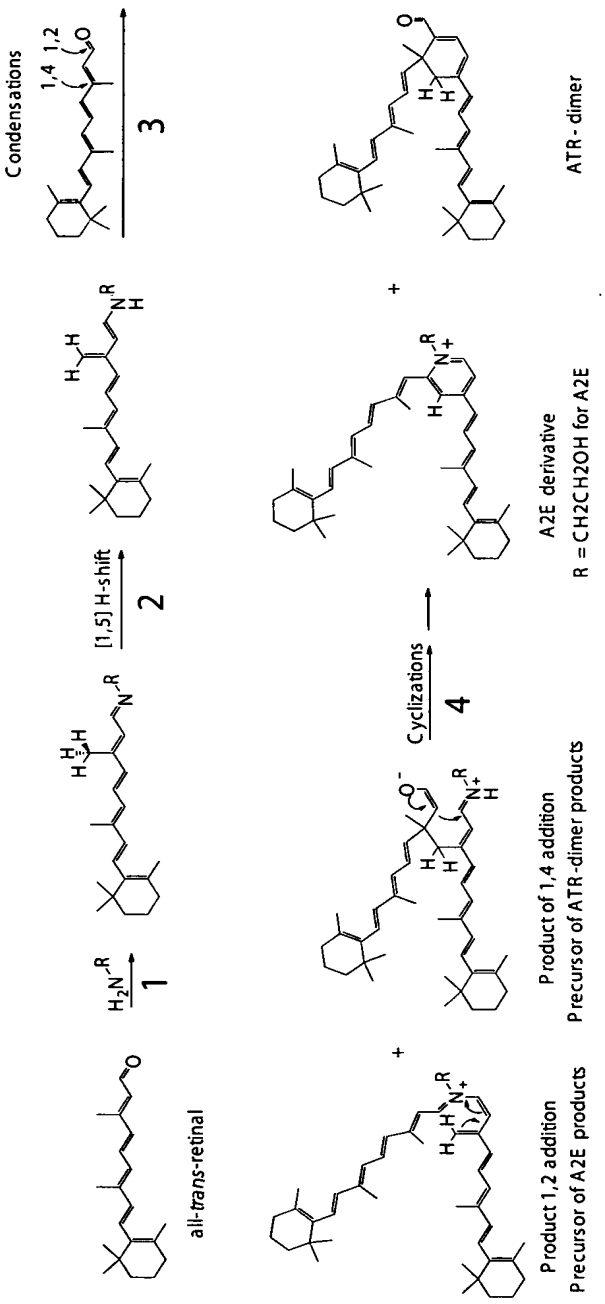

all-trans-retinal
H2N-R
1
[1,5] H-shift
2
Condensations
1,4 1,2
3
Cyclizations
4
Product 1,2 addition
Precursor of A2E products
Product of 1,4 addition
Precursor of ATR-dimer products
A2E derivative
R = CH2CH2OH for A2E
ATR- dimer

FIG 2.

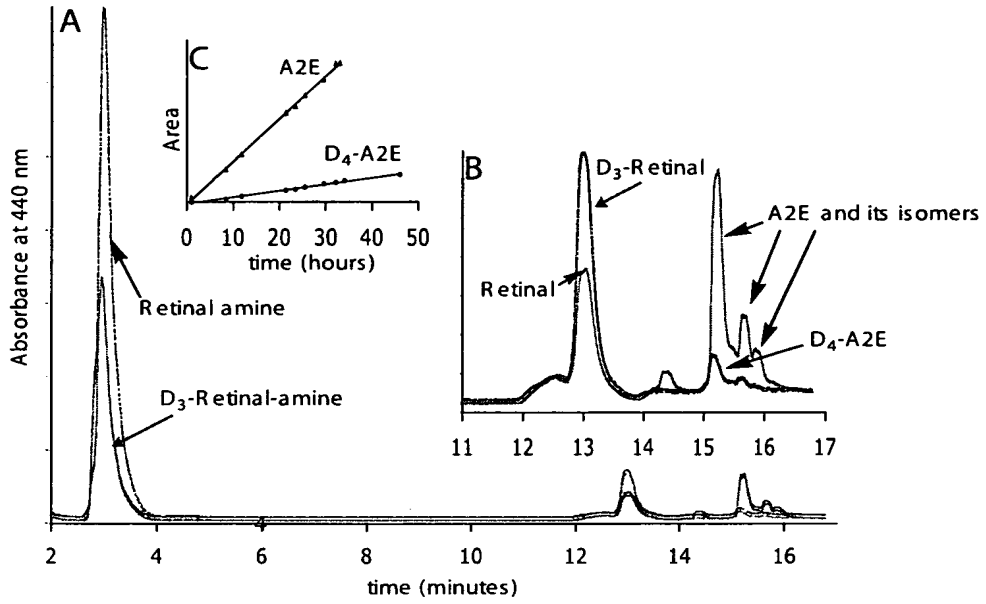

A
B
C
Absorbance at 440 nm
Retinal amine
D3-Retinal-amine
time (minutes)
2
4
6
8
10
12
14
16
Area
A2E
D4-A2E
0 10 20 30 40 50
time (hours)
D3-Retinal
Retinal
A2E and its isomers
D4-A2E
11 12 13 14 15 16 17

FIG 3.

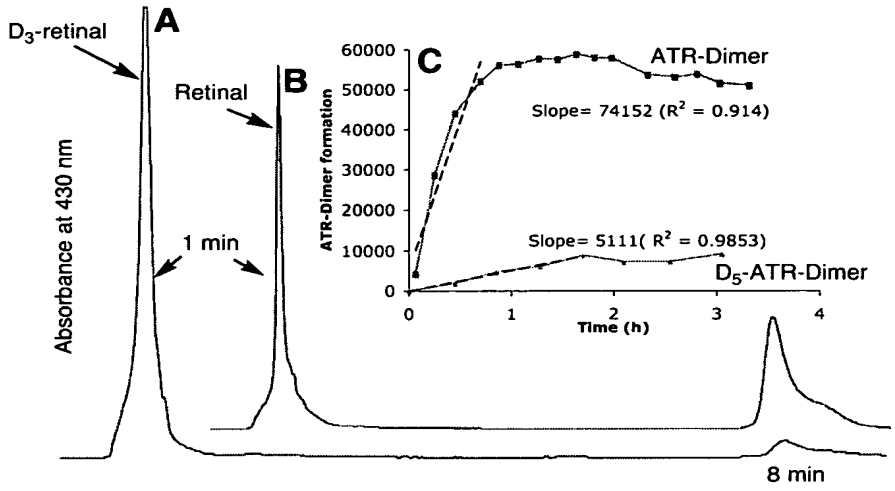

D3-retinal
A
Retinal
B
1 min
Absorbance at 430 nm
8 min
C
ATR-Dimer formation
60000
50000
40000
30000
20000
10000
0
ATR-Dimer
Slope= 74152 (R2 = 0.914)
Slope= 5111(R2 = 0.9853)
D5-ATR-Dimer
0
1
2
3
4
Time (h)

FIG 4.

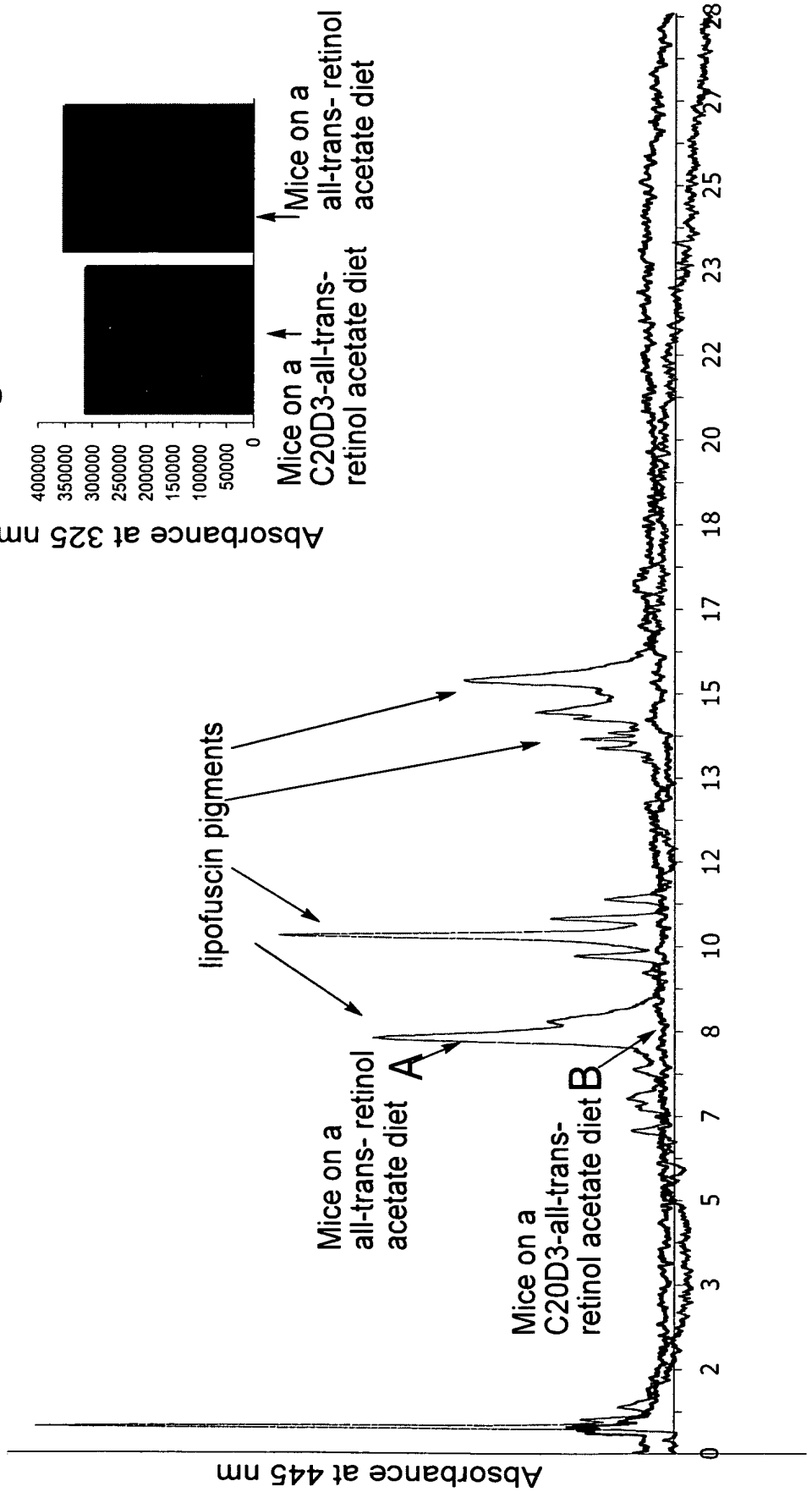

Absorbance at 445 nm
0
2
3
5
7
8
10
12
13
15
17
18
20
22
23
25
27
28
lipofuscin pigments
Mice on a all-trans- retinol acetate diet
A
Mice on a C20D3-all-trans-retinol acetate diet
B
C
Absorbance at 325 nm
400000
350000
300000
250000
200000
150000
100000
50000
0
Mice on a C20D3-all-trans-retinol acetate diet
Mice on a all-trans- retinol acetate diet

FIG 5.

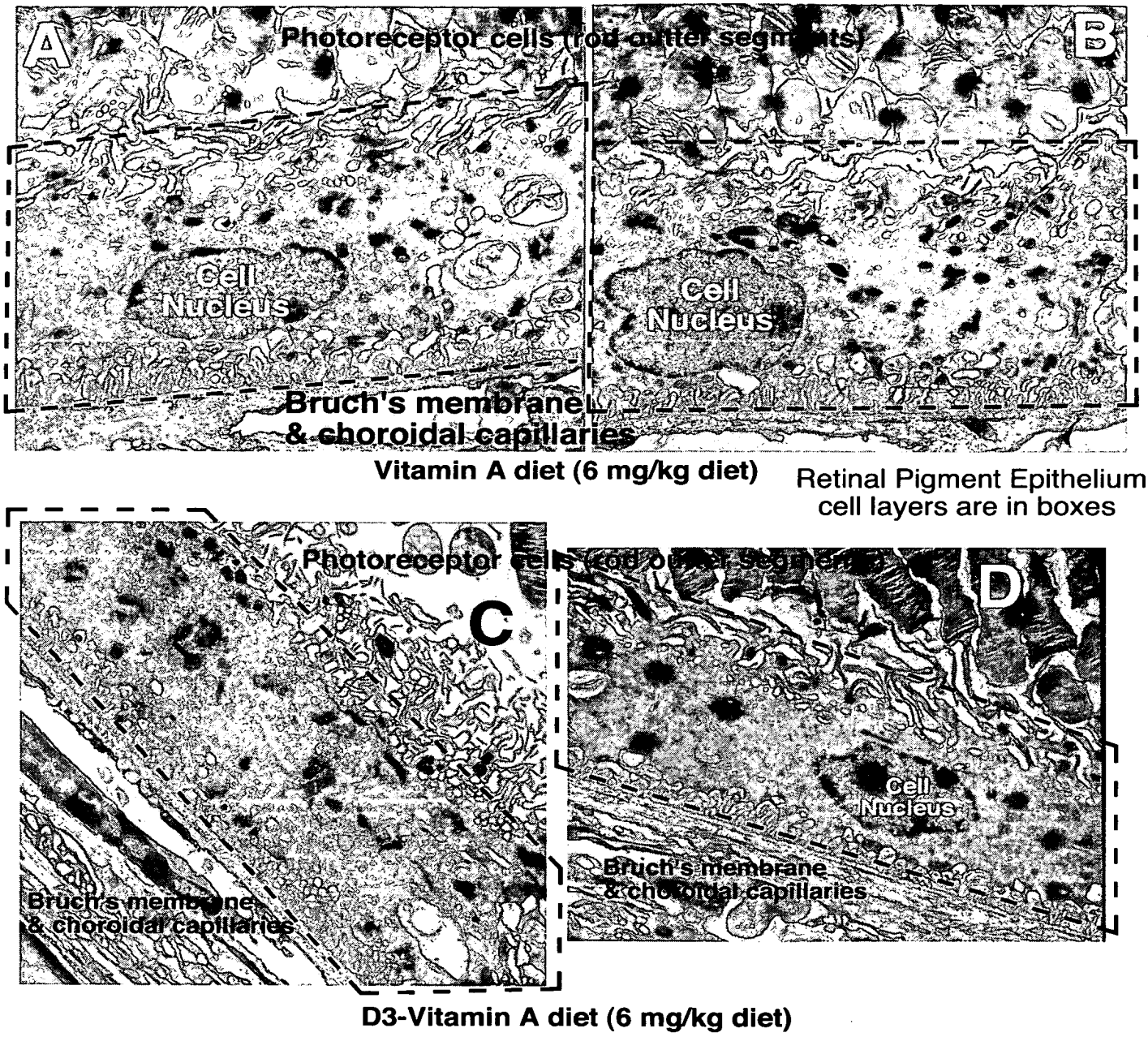

A
Photoreceptor cells (rod outer segments)
Cell Nucleus
Bruch's membrane & choroidal capillaries
B
Cell Nucleus
Vitamin A diet (6 mg/kg diet)
Retinal Pigment Epithelium cell layers are in boxes
C
Photoreceptor cells (rod outer segments)
Bruch's membrane & choroidal capillaries
D
Cell Nucleus
Bruch's membrane & choroidal capillaries
D3-Vitamin A diet (6 mg/kg diet)

FIG 6.

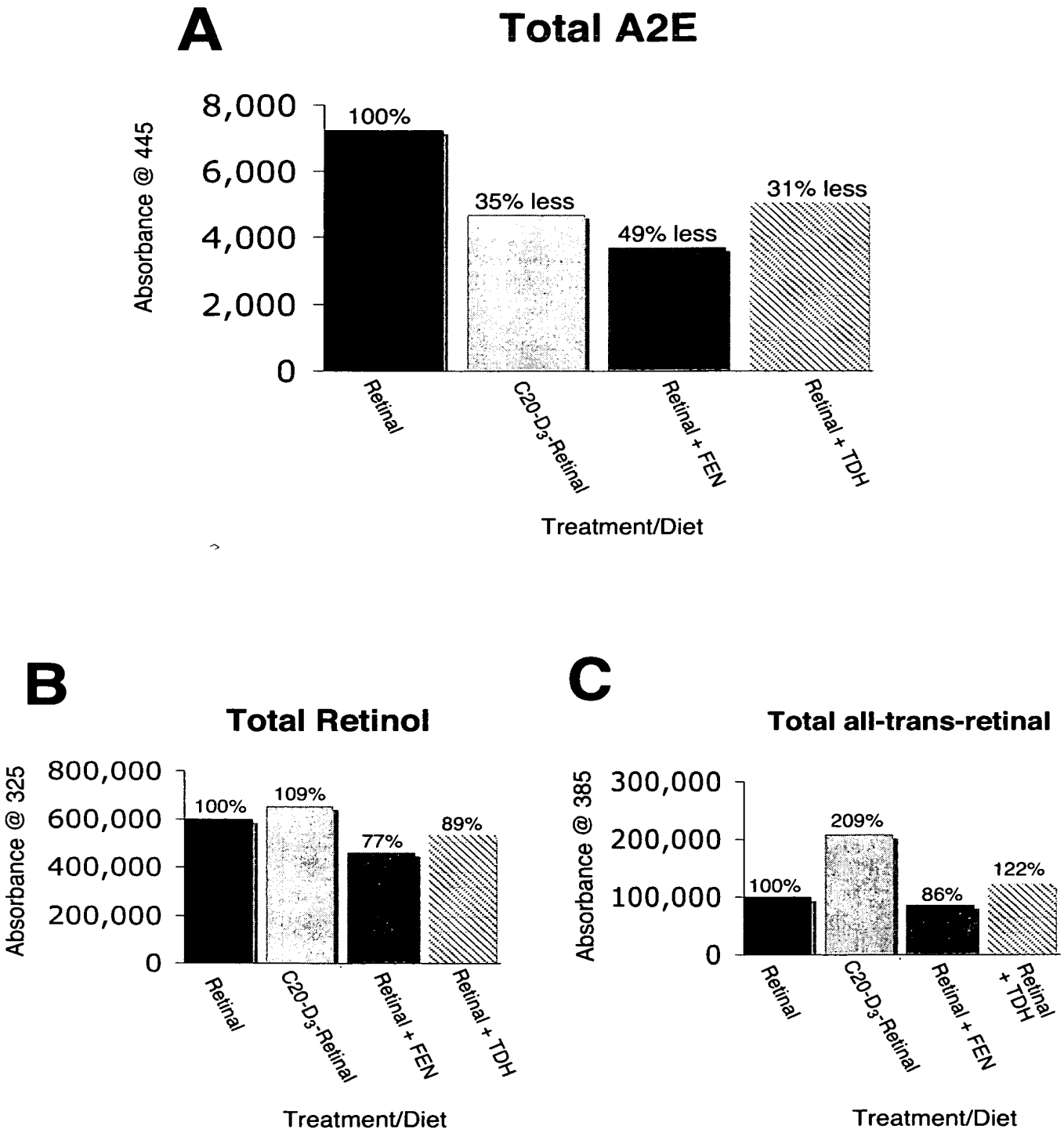

A
Total A2E
Absorbance @ 445
8,000
6,000
4,000
2,000
0
100%
35% less
49% less
31% less
Retinal
C20-D3-Retinal
Retinal + FEN
Retinal + TDH
Treatment/Diet
B
Total Retinol
Absorbance @ 325
800,000
600,000
400,000
200,000
0
100%
109%
77%
89%
Retinal
C20-D3-Retinal
Retinal + FEN
Retinal + TDH
Treatment/Diet
C
Total all-trans-retinal
Absorbance @ 385
300,000
200,000
100,000
0
100%
209%
86%
122%
Retinal
C20-D3-Retinal
Retinal + FEN
Retinal + TDH
Treatment/Diet

FIG. 7.

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(54) Title: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

(57) 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 C_{20}-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-frans-retinal (ATR) substrate with a C_{20}-D_3-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 C_{20}-retinoid and a pharmaceutically acceptable carrier are also provided.

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COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENRATION

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SIGNATURE Charles M. Avigliano Date September 12, 2007

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COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION

GOVERNMENT FUNDING

[0001] Work described herein was funded, in whole or in part, by the National Eye Institute of the National Institutes of Health, Grant EY T32 013933. The United States government may have certain rights in the invention.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds, compositions, and methods to treat or ameliorate macular degeneration without adverse visual effects. More particularly, the present invention relates to compounds and compositions that may be used to treat or ameliorate 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 macular degeneration in a mammal by administering to a mammal in need of such treatment an effective amount of the compounds and/or compositions above.

BACKGROUND OF THE INVENTION

[0003] 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 occurs in three out of ten people over the age of 75. 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 (Doyne Honeycomb or Dominant Radial Drusen) (1). Stargardt Disease is the most common form of inherited juvenile macular degeneration, affecting about 1 in 10,000 children.

[0004] 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.

[0005] The above listed macular dystrophies are all marked by the accumulation of lipofuscin, fluorescent deposits, in the retinal pigment epithelium (RPE) cell layer (2-5). 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 (6, 7). These toxic retinal dimers have been shown to cause RPE cell death, which is thought to lead to photoreceptor cell degeneration and vision loss (8, 9). Slowing the visual cycle using RPE 65 antagonists (10, 11) or retarding the delivery of vitamin A (retinol) to the RPE by, *e.g.*, limiting dietary intake of vitamin A (12) or blocking serum retinol binding proteins (13) 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 (5).

[0006] 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. Recently proposed therapeutic approaches to limit lipofuscin formation are based upon slowing the visual cycle (1, 10, 11, 12). A side effect of such

therapies is delayed dark adaptation, which hinders a patient's ability to adjust to dim lighting. Moreover, appreciable slowing of the visual cycle is undesirable in disorders in which delayed dark adaptation is already a clinical symptom, such as in AMD and Stargardt.

[0007] Accordingly, it would be advantageous to provide treatments for macular degeneration that do not have these side effects. In particular, it would be advantageous to provide a compounds, compositions, and methods that impede or halt the accumulation of lipofuscin or age pigments in the RPE cells of the retina without slowing the visual cycle.

SUMMARY OF THE INVENTION

[0008] 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 C_{20}-retinal in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

[0009] 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 C_{20}-retinal in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

[0010] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina containing a substituted C_{20}-retinal and pharmaceutically acceptable carrier.

[0011] 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 C_{20}-D_3-retinal substrate under conditions sufficient to form A2E.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 is a reaction scheme showing the biosynthesis of A2E and ATR-dimer from all-trans-retinal.

[0013] Figure 2 is a typical HPLC trace for reactions of all-*trans*-retinal and C_{20}-D_3-retinal with ethanol amine to form A2E at three days reaction time. The peak at 6.15 minutes is A2E.

[0014] Figure 3 shows a plot of the area under the HPLC peak at 6.15 minutes plotted against time of reaction of all-*trans*-retinal and C_{20}-D_3-retinal with ethanol amine to form A2E. The resulting points were fitted to a line.

DETAILED DESCRIPTION OF THE INVENTION

[0015] When the C_{20} hydrogens of all-*trans*-retinal are replaced by fluorine atoms, the formation of A2E is eliminated, as measured by monitoring the disappearance of all-*trans*-retinal and the emergence of 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 Figure 1. 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 C_{20}. Subsequent reaction with another molecule of retinal either by 1,2- or 1,4-addition followed by cyclizations yields reduced A2E or ATR-dimer respectively. A2E is subsequently formed after spontaneous oxidation in air.

[0016] It has been shown that replacing certain C-H bonds with C-F bonds in retinal (*i.e.*, C_{20}-F_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 C_{20} with fluorine the [1,5] hydrogen shift step is blocked (14). In such treatment, the levels of all-trans-retinal remain normal, however, isotope substitution is expected to hamper the formation of A2E and ATR-dimer.

Accordingly, C_{20}-F_3-retinal is expected to appreciably slow A2E and ATR-dimer biosynthesis and its effect on vision. An overall decrease in lipofuscin deposits, not simply a decrease in A2E and ATR-dimer formation, will lead to a decrease in the formation of RPE lipofuscin. Moreover, in this manner, the role A2E and ATR-dimers play in the formation of the other constituents of lipofuscin that have yet to be characterized may be elucidated.

[0017] A small change in the reaction rate of all-*trans*-retinal is expected to translate into a large decrease in RPE lipofuscin formation over a lifetime. This method will slow the formation of the toxic pigments and will not slow visual cycle kinetics, because the regeneration of 11-*cis*-retinal does not involve the breaking of the C_{20} hydrogen bond. Moreover, fluorinated analogs are considered relatively safe compounds and are often used in human studies. Therefore, treatment with C_{20}-F_3-retinal will be particularly useful in impeding lipofuscin formation in humans who suffer from Stargardt Disease.

[0018] C_{20}-D_3-retinal will also be useful as a therapy to treat or ameliorate macular degeneration without adverse visual effects. When C_{20} hydrogens are replaced by deuteriums, A2E formation is seven- to eight-times slower. (Figure 1.) This kinetic isotope effect will slow A2E formation *in vivo*. Deuterated vitamin A is widely used in humans and shows no toxicity (15, 16). Thus, a treatment using C_{20}-D_3-retinal should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects.

[0019] In addition, an efficient method for the large-scale preparation of C_{20}-D_3-retinal (17) by deuterium exchange on all-*trans*-retinal in the presence of deuterated methanol, D_2O and K_2CO_3 has been developed.

[0020] 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 C_{20}-retinal in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C_{20}-retinal is selected from the

group consisting of C_{20}-D_3-retinal and C_{20}-F-retinal. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, all-*trans*-retinal (ATR)-dimer, and combinations thereof.

[0021] Preferably, the substituted C_{20}-retinal is administered as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C_{20}-retinal is administered as a unit dosage form.

[0022] 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 C_{20}-retinal in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Preferably, the substituted C_{20}-retinal is selected from the group consisting of C_{20}-D_3-retinal and C_{20}-F-retinal. Preferably, the lipofuscin pigment is selected from the group consisting of A2E, ATR-dimer, and combinations thereof.

[0023] Preferably, the substituted C_{20}-retinal is administered as part of a pharmaceutical or a nutraceutical composition. Preferably, the substituted C_{20}-retinal is administered as a unit dosage form.

[0024] In one embodiment, the disease is macular degeneration. For example, the disease maybe selected from the group consisting of Stargardt, Vitelliform or Best (VMD), Sorsby's Fundus Dystrophy, and Malattia Leventinese. Preferably, the administration step includes replacing a component of the patient's diet's that contains all-*trans*-retinal with a component that contains a substituted C_{20}-retinal.

[0025] An additional embodiment of the present invention is a composition for retarding formation of a lipofuscin pigment in the retina containing a substituted C_{20}-retinal and pharmaceutically acceptable carrier. Preferably, the substituted C_{20}-retinal is selected from the group consisting of C_{20}-D_3-retinal and C_{20}-F-retinal. Preferably, the composition is

in a unit dosage form. Preferably, the composition is a vitamin supplement or a pharmaceutical formulation.

[0026] 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 C_{20}-D_3-retinal substrate under conditions sufficient to form A2E.

[0027] Effective dosage forms, modes of administration, and dosage amounts 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 animal, 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. 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.

[0028] A compound of the present invention may be administered in any desired and effective manner: as pharmaceutical compositions for oral ingestion, 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.

[0029] 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. 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.).

[0030] 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.

[0031] The pharmaceutical compositions or vitamin supplements of the invention may, optionally, contain additional ingredients and/or materials commonly used in such pharmaceutical compositions or vitamin supplements. 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 monosterate; (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 monosterate, 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.

[0032] Pharmaceutical compositions or vitamin supplements 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.

[0033] 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.

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] In some cases, in order to prolong the effect of a drug (*e.g.*, pharmaceutical formulation or vitamin supplement), 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.

[0039] 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.

[0040] 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.

[0041] 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 C_{20} hydrogens of all-*trans*-retinal with deuteriums slows the formation of A2E

[0042] All-*trans*-retinal (0.1 gram) was added to a first vial and C_{20}-D_3-retinal (0.1 gram, greater than 90% deuterium incorporation at C_{20} as shown by mass spectrometry (not shown)) was added to a second vial. 1 milliliter of a solution containing equimolar amounts of ethanol amine and acetic acid in anhydrous methanol was added to each vial, giving final

ratios of 0.5 molar equivalents to the respective retinals. 10 microliter aliquots were removed from each vial periodically. The aliquots were diluted with 1 milliliter of methanol and subjected to high performance liquid chromatography (HPLC) with a UV-VIS detector set to 400 nanometers.

[0043] Formation of A2E was measured by monitoring the appearance of a peak at 6.15 minutes. A typical HPLC trace after three days for the reactions of all-*trans*-retinal and C_{20}-D_3-retinal with ethanol amine to form A2E is shown in Figure 2. For both reactions the area of the peak at 6.15 minutes was plotted against time and the resulting points were fitted to a line (Figure 3). The slopes of the lines were 2 and 0.5 for all-*trans*-retinal and C_{20}-D_3-retinal, respectively. These results demonstrate that the formation of A2E is slowed by a factor of 4 by incorporation of deuterium atoms at C_{20} of all-*trans*-retinal.

EXAMPLE 2

C_{20}-D_3-retinal impedes the accumulation of the RPE lipofuscin deposits and A2E and ATR-dimer pigments

Animal model

[0044] $Abcr^{-/-}$ mice were developed as an animal model of human recessive Stargardt Disease (5). As in humans, with recessive Stargardt disease, $abcr^{-/-}$ mice exhibit large lipofuscin deposits in the RPE and delayed dark adaptation. This mouse model provides a way to test methods for limiting RPE lipofuscin formation, and the effect of such methods on age-related macular degeneration and other macular dystrophies.

[0045] The mice are divided into the following groups: i) a control group fed only retinal acetate, ii) a test group in which 100% of vitamin A is derived from ingestion of C_{20}-D_3-retinal acetate, and iii) a test group in which 75% of vitamin A is derived from ingesting C_{20}-D_3-retinal acetate and 25% of vitamin A is derived from ingesting retinal acetate. (The third

group is perhaps the best approximation of any potential human therapy where natural vitamin A, in the form of carotenoids or retinol, may be difficult to fully eliminate from the diet.)

[0046] Using breeding pairs, nine *abcr*$^{-/-}$ mice are bred. The pups are weaned at twenty days and male and females are placed in separate cages. All three groups are raised under the standard conditions on purified diets containing the corresponding retinal acetate or C_{20}-D_3-retinal acetate (diets manufactured by Harlan Teklad, Madison, Wisconsin). At four months of age, the mice are evaluated as summarized below and described in detail in the literature (10, 11, 12, 13). An additional control group is evaluated at the start of dietary treatment. All experiments are repeated in triplicate, *i.e.*, 9x3 mice are studied.

Electroretinograms

[0047] The effect of C_{20}-D_3-retinal on delayed dark adaptation, is assayed by electroretinogram measurements (10). Briefly, mice are dark adapted overnight and situated for ERG recordings as previously described (Washington, et al *Photochemical and Photobiological Sciences,* 2007). Each mouse is then exposed to a rod bleaching light for 10 minutes and recovery of rod sensitivity is measured by stimulation with scotopic flashes at five-minute intervals until a constant b-wave amplitude is achieved (approximately 50 minutes).

[0048] The cause of delayed dark adaptation in patients with abcr defects is poorly understood. In addition to evaluating C_{20}-D_3-retinal as a therapeutic drug, the information derived from this study is used to determine whether delayed dark adaptation is a result of all-*trans*-retinal accumulation in the disk or is a result of inhibition of steps of the retinoid metabolism that take place in the RPE as a result of lipofuscin or A2E/ATR-dimer mediated RPE damage.

Lipofuscin accumulation:

[0049] Lipofuscin accumulation is qualitatively assayed for all animals by comparing average values of fundus autofluorescence (emission: 515-540 nm (18)) as measured by a GFP imaging fluorometer (Qubit systems, Kingston, ON). Lipofuscin granules are measured by histological examination by transmission electron microscopy of the right eye (11). Further evaluation of the left eye is made by lipofuscin fluorescence as measured by histological examination by fluorescence microscopy (13).

A2E and ATR-dimer formation:

[0050] A2E and ATR-dimer formation is quantitatively assayed by extraction followed by HPLC analysis (10). Briefly, posterior eyecups from each group are dissected, pooled, homogenized and extracted three times with $CHCl_3$:MeOH (2:1) solution. The extracts are filtered, concentrated, and quantified by reverse phase liquid chromatography. Dark adaptation times will be compared with lipofuscin deposits and A2E and ATR-dimer concentrations in all nine mice from each group (control, fed and partially fed).

EXAMPLE 3

Long-term treatment with C_{20}-D_3-retinal impedes the accumulation of the RPE lipofuscin deposits and A2E and ATR-dimer pigments and mitigates the effect on dark adaptation

Animal Model

[0051] Sprague Dawley rats, a general model for the study of human health and disease, are used. These rats have a life span of 2.5 - 3.5 years and a food intake of approximately 5g/100g body weight/day. As these rats age, there is a progressive increase in lipofuscin accumulation (19). Furthermore, at over two years of age there is a marked increase in dark adaptation times (20).

[0052] The relationship between C_{20}-D_3-retinal acetate and lipofuscin accumulation will be determined. Although a direct link between age related lipofuscin accumulation and delayed dark adaptation in this rat model has not been shown, it would be of interest to determine whether the C_{20}-D_3-retinal analog decreases dark adaptation time, because in humans delayed dark adaptation is an early sign of Stargardt and AMD.

[0053] Two groups of one-month old rats (60 per group), a control group raised on retinal acetate and a test group raised on C_{20}-D_3-retinal acetate, are used. At six-month intervals, ten rats from each group will have dark adaptation times measured by electroretinogram (modified for rats (21)) and fundus autofluorescence will be measured. Six of the ten rats will undergo A2E and ATR-dimer quantification, and four rays will undergo histological examination for lipofuscin granules. Thus, the rats are evaluated at 6, 12, 18, and 24, 30, and 36 months of age, as described.

[0054] It is expected that the rats in the test group will have decreased lipofuscin accumulation compared to the control group.

CITED DOCUMENTS

[0055] The following documents, which have been cited above, are incorporated by reference as if recited in full herein:

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[0056] 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 C_{20}-retinal in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

2. The method according to claim 1, wherein the substituted C_{20}-retinal is selected from the group consisting of C_{20}-D_3-retinal and C_{20}-F-retinal.

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 C_{20}-retinal is administered as part of a pharmaceutical or a nutraceutical composition.

5. The method according to claim 1, wherein the substituted C_{20}-retinal 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 C_{20}-retinal in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina.

7. The method according to claim 6, wherein the substituted C_{20}-retinal is selected from the group consisting of C_{20}-D_3-retinal and C_{20}-F-retinal.

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 C_{20}-retinal is administered as part of a pharmaceutical nutraceutical composition

10. The method according to claim 6, wherein the substituted C_{20}-retinal 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, 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 all-*trans*-retinal with a component that contains a substituted C_{20}-retinal.

14. A composition for retarding formation of a lipofuscin pigment in the retina comprising a substituted C_{20}-retinal and pharmaceutically acceptable carrier.

15. A composition according to claim 14, wherein the substituted C_{20}-retinal is selected from the group consisting of C_{20}-D_3-retinal and C_{20}-F-retinal.

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 A2E comprising replacing an all-*trans*-retinal (ATR) substrate with a C_{20}-D_3-retinal substrate under conditions sufficient to form A2E.

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 C_{20}-retinal in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Further provided are methods of retarding formation of A2E by replacing an all-*trans*-retinal (ATR) substrate with a C_{20}-D_3-retinal substrate under conditions sufficient to form A2E. Compositions for retarding formation of a lipofuscin pigment in the retina containing a substituted C_{20}-retinal and a pharmaceutically acceptable carrier are also provided.

Title: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
Inventor(s): Ilyas WASHINGTON
Express Mail #: ER 248806944 US

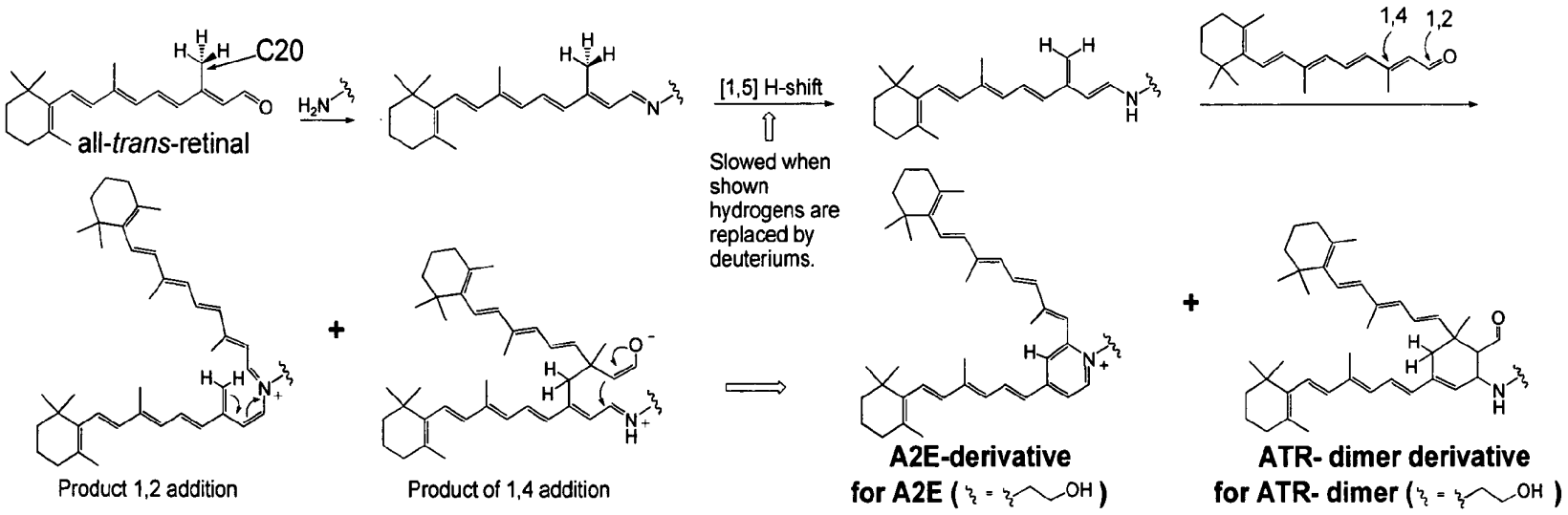


FIGURE 1

Title: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
Inventor(s): Ilyas WASHINGTON
Express Mail #: ER 248806944 US

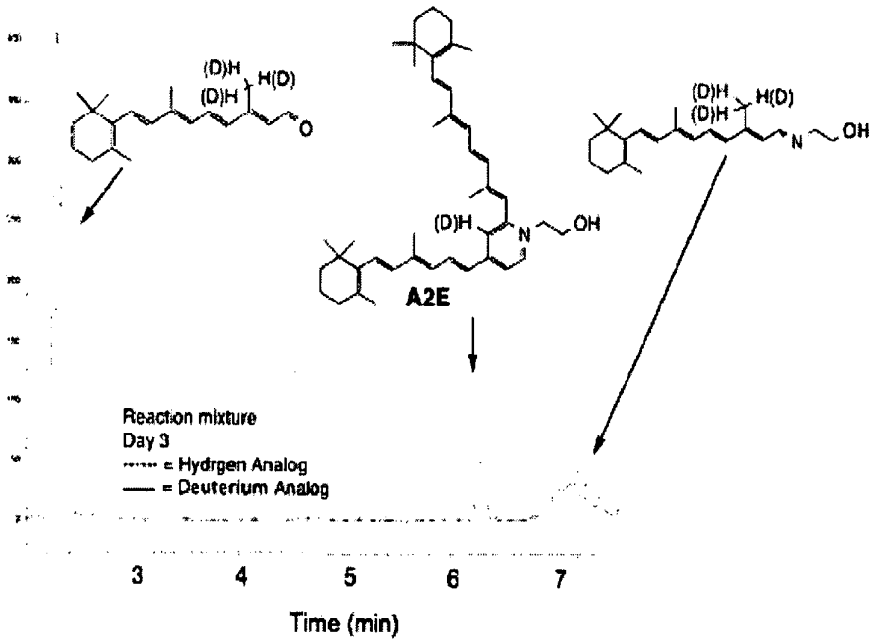


FIGURE 2

Title: COMPOSITIONS AND METHODS FOR TREATING MACULAR DEGENERATION
Inventor(s): Ilyas WASHINGTON
Express Mail #: ER 248806944 US

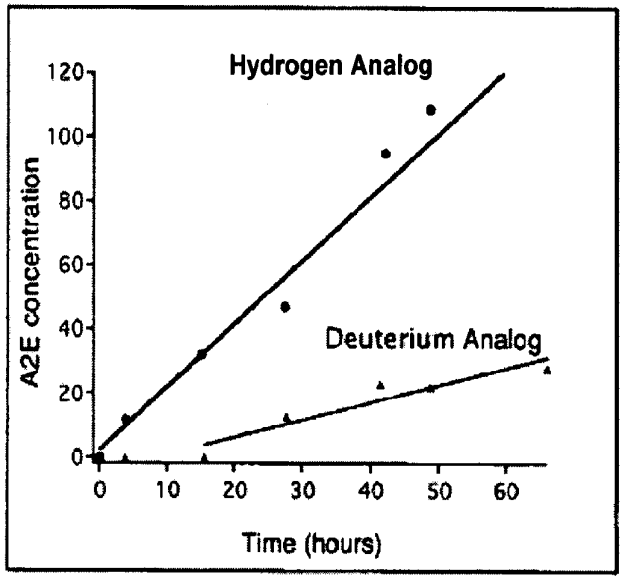


FIGURE 3

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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			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	03/10/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 49	Minus	** 49	= 0	X $26 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	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))									
	☐ 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".
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Legal Instrument Examiner:
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