UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4

CONFIRMATION NO. 8618

POWER OF ATTORNEY NOTICE

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

OC000000137523309

Date Mailed: 03/07/2023

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/28/2023.

- The Power of Attorney to you in this application has been revoked by the applicant.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**.

/sltorres/

Petitioner Fresenius Ex. 1002, 0001

UNITED STATES PATENT AND TRADEMARK OFFICE

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P.O. Box 1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4

CONFIRMATION NO. 8618

191459
A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743

POA ACCEPTANCE LETTER

OC000000137523311

Date Mailed: 03/07/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/28/2023.

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**.

/sltorres/

Petitioner Fresenius Ex. 1002, 0002

PTO/AIA/82 (07-17)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 191459

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(c).

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

[X] The address associated with Customer Number: 191459

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, 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 /Frank R. Cottingham/	Date 13 January 2023
Name Frank R. Cottingham, Ph.D., J.D.	Telephone
Title Vice President, Associate General Counsel, Intellectual Property	

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 update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 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.

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.

PTO/AIA/96 (08-12)
Approved for use through 11/30/2020. 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.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.

Application No./Patent No.: 10,828,345 Filed/Issue Date: November 10, 2020

Titled: Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

Regeneron Pharmaceuticals, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

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 047899, Frame 0083, or for which a copy thereof is attached.

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.

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.**

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

PTO/AIA/96 (08-12)
Approved for use through 11/30/2020. 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.

STATEMENT UNDER 37 CFR 3.73(c)

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.

4. 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.

5. 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.

6. 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).

☐ As required by 37 CFR 3.73(c)(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.

/Michael W. Lewis/	February 28, 2023
Signature	Date
Michael W. Lewis	76,829
Printed or Typed Name	Title or Registration 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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/159,282	**02/28/2023 02:36:57 PM ET**	**REGN-008CIPCON4**

Title of Invention

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	10828345
CONFIRMATION #	8618	FILED BY	Kathi Moore
PATENT CENTER #	61663202	FILING DATE	10/12/2018
CUSTOMER #	96387	FIRST NAMED INVENTOR	George D. Yancopoulos
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Michael Lewis

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P35056US07-373c.pdf	3	Assignee showing of ownership per 37 CFR 3.73	110 KB
POA-Regeneron.pdf	2	Power of Attorney	3810 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P35056US07-373c.pdf	57E1DBB8DCEE9526B3632F84E82368CD4EE7EA612BAFA22F B0B6A2DFB437D93749498C1005FF1187703BB6927FF334B4F5 15C3514620AED61876097D035C2F6F

POA-Regeneron.pdf

BDECE05D2F51BBCDB37E674E496644E6B6A6D74B020A14B4
FE816D8015E1EC9283171078BA0A0E1076CA395ADB4C661BA
9E9C16DA415BC049CBFF10B715A0675

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 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

CERTIFICATE OF CORRECTION

PATENT NO. : 10,828,345 B2
APPLICATION NO. : 16/159282
DATED : November 10, 2020
INVENTOR(S) : Yancopoulos

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

In the Specification

At Column 15, Line 5, please correct from "gained ≤15 ETDRS" to read --gained ≥15 ETDRS--.

At Column 15, Lines 9-10, please correct from "gained ≤15 ETDRS" to read --gained ≥15 ETDRS--.

At Column 15, Line 12, please correct from "gained ≤15 letters" to read --gained ≥15 letters--.

Signed and Sealed this
Twenty-ninth Day of March, 2022

Drew Hirshfeld
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 03/22/2022

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
03/22/2022	ELECTRONIC

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

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

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

docket@bozpat.com

Petitioner Fresenius Ex. 1002, 0011

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

Patent No.: 10828345
Issue Date: 11/10/2020
Appl. No.: 16/159,282
Filed: 10/12/2018

PART (A) RESPONSE FOR CERTIFICATES OF CORRECTION

This is a decision on the Certificate of Correction request filed 04 March 2022.

The request for issuance of Certificate of Correction for the above-identified correction(s) under the provisions of 37 CFR 1.322 and/or 1.323 is hereby:

(Check one)
☑ Approved ☐ Approved in Part ☐ Denied

Comments: ____

PART (B) PETITION UNDER 37 CFR 1.324 OR 37 CFR 1.48

☐ This is a decision on the petition filed ____ to correct inventorship under 37 CFR 1.324.

☐ This is a decision on the request under 37 CFR 1.48, petition filed ____. In view of the fact that the patent has already issued, the request under 37 CFR 1.48 has been treated as a petition to correct inventorship under 37 CFR 1.324.

The petition is hereby: ☐ Granted ☐ Dismissed

Comment: ____

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/JOANNE HAMA/
Supervisory Patent Examiner, Art Unit 1647
Technology Center 1600
Phone: (571)272-2911

Certificates of Correction Branch email: CustomerServiceCoC@uspto.gov CoC Central Phone Number: (703) 756-1814

Electronically Filed		
PETITION FOR CERTIFICATE OF CORRECTION Address to: Mail Stop Certificate of Correction Branch Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-008CIPCON4
	First Named Inventor	George D. Yancopoulos
	Patent Number	10,828,345
	Issue Date	November 10, 2020
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Transmitted herewith for filing is a Certificate of Correction for the above-identified patent. This request is being submitted to correct typographical errors made during the printing of the patent in a manner that does not correspond to the language (specific symbol) shown in the originally filed specification.

It is believed that no fee is due since the error was made by the Patent and Trademark Office. If for any reason a fee is found to be necessary, the Commissioner is authorized to charge such fee to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 4 March 2022

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

PTO/SB/44 (09-07)
Approved for use through 01/31/2020. 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. : 10,828,345

APPLICATION NO. : 16/159,282

ISSUE DATE : November 10, 2020

INVENTOR(S) : George D. Yancopoulos

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 15, line 5, please correct the specification from "gained ≤15 ETDRS" to read --gained ≥15 ETDRS--.

At column 15, lines 9-10, please correct the specification from "gained ≤15 ETDRS" to read --gained ≥15 ETDRS--.

At column 15, line 12, please correct the specification from "gained ≤15 letters" to read --gained ≥15 letters--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Pkwy, Suite 200
Redwood City, California 94065

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. 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 1.0 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: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Electronic Acknowledgement Receipt

EFS ID:	45146458
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	04-MAR-2022
Filing Date:	12-OCT-2018
Time Stamp:	12:36:43
Application Type:	Utility under 35 USC 111(a)

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	Request for Certificate of Correction	REGN-008CIPCON4_2022-03-04_Petition_COC.pdf	21392 e153970ae209c88ad514f43251991e03fe2b1a67	no	1

Warnings:

Information:					
2	Request for Certificate of Correction	REGN-008CIPCON4_2022-03-04_COC.pdf	28252 0c433bdefc136a099c7ce351f4672a27d8fade23	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	49644	

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.
16/159,282	11/10/2020	10828345	REGN-008CIPCON4	8618

96387 7590 10/21/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

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

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

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

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

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

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY
George D. Yancopoulos, Yorktown Heights, 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.

Petitioner Fresenius Ex. 1002, 0017

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
16159282	12-Oct-2018	George Yancopoulos	REGN-008CIPCON4	8618

TITLE OF INVENTION :

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1647	134100	JON LOCKARD

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1000	$0	$1000	22-Oct-2020	$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
96387 Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY CA 94065 UNITED STATES 650 327 3400 docket@bozpat.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ 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.

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____

☒ If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency or credit any overpayment, to Deposit Account Number 500815 . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. THOMAS TRIOLO
2. KARL BOZICEVIC
3.

5.Assignee Name(s) and Residence Data To Be Printed

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.

Name	City	State	Country	Category
REGENERON PHARMACEUTICALS, INC.	Tarrytown	NEW YORK	united states	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Karl Bozicevic/	**Date**	10-08-2020
Name	Karl Bozicevic	**Registration Number**	28807

Petitioner Fresenius Ex. 1002, 0019

Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	40792313
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	08-OCT-2020
Filing Date:	12-OCT-2018
Time Stamp:	13:15:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1000
RAM confirmation Number	E202008D15282363
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Web85b.pdf	46437 f07aca009d2399c73b547cd58ea598fae14619cf	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32277 085eb18b4fd16f973aeacd73471df08453001314	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	78714		

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
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NOTICE OF ALLOWANCE AND FEE(S) DUE

96387 7590 07/22/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/22/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	10/22/2020

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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

Petitioner Fresenius Ex. 1002, 0024

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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)

96387 7590 07/22/2020
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	10/22/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Petitioner Fresenius Ex. 1002, 0025

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.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 07/22/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/22/2020

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.

Petitioner Fresenius Ex. 1002, 0026

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 30 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.

Petitioner Fresenius Ex. 1002, 0027

Notice of Allowability	Application No. 16/159,282	Applicant(s) Yancopoulos, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

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

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

1. ☑ This communication is responsive to the Request for Continued Examination filed 30 June 2020.
   ☐ 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 32-42 (renumbered as claims 1-11, respectively) . 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 _____.
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 _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Notice of Pre-AIA or AIA Status

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

DETAILED CORRESPONDENCE

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 30 June 2020 has been entered.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 30 June 2020 and 16 July 2020 have been considered by the examiner.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance: The information disclosure statements (IDS) filed 30 June 2020 and 16 July 2020 have been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax 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.

/J. M. L./
Examiner, Art Unit 1647
July 16, 2020

/Christine J Saoud/
Primary Examiner, Art Unit 1647

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	179	F	2013-01-01
C07K	/	16	/	22	I	2013-01-01
C07K	/	14	/	71	I	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2319	/	32	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/JON M LOCKARD/ Examiner, Art Unit 1647	16 July 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	19 July 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200716

Petitioner Fresenius Ex. 1002, 0031

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JON M LOCKARD/ Examiner, Art Unit 1647	16 July 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	19 July 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200716

Petitioner Fresenius Ex. 1002, 0032

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JON M LOCKARD/ Examiner, Art Unit 1647	16 July 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	19 July 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Petitioner Fresenius Ex. 1002, 0033

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	NONE	03/29/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/29/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/29/2019	JML
PALM: Inventor search.	03/29/2019	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	09/25/2019	JML
PALM: Inventor search.	09/25/2019	JML

Petitioner Fresenius Ex. 1002, 0034

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	EAST (USPAT): See attached search history.	03/25/2020	JML
	PALM: Inventor search.	03/25/2020	JML
	EAST (USPAT): See attached search history.	07/16/2020	JML
	PALM: Inventor search.	07/16/2020	JML

Petitioner Fresenius Ex. 1002, 0035

Receipt date: 07/16/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	5	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2019/0290725	2019-09-26	Vitti et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2004/106378 A2	2004-12-09	Regeneron Pharmaceuticals, Inc.		
	2	WO 2005/000895 A2	2005-01-05	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	BENZ et al. "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose- and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" ARVO Annual Meeting Abstract (May 2007)	
	2	DO et al. "Results of a Phase 1 Study of Intravitreal VEGF Trap in Subjects with Diabetic Macular Edema: The CLEAR-IT DME Study" ARVO Annual Meeting Abstract (May 2007)	
	3	DO et al. "VEGF Trap-Eye Vision-specific Quality of Life through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial" ARVO Annual Meeting Abstract (April 2009)	
	4	HALLER et al., "VEGF Trap-Eye In CRVO: Primary Endpoint Results of the Phase 3 COPERNICUS Study" ARVO Annual Meeting Abstract (April 2011)	
	5	HEIER et al., "CLEAR-IT 2: Phase 2, Randomized Controlled Dose and Interval-Ranging Study of Intravitreal VEFG Trap Eye in Patients with Neovascular Age-Related Macular Degeneration: Predictive Factors for Visual Acuity" ARVO Annual Meeting Abstract (April 2009)	
	6	HEIER et al., "The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing" Ophthalmology 2011;118:1098–1106 (June 2011)	
	7	HEIER et al., "The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing: Erratum" Ophthalmology 2011;118:1700 (September 2011)	
	8	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320775 "Safety and Tolerability of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration" 70 pages, Latest version submitted June 8, 2011 on ClinicalTrials.gov (NCT00320775_2006-2011)	

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 07/16/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
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				Examiner Name	Jon McClelland Lockard
Sheet	2	of	5	Attorney Docket Number	REGN-008CIPCON4

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	9	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320775 "Safety and Tolerability of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration" 10 pages, Latest version submitted March 16, 2015 on ClinicalTrials.gov (NCT00320775_2015)	
	10	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320788 "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)" 71 pages, Latest version submitted December 1, 2011 on ClinicalTrials.gov (NCT00320788_2006-2011)	
	11	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320788 "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)" 31 pages, Latest version submitted January 27, 2012 on ClinicalTrials.gov (NCT00320788_2012)	
	12	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320814 "Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema" 30 pages, Latest version submitted June 8, 2011 on ClinicalTrials.gov (NCT00320814_2006-2011)	
	13	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00509795 "Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)" 318 pages, Latest version submitted December 1, 2011 on ClinicalTrials.gov (NCT00509795_2007-2011)	
	14	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00509795 "Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)" 200 pages, Latest version submitted December 20, 2012 on ClinicalTrials.gov (NCT00509795_2012)	
	15	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00527423 "Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD" 64 pages, Latest version submitted November 1, 2011 on ClinicalTrials.gov (NCT00527423_2007-2011)	
	16	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00527423 "Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD" 42 pages, Latest version submitted June 10, 2013 on ClinicalTrials.gov (NCT00527423_2012-2013)	
	17	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" 667 pages, Latest version submitted December 16, 2011 on ClinicalTrials.gov (NCT00637377_2008-2011)	
	18	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" 289 pages, Latest version submitted November 28, 2014 on ClinicalTrials.gov (NCT00637377_2012-2014)	

Examiner Signature		Date Considered	

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Receipt date: 07/16/2020

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				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	3	of	5	Attorney Docket Number	REGN-008CIPCON4

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	19	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00789477 "DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)" 135 pages, Latest version submitted May 2, 2011 on ClinicalTrials.gov (NCT00789477_2008-2011)	
	20	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00789477 "DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)" 53 pages, Latest version submitted August 28, 2014 on ClinicalTrials.gov (NCT00789477_2013-2014)	
	21	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00943072 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)" 98 pages, Latest version submitted May 9, 2011 on ClinicalTrials.gov (NCT00943072_2009-2011)	
	22	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00943072 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)" 64 pages, Latest version submitted April 16, 2013 on ClinicalTrials.gov (NCT00943072_2012-2013)	
	23	MAJOR et al., "DA VINCI: DME and VEGF Trap-Eye: Investigation of Clinical Impact: Phase 2 Study in Patients with Diabetic Macular Edema (DME)" ARVO Annual Meeting Abstract (April 2010)	
	24	NGUYEN et al., "Randomized, Double-masked, Active-controlled Phase 3 Trial of the Efficacy and Safety of Intravitreal VEGF Trap-Eye in Wet AMD: One-year Results of the VIEW 1 Study" ARVO Annual Meeting Abstract (April 2011)	
	25	NGUYEN et al., "Results of a Phase I, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreous VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration" ARVO Annual Meeting Abstract (May 2006)	
	26	Regeneron SEC Form 10-K (February 27, 2008)	
	27	Regeneron SEC Form 10-K (February 26, 2009)	
	28	Regeneron SEC Form 10-K (February 17, 2011)	
	29	Regeneron SEC Form 10-Q (May 8, 2006)	
	30	Regeneron SEC Form 10-Q (August 8, 2006)	
	31	Regeneron SEC Form 10-Q (November 6, 2006)	
	32	Regeneron SEC Form 10-Q (May 4, 2007)	
	33	Regeneron SEC Form 10-Q (August 3, 2007)	
	34	Regeneron SEC Form 10-Q (April 30, 2009)	
	35	Regeneron SEC Form 10-Q (November 3, 2009)	
	36	Regeneron SEC Form 10-Q (April 29, 2010)	
	37	Regeneron SEC Form 10-Q (July 28, 2010)	
	38	Regeneron SEC Form 10-Q (October 28, 2010)	
	39	Regeneron SEC Form 10-Q (May 3, 2011)	
	40	Regeneron SEC Form 10-Q (July 28, 2011)	
	41	Regeneron SEC Form 10-Q (October 27, 2011)	

Examiner Signature		Date Considered	

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Sheet	4	of	5	Attorney Docket Number	REGN-008CIPCON4

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	42	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 1, 2006" (May 2, 2006)	
	43	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 3, 2006" (May 5, 2006)	
	44	Regeneron SEC Form 8-K Exhibit: "Slides presented at the Company's 2006 Annual Meeting of Shareholders held on June 9, 2006" (June 9, 2006)	
	45	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 2, 2007" (May 3, 2007)	
	46	Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007)	
	47	Regeneron SEC Form 8-K Exhibit: "Press Release dated October 1, 2007" (October 1, 2007)	
	48	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 6, 2007" (November 6, 2007)	
	49	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 1, 2008" (May 2, 2008)	
	50	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 4, 2008" (November 4, 2008)	
	51	Regeneron SEC Form 8-K Exhibit: "99(a) Slides that Regeneron Pharmaceuticals, Inc. intends to use in conjunction with meetings with investors at the J.P. Morgan 27th Annual Healthcare Conference in San Francisco on January 12-15, 2009." (January 9, 2009)	
	52	Regeneron SEC Form 8-K Exhibit: "Press Release dated April 30, 2009" (May 1, 2009)	
	53	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 3, 2009." (November 4, 2009)	
	54	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME) dated December 20, 2010." (December 20, 2010)	
	55	Regeneron SEC Form 8-K Exhibit: "Press Release dated February 17, 2011" (February 18, 2011)	
	56	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Second Phase 3 Study in Central Retinal Vein Occlusion, dated April 27, 2011" (April 27, 2011)	
	57	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 3, 2011." (May 3, 2011)	
	58	Regeneron SEC Form 8-K Exhibit: "Press Release, dated June 17, 2011, Announcing that EYLEA™ (aflibercept ophthalmic solution) Received Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee." (June 21, 2011)	
	59	Regeneron SEC Form 8-K Exhibit: "Presentation entitled VEGF Trap-Eye in CRVO: 1-year Results of the Phase 3 COPERNICUS Study" (August 22, 2011)	
	60	Regeneron SEC Form 8-K Exhibit: "Press Release Announcing FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration, dated November 18, 2011" (November 21, 2011)	

Examiner Signature		Date Considered	

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	61	Regeneron Pharmaceuticals Inc., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	62	Regeneron Pharmaceuticals Inc., "An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients with Diabetic Macular Edema" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	63	Regeneron Pharmaceuticals Inc., "Optical Coherence Tomography Outcomes of a Phase 1, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreal VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration: The CLEAR-IT 1 Study" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	64	Regeneron Pharmaceuticals Inc., " VIEW 1 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) " presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (February 12, 2011)	
	65	Regeneron Pharmaceuticals Inc., " VIEW 2 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) " presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (February 12, 2011)	
	66	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results" presented at the 2007 Retina Society Conference in Boston, Massachusetts (September 30, 2007)	
	67	Regeneron 2008 Annual Report	
	68	Regeneron 2009 Annual Report and 10-K	
	69	Regeneron 2010 Annual Report and 10-K	
	70	RUDGE et al. "Clinical Development of VEGF Trap" In: Figg W.D., Folkman J. (eds) Angiogenesis (2008)	
	71	SCHMIDT-ERFURTH et al. "Primary Results of an International Phase III Study Using Intravitreal VEGF Trap-Eye Compared to Ranibizumab in Patients with Wet AMD (VIEW 2)" ARVO Annual Meeting Abstract (April 2011)	
	72	SLAKTER et al., "Influence of Baseline Angiographic Classification on Outcomes in the CLEAR-IT 2 Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration" ARVO Annual Meeting Abstract (April 2010)	
	73	SLAKTER et al., "A Phase 2, Randomized, Controlled Dose-and Interval-Ranging Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration: Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) Outcomes at 1 Year" ARVO Annual Meeting Abstract (April 2009)	

Examiner Signature	/JON M LOCKARD/	Date Considered	07/16/2020

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Inventor Information for 16/159282

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Grz

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L2	167	l1 same ((chimer$ or fusion) with vegf)	USPAT	OR	ON	2020/07/16 21:55
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L4	845	l1 and ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2020/07/16 21:55
L5	66	l2 and ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2020/07/16 21:55
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L8	7	l7 and (eye ocular macular).clm.	USPAT	OR	ON	2020/07/16 21:56

7/16/2020 9:56:27 PM
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Receipt date: 06/30/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

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	1				
	2				

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	1					
	2					

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	Bayer Investor News, "VEGF Trap-Eye: New Data Confirm Successes in the Treatment of Age-related Macular Degeneration" (September 28, 2008)	
	2	Regeneron Press Release "Positive Interim Phase 2 Data Reported For VEGF Trap-Eye In Age-Related Macular Degeneration" (March 27, 2007)	
	3	Regeneron Press Release "VEGF TRAP-Eye Phase 2 Wet AMD Results Reported At Arvo Annual Meeting" (May 9, 2007)	
	4	Regeneron Press Release "Regeneron Reports Second Quarter Financial And Operating Results" (August 1, 2007)	
	5	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer Healthcare Initiate Phase 3 Global Development Program for VEGF Trap-Eye In Wet Age-Related Macular Degeneration (AMD)" (August 2, 2007)	
	6	Regeneron Press Release "Regeneron Announces Positive Primary Endpoint Results From A Phase 2 Study Of VEGF Trap-Eye In Age-Related Macular Degeneration" (October 1, 2007)	
	7	Regeneron Press Release "Regeneron Reports Fourth Quarter And Full Year 2007 Financial And Operating Results" (February 27, 2008)	
	8	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration" (April 28, 2008)	
	9	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer HealthCare Announce VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2 Study in Patients with Age-related Macular Degeneration" (August 19, 2008)	

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Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

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	10	Regeneron Pharmaceuticals, Inc. "Regeneron Reports Full Year and Fourth Quarter 2008 Financial and Operating Results" (February 26, 2009)	
	11	Regeneron Pharmaceuticals, Inc. "Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion" (April 30, 2009)	
	12	Regeneron Press Release "First Patient Enrolled In Regeneron And Bayer Healthcare VEGF Trap-Eye Phase 3 Program In Central Retinal Vein Occlusion" (July 23, 2009)	
	13	Regeneron Press Release "Regeneron Schedules November 22, 2010 Teleconference And Webcast To Discuss Results Of Two Phase 3 Studies With VEGF Trap-Eye In Wet Age-Related Macular Degeneration" (November 19, 2010)	
	14	Regeneron Press Release "Regeneron And Bayer Start Phase 3 Trial To Extend Ophthalmology Research & Development Program For VEGF Trap-Eye In Asia" (January 18, 2011)	
	15	Regeneron Press Release "Regeneron To Webcast Investor Briefing On VEGF Trap-Eye Clinical Program On Sunday, February 13th At 9 Am Et" (February 9, 2011)	
	16	Regeneron Press Release "Regeneron Submits Biologics License Application To FDA For VEGF Trap-Eye For Treatment Of Wet Age-Related Macular Degeneration" (February 22, 2011)	
	17	Regeneron Press Release "Regeneron And Bayer Announce Start Of Phase 3 Clinical Program In Diabetic Macular Edema" (April 8, 2011)	
	18	Regeneron Pharmaceuticals, Inc., "FDA Grants Priority Review for VEGF Trap-Eye for the Treatment of Wet Age-Related Macular Degeneration" (April 18, 2011)	
	19	Regeneron Press Release "VEGF Trap-Eye Submitted for EU Marketing Authorization for Treatment of Wet Age-Related Macular Degeneration (June 7, 2011)"	
	20	Regeneron Pharmaceuticals, Inc., "Regeneron Announces EYLEA™ (aflibercept ophthalmic solution) Receives Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee" (June 17, 2011)	
	21	Regeneron Press Release "Regeneron Announces Clinical Presentations at ASRS 2011 Annual Meeting" (August 17, 2011)	
	22	Regeneron Pharmaceuticals, Inc., "Regeneron Announces FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration: CORRECTED (November 18, 2011)	
	23	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer Initiate Phase 3 Clinical Program for the Treatment of Wet Age-Related Macular Degeneration in China" (November 28, 2011)	
	24	Regeneron Pharmaceuticals, Inc., "Two Year Results of Phase 3 Studies with EYLEA™ (aflibercept) Injection in wet AMD Show Sustained Improvement in Visual Acuity" (December 5, 2011)	

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EFS ID:	40025576
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	16-JUL-2020
Filing Date:	12-OCT-2018
Time Stamp:	17:32:18
Application Type:	Utility under 35 USC 111(a)

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	Non Patent Literature	57_20110503_REGENERON_PHARMACEUTICALS_INC_8-K_5_3.pdf	264229 106fb3f1a49444514a48ba37aa2eaf95873b6f04	no	13

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11	Non Patent Literature	67_Regeneron_2008_Annual_Report.pdf	1596074 8dbf34e475eefe9794c43995ca33ef81563cbc25	no	20
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24	Non Patent Literature	72_Slakter_April_2010.pdf	47042 d8d7034c70348f55158f851e2a7921f4ae6a7c7c	no	2
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	5	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

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	1				

U.S. PATENT APPLICATION PUBLICATIONS

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	1	2019/0290725	2019-09-26	Vitti et al.	

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	1	WO 2004/106378 A2	2004-12-09	Regeneron Pharmaceuticals, Inc.		
	2	WO 2005/000895 A2	2005-01-05	Regeneron Pharmaceuticals, Inc.		

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	1	BENZ et al. "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose- and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" ARVO Annual Meeting Abstract (May 2007)	
	2	DO et al. "Results of a Phase 1 Study of Intravitreal VEGF Trap in Subjects with Diabetic Macular Edema: The CLEAR-IT DME Study" ARVO Annual Meeting Abstract (May 2007)	
	3	DO et al. "VEGF Trap-Eye Vision-specific Quality of Life through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial" ARVO Annual Meeting Abstract (April 2009)	
	4	HALLER et al., "VEGF Trap-Eye In CRVO: Primary Endpoint Results of the Phase 3 COPERNICUS Study" ARVO Annual Meeting Abstract (April 2011)	
	5	HEIER et al., "CLEAR-IT 2: Phase 2, Randomized Controlled Dose and Interval-Ranging Study of Intravitreal VEFG Trap Eye in Patients with Neovascular Age-Related Macular Degeneration: Predictive Factors for Visual Acuity" ARVO Annual Meeting Abstract (April 2009)	
	6	HEIER et al., "The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing" Ophthalmology 2011;118:1098–1106 (June 2011)	
	7	HEIER et al., "The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing: Erratum" Ophthalmology 2011;118:1700 (September 2011)	
	8	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320775 "Safety and Tolerability of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration" 70 pages, Latest version submitted June 8, 2011 on ClinicalTrials.gov (NCT00320775_2006-2011)	

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	9	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320775 "Safety and Tolerability of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration" 10 pages, Latest version submitted March 16, 2015 on ClinicalTrials.gov (NCT00320775_2015)	
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	11	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320788 "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)" 31 pages, Latest version submitted January 27, 2012 on ClinicalTrials.gov (NCT00320788_2012)	
	12	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320814 "Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema" 30 pages, Latest version submitted June 8, 2011 on ClinicalTrials.gov (NCT00320814_2006-2011)	
	13	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00509795 "Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)" 318 pages, Latest version submitted December 1, 2011 on ClinicalTrials.gov (NCT00509795_2007-2011)	
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	16	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00527423 "Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD" 42 pages, Latest version submitted June 10, 2013 on ClinicalTrials.gov (NCT00527423_2012-2013)	
	17	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" 667 pages, Latest version submitted December 16, 2011 on ClinicalTrials.gov (NCT00637377_2008-2011)	
	18	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" 289 pages, Latest version submitted November 28, 2014 on ClinicalTrials.gov (NCT00637377_2012-2014)	

Examiner Signature		Date Considered	

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	19	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00789477 "DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)" 135 pages, Latest version submitted May 2, 2011 on ClinicalTrials.gov (NCT00789477_2008-2011)	
	20	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00789477 "DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)" 53 pages, Latest version submitted August 28, 2014 on ClinicalTrials.gov (NCT00789477_2013-2014)	
	21	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00943072 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)" 98 pages, Latest version submitted May 9, 2011 on ClinicalTrials.gov (NCT00943072_2009-2011)	
	22	Information from ClinicalTrials.gov archive History of Changes for Study: NCT00943072 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)" 64 pages, Latest version submitted April 16, 2013 on ClinicalTrials.gov (NCT00943072_2012-2013)	
	23	MAJOR et al., "DA VINCI: DME and VEGF Trap-Eye: Investigation of Clinical Impact: Phase 2 Study in Patients with Diabetic Macular Edema (DME)" ARVO Annual Meeting Abstract (April 2010)	
	24	NGUYEN et al., "Randomized, Double-masked, Active-controlled Phase 3 Trial of the Efficacy and Safety of Intravitreal VEGF Trap-Eye in Wet AMD: One-year Results of the VIEW 1 Study" ARVO Annual Meeting Abstract (April 2011)	
	25	NGUYEN et al., "Results of a Phase I, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreous VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration" ARVO Annual Meeting Abstract (May 2006)	
	26	Regeneron SEC Form 10-K (February 27, 2008)	
	27	Regeneron SEC Form 10-K (February 26, 2009)	
	28	Regeneron SEC Form 10-K (February 17, 2011)	
	29	Regeneron SEC Form 10-Q (May 8, 2006)	
	30	Regeneron SEC Form 10-Q (August 8, 2006)	
	31	Regeneron SEC Form 10-Q (November 6, 2006)	
	32	Regeneron SEC Form 10-Q (May 4, 2007)	
	33	Regeneron SEC Form 10-Q (August 3, 2007)	
	34	Regeneron SEC Form 10-Q (April 30, 2009)	
	35	Regeneron SEC Form 10-Q (November 3, 2009)	
	36	Regeneron SEC Form 10-Q (April 29, 2010)	
	37	Regeneron SEC Form 10-Q (July 28, 2010)	
	38	Regeneron SEC Form 10-Q (October 28, 2010)	
	39	Regeneron SEC Form 10-Q (May 3, 2011)	
	40	Regeneron SEC Form 10-Q (July 28, 2011)	
	41	Regeneron SEC Form 10-Q (October 27, 2011)	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
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NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	42	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 1, 2006" (May 2, 2006)	
	43	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 3, 2006" (May 5, 2006)	
	44	Regeneron SEC Form 8-K Exhibit: "Slides presented at the Company's 2006 Annual Meeting of Shareholders held on June 9, 2006" (June 9, 2006)	
	45	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 2, 2007" (May 3, 2007)	
	46	Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007)	
	47	Regeneron SEC Form 8-K Exhibit: "Press Release dated October 1, 2007" (October 1, 2007)	
	48	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 6, 2007" (November 6, 2007)	
	49	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 1, 2008" (May 2, 2008)	
	50	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 4, 2008" (November 4, 2008)	
	51	Regeneron SEC Form 8-K Exhibit: "99(a) Slides that Regeneron Pharmaceuticals, Inc. intends to use in conjunction with meetings with investors at the J.P. Morgan 27th Annual Healthcare Conference in San Francisco on January 12-15, 2009." (January 9, 2009)	
	52	Regeneron SEC Form 8-K Exhibit: "Press Release dated April 30, 2009" (May 1, 2009)	
	53	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 3, 2009." (November 4, 2009)	
	54	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME) dated December 20, 2010." (December 20, 2010)	
	55	Regeneron SEC Form 8-K Exhibit: "Press Release dated February 17, 2011" (February 18, 2011)	
	56	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Second Phase 3 Study in Central Retinal Vein Occlusion, dated April 27, 2011" (April 27, 2011)	
	57	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 3, 2011." (May 3, 2011)	
	58	Regeneron SEC Form 8-K Exhibit: "Press Release, dated June 17, 2011, Announcing that EYLEA™ (aflibercept ophthalmic solution) Received Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee." (June 21, 2011)	
	59	Regeneron SEC Form 8-K Exhibit: "Presentation entitled VEGF Trap-Eye in CRVO: 1-year Results of the Phase 3 COPERNICUS Study" (August 22, 2011)	
	60	Regeneron SEC Form 8-K Exhibit: "Press Release Announcing FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration, dated November 18, 2011" (November 21, 2011)	

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	61	Regeneron Pharmaceuticals Inc., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	62	Regeneron Pharmaceuticals Inc., "An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients with Diabetic Macular Edema" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	63	Regeneron Pharmaceuticals Inc., "Optical Coherence Tomography Outcomes of a Phase 1, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreal VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration: The CLEAR-IT 1 Study" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	64	Regeneron Pharmaceuticals Inc., " VIEW 1 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) " presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (February 12, 2011)	
	65	Regeneron Pharmaceuticals Inc., " VIEW 2 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) " presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (February 12, 2011)	
	66	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results" presented at the 2007 Retina Society Conference in Boston, Massachusetts (September 30, 2007)	
	67	Regeneron 2008 Annual Report	
	68	Regeneron 2009 Annual Report and 10-K	
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	70	RUDGE et al. "Clinical Development of VEGF Trap" In: Figg W.D., Folkman J. (eds) Angiogenesis (2008)	
	71	SCHMIDT-ERFURTH et al. "Primary Results of an International Phase III Study Using Intravitreal VEGF Trap-Eye Compared to Ranibizumab in Patients with Wet AMD (VIEW 2)" ARVO Annual Meeting Abstract (April 2011)	
	72	SLAKTER et al., "Influence of Baseline Angiographic Classification on Outcomes in the CLEAR-IT 2 Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration" ARVO Annual Meeting Abstract (April 2010)	
	73	SLAKTER et al., "A Phase 2, Randomized, Controlled Dose-and Interval-Ranging Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration: Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) Outcomes at 1 Year" ARVO Annual Meeting Abstract (April 2009)	

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 January 2005 (06.01.2005)

PCT

(10) International Publication Number
WO 2005/000895 A2

(51) International Patent Classification[7]: C07K 14/71

(21) International Application Number:
PCT/US2004/021059

(22) International Filing Date: 29 June 2004 (29.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/609,775 30 June 2003 (30.06.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: VEGF TRAPS AND THERAPEUTIC USES THEREOF

(57) Abstract: Nucleic acid molecules and multimeric proteins capable of binding vascular endothelial growth factor (VEGF). VEGF traps are disclosed which are therapeutically useful for treating VEGF-associated conditions and diseases, and are specifically designed for local administration to specific organs, tissues, and/or cells.

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VEGF TRAPS AND THERAPEUTIC USES THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention encompasses fusion polypeptides capable of binding vascular endothelial cell growth factor (VEGF), VEGF family members, and splice variants with specifically desirable characteristics, as well as therapeutic methods of use.

BRIEF SUMMARY OF THE INVENTION

[0002] In a first aspect, the invention features an isolated nucleic acid molecule encoding a fusion polypeptide comprising receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, wherein R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 (Flt1D2), R2 is VEGF receptor component Ig domain 3 of Flk-1 (Flk1D3), and R3 is VEGF receptor component Ig domain 3 of Flt-4 (Flt1D3 or R3), and wherein $X \geq 1$ and $Y \geq 1$.

[0003] In a related second aspect, the invention features a monomeric VEGF trap or fusion polypeptide comprising VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$ wherein $X \geq 1$, $Y \geq 1$, and R1, R2, and R3 are as defined above. The VEGF receptor components R1, R2, and R3, may be connected directly to each other or connected via one or more spacer sequences. In one specific embodiment, the monomeric VEGF trap is $(R1R2)_X$, were X=2. In a more specific embodiment, the monomeric VEGF trap is SEQ ID NO:24, or a functionally equivalent amino acid variant thereof. The invention encompasses a monomeric VEGF trap consisting essentially of VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and functionally equivalent amino acid variants thereof.

[0004] In a third aspect, the invention features an isolated nucleic acid molecule encoding a fusion polypeptide comprising VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and a fusion partner (FP) component selected from the group consisting of a multimerizing component (MC), a serum protein, or a molecule capable of binding a serum protein. In a preferred embodiment, FP is a multimerizing component (MC) capable of interacting with a multimerizing component on another fusion polypeptide to form a multimeric structure, e.g., a dimer or trimer. Most preferably, the MC is selected from the group consisting of (i) a multimerizing component comprising a cleavable region (C-region), (ii) a truncated multimerizing component, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain. Further encompassed are fusion polypeptides consisting essentially of $(R1R2)_X$ and/or $(R1R3)_Y$, and FP. In a preferred embodiment, the fusion polypeptide consists essentially of $(R1R2)_X$ and MC.

[0005] In a fourth aspect, the invention features a fusion polypeptide comprising VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and FP, as described above. The receptor components may be arranged in different orders, for example, $(R1R2)_X$-FP; $(R1R2)_X$-FP-$(R1R2)_X$; FP-$(R2R1)_X$, etc. The components of the fusion polypeptide may be connected directly to each other, or connected via a spacer sequence.

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[0006] In a fifth aspect, the invention features a VEGF trap, comprising a multimer of two or more fusion polypeptides consisting of VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and FP, wherein the FP component is a multimerizing component (MC) comprising a C-region. The C-region may be naturally occurring or artificial, and may occur at any point within the multimerizing component, and functions to allow cleavage of a parent MC to a truncated MC. A VEGF trap composed of two or more fusion polypeptides having at least one truncated MC is termed a "truncated mini-trap."

[0007] The C-region may be created in MC by insertion, deletion, or mutation, such that an enzymatically or chemically cleavable site is created. The C-region may be created in any MC and at any position within the MC; preferably, the C-region is created in a full length Fc domain, or a fragment thereof, or a C_H3 domain. The C-region may be a site cleavable by an enzyme, such as, thrombin, ficin, pepsin, matrilysin, or prolidase or cleavable chemically by, for example, formic acid or $CuCl_2$.

[0008] In a sixth related aspect, the invention features a truncated VEGF mini-trap which is a multimeric protein comprising two or more fusion polypeptides consisting of $(R1R2)_X$ and/or $(R1R3)_Y$ and a multimerizing component which is a truncated by cleavage from a parent MC comprising a C-region (tMC).

[0009] In a seventh aspect, the invention features a fusion polypeptide consisting of VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$ and a MC, wherein the MC is an amino acid sequence between 1 to about 200 amino acids in length comprising at least one cysteine residue, wherein the at least one cysteine residue is capable of forming a disulfide bond with a cysteine residue present in the MC of another fusion polypeptide (cMC). In a preferred embodiment, cMC is an amino acid sequence between 1-50 amino acids in length comprising at least one cysteine residue. In a more preferred embodiment, cMC is an amino acid sequence between 1-15 amino acids in length comprising at least one amino acid. In an even more preferred embodiment, cMC is an amino acid sequence between 1-10 amino acids in length comprising 1-2 cysteine residues. One exemplification of this embodiment of the invention is shown in SEQ ID NO:27 having a signal sequence (1-26) followed by R1 (27-129) and R2 (130-231) components, followed by a nine amino acid sequence ending in a cysteine residue. In another embodiment, shown in SEQ ID NO:28, a signal sequence (1-26) is followed by R1 (27-129) and R2 (130-231) components, followed by a six amino acid sequence ending in a cysteine residue.

[0010] In an eighth aspect, the invention features a VEGF mini-trap, comprising a multimer of two or more fusion polypeptides consisting of $(R1R2)_X$ and/or $(R1R3)_Y$ and a cMC. In a more specific embodiment, the mini-trap is a dimer. One exemplification of this embodiment of the mini-trap of the invention is a dimer of the fusion polypeptide shown in SEQ ID NO:2, wherein each fusion polypeptide (R1R2-cMC) has a molecular weight of 23.0 kD and a pI of 9.22.

[0011] In another embodiment, cMC is 4 amino acids in length consisting of two cysteine residues, for example, XCXC (SEQ ID NO:3). In one exemplification of this embodiment of the invention, the mini-trap consists of the VEGF receptor components of the invention, and a cMC consisting of ACGC (SEQ ID NO:4). One exemplification of this embodiment of the mini-trap of the invention is

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a dimer of the fusion polypeptide shown in SEQ ID NO:5, wherein each monomer has a molecular weight of 23.2 kD and a pI of 9.22. Another exemplification of this embodiment of the invention is shown in SEQ ID NO:26 having a signal sequence (1-26) followed by R1 (27-129) and R2 (130-231) components, followed by a nine amino acid sequence ending in CPPC.

[0012] In all embodiments of the VEGF trap of the invention (including truncated VEGF mini-trap, VEGF mini-traps, and monomeric VEGF mini-traps), a signal sequence (S) may be included at the beginning (or N-terminus) of the fusion polypeptide of the invention. The signal sequence may be native to the cell, recombinant, or synthetic. When a signal sequence is attached to the N-terminus of a first receptor component, thus a fusion polypeptide may be designated as, for example, S-$(R1R2)_X$.

[0013] The components of the fusion polypeptide may be connected directly to each other or be connected via spacers. In specific embodiments, one or more receptor and/or fusion partner components of the fusion polypeptide are connected directly to each other without spacers. In other embodiments, one or more receptor and/or fusion partner components are connected with spacers.

[0014] The invention encompasses vectors comprising the nucleic acid molecules of the invention, including expression vectors comprising the nucleic acid molecule operatively linked to an expression control sequence. The invention further encompasses host-vector systems for the production of a fusion polypeptide which comprise the expression vector, in a suitable host cell; host-vector systems wherein the suitable host cell is a bacterial, yeast, insect, mammalian cell; an *E. coli* cell, or a COS or CHO cell. Additional encompassed are VEGF traps of the invention modified by acetylation or pegylation. Methods for acetylating or pegylating a protein are well known in the art.

[0015] In a related ninth aspect, the invention features a method of producing a VEGF trap of the invention, comprising culturing a host cell transfected with a vector comprising a nucleic acid sequence of the invention, under conditions suitable for expression of the protein from the host cell, and recovering the fusion polypeptides so produced.

[0016] The VEGF traps of the invention are therapeutically useful for treating any disease or condition which is improved, ameliorated, or inhibited by removal, inhibition, or reduction of VEGF. A non-exhaustive list of specific conditions improved by inhibition or reduction of VEGF include, for example, undesirable plasma leakage or vascular permeability, undesirable blood vessel growth, e.g., such as in a tumor, edema associated with inflammatory disorders such as psoriasis or arthritis, including rheumatoid arthritis; asthma; generalized edema associated with burns; ascites and pleural effusion associated with tumors, inflammation or trauma; chronic airway inflammation; asthma; capillary leak syndrome; sepsis; kidney disease associated with increased leakage of protein; pancreatic ductal adenocarcinoma (PDAC) and eye disorders such as age related macular degeneration and diabetic retinopathy. The VEGF mini-trap is particularly useful in treatment of eye disorders, and as an adjuvant to eye surgeries, including glaucoma surgery; and the treatment of intra-ocular tumors, such as for example, uveal melanoma, retinoblastoma, via intravitreal delivery.

[0017] Accordingly, in a tenth aspect, the invention features a therapeutic method for the treatment of a VEGF-related disease or condition, comprising administering a VEGF trap of the invention to a subject suffering from a VEGF-related disease or condition. Although any mammal

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can be treated by the therapeutic methods of the invention, the subject is preferably a human patient suffering from or at risk of suffering from a condition or disease which can be improved, ameliorated,-inhibited or treated with a VEGF trap.

[0018] In a eleventh aspect, the invention further features diagnostic and prognostic methods, as well as kits for detecting, quantitating, and/or monitoring VEGF with the mini-traps of the invention.

[0019] In a twelfth aspect, the invention features pharmaceutical compositions comprising a VEGF trap of the invention with a pharmaceutically acceptable carrier. Such pharmaceutical compositions may comprise a dimeric fusion polypeptide trap, or nucleic acids encoding the fusion polypeptide. The mini-traps of the invention find specific uses in conditions in which a VEGF trap with reduced serum half life (e.g., faster clearance), and/or increased tissue penetration due to smaller size is desirable. Specific applications for the VEGF mini-trap include, for example, diseases where local administration to a specific tissue or cell is desirable. Examples of such a condition or disease are ocular diseases of the eye.

[0020] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0021] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only the appended claims.

[0022] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0023] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe the methods and/or materials in connection with which the publications are cited.

General Description

[0024] The invention encompasses a VEGF trap capable of binding and inhibiting VEGF activity which is a monomer or multimer of one or more fusion polypeptides. The molecules of the invention bind and inhibit the biological action of VEGF and/or the physiological reaction or response. For a description of VEGF-receptor-based antagonist VEGF traps Flt1D2.Flk1D3.FcΔC1(a) (SEQ ID NOs:7-8) and VEGFR1R2-FcΔC1(a) (SEQ ID NOs:9-10), see PCT WO/0075319, the contents of which is incorporated in its entirety herein by reference.

[0025] The mini-trap of the invention is smaller than the full sized trap, e.g., about 50 - 60 kD

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versus 120 kD of the parent trap, and include monomeric traps consisting essentially of VEGF receptor domains $(R1R2)_X$, $(R1R3)_Y$, or combinations thereof, traps generated by cleavage of a portion of a parent multimerized trap having a fusion partner component which is a multimerizing component (MC) containing a cleavage region (C-region); or by attaching a cysteine residue or amino acid sequence containing one or more cysteine residues to or between receptor component domains. In specific embodiments, the mini-trap of the invention is less than about 60 kD as measured by SDS-PAGE analysis; more preferably, about 50 kD; even more preferably about 20-30 kD; or is about 25 kD and capable of binding VEGF with an affinity comparable to a full-sized parent trap described in PCT/US00/14142.

Nucleic Acid Constructs and Expression

[0026] The present invention provides for the construction of nucleic acid molecules encoding fusion polypeptides capable of binding VEGF alone or multimerized VEGF traps. The nucleic acid molecules of the invention may encode wild-type R1, R2, and/or R3 receptor components, or functionally equivalent variants thereof. Amino acid sequence variants of the R1, R2 and/or R3 receptor components of the traps of the invention may also be prepared by creating mutations in the encoding nucleic acid molecules. Such variants include, for example, deletions from, or insertions or substitutions of, amino acid residues within the amino acid sequence of R1, R2 and/or R3. Any combination of deletion, insertion, and substitution may be made to arrive at a final construct, provided that the final construct possesses the ability to bind and inhibit VEGF.

[0027] These nucleic acid molecules are inserted into a vector that is able to express the fusion polypeptides when introduced into an appropriate host cell. Appropriate host cells include, but are not limited to, bacterial, yeast, insect, and mammalian cells. Any of the methods known to one skilled in the art for the insertion of DNA fragments into a vector may be used to construct expression vectors encoding the fusion polypeptides of the invention under control of transcriptional/translational control signals.

[0028] Expression of the nucleic acid molecules of the invention may be regulated by a second nucleic acid sequence so that the molecule is expressed in a host transformed with the recombinant DNA molecule. For example, expression may be controlled by any promoter/enhancer element known in the art. Promoters which may be used to control expression of the chimeric polypeptide molecules include, but are not limited to, a long terminal repeat (Squinto et al. (1991) Cell 65:1-20); SV40 early promoter region, CMV, M-MuLV, thymidine kinase promoter, the regulatory sequences of the metallothionine gene; prokaryotic expression vectors such as the b-lactamase promoter, or the tac promoter (see also Scientific American (1980) 242:74-94); promoter elements from yeast or other fungi such as Gal 4 promoter, ADH, PGK, alkaline phosphatase, and tissue-specific transcriptional control regions derived from genes such as elastase I.

[0029] Expression vectors capable of being replicated in a bacterial or eukaryotic host comprising the nucleic acid molecules of the invention are used to transfect the host and thereby direct expression of such nucleic acids to produce the fusion polypeptides of the invention, which form traps capable of binding to VEGF. Transfected cells may transiently or, preferably, constitutively

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and permanently express the VEGF traps of the invention.

[0030] The traps of the invention may be purified by any technique which allows for the subsequent formation of a stable, biologically active trap. For example, and not by way of limitation, the factors may be recovered from cells either as soluble proteins or as inclusion bodies, from which they may be extracted quantitatively by 8M guanidinium hydrochloride and dialysis (see, for example, US Patent No. 5,663,304). In order to further purify the factors, conventional ion exchange chromatography, hydrophobic interaction chromatography, reverse phase chromatography or gel filtration may be used.

VEGF Receptor Components

[0031] The VEGF receptor components of the VEGF mini trap consist of the Ig domain 2 of Flt-1 (Flt1D2) (R1), the Ig domain 3 of Flk-1 (Flk1D3) (R2) (together, R1R2), and/or R1 and Ig domain 3 of Flt-4 (Flt1D3) (R3) (together, R1R3). The term "Ig domain" of Flt-1, Flt-4, or Flk-1 is intended to encompass not only the complete wild-type domain, but also insertional, deletional, and/or substitutional variants thereof which substantially retain the functional characteristics of the intact domain. It will be readily apparent to one of skill in the art that numerous variants of the above Ig domains can be obtained which will retains substantially the same functional characteristics as the wild-type domain.

[0032] The term "functional equivalents" when used in reference to R1, R2, or R3, is intended to encompass an R1, R2, or R3 domain with at least one alteration, e.g., a deletion, addition, and/or substitution, which retains substantially the same functional characteristics as does the wild type R1, R2, or R3 domain, that is, a substantially equivalent binding to VEGF. It will be appreciated that various amino acid substitutions can be made in R1, R2, or R3 without departing from the spirit of the invention with respect to the ability of these receptor components to bind and inactivate VEGF. The functional characteristics of the traps of the invention may be determined by any suitable screening assay known to the art for measuring the desired characteristic. Examples of such assays are described in the experimental section below which allow determination of binding characteristics of the traps for VEGF (Kd), as well as their half-life of dissociation of the trap-ligand complex ($T_{1/2}$). Other assays, for example, a change in the ability to specifically bind to VEGF can be measured by a competition-type VEGF binding assay. Modifications of protein properties such as thermal stability, hydrophobicity, susceptibility to proteolytic degradation, or tendency to aggregate may be measured by methods known to those of skill in the art.

[0033] The components of the fusion polypeptide may be connected directly to each other or be connected via spacers. Generally, the term "spacer" (or linker) means one or more molecules, e.g., nucleic acids or amino acids, or non-peptide moieties, such as polyethylene glycol, which may be inserted between one or more component domains. For example, spacer sequences may be used to provide a desirable site of interest between components for ease of manipulation. A spacer may also be provided to enhance expression of the fusion polypeptide from a host cell, to decrease steric hindrance such that the component may assume its optimal tertiary structure and/or interact appropriately with its target molecule. For spacers and methods of identifying desirable spacers, see,

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for example, George et al. (2003) Protein Engineering 15:871-879, herein specifically incorporated by reference. A spacer sequence may include one or more amino acids naturally connected to a receptor component, or may be an added sequence used to enhance expression of the fusion polypeptides, provide specifically desired sites of interest, allow component domains to form optimal tertiary structures and/or to enhance the interaction of a component with its target molecule. In one embodiment, the spacer comprises one or more peptide sequences between one or more components which is (are) between 1-100 amino acids, preferably 1-25.

[0034] In the most specific embodiments, R1 is amino acids 27-126 of SEQ ID NO:8, or 1-126 of SEQ ID NO:8 (including the signal sequence 1-26); or amino acids 27-129 of SEQ ID NO:10, or 1-129 of SEQ ID NO:10 (including the signal sequence at 1-26). In the most specific embodiments, R2 is amino acids 127-228 of SEQ ID NO:8, or amino acids 130-231 of SEQ ID NO:10. In the most specific embodiments, R3 is amino acids 127-225 of SEQ ID NO: 13 (without a signal sequence). When, for example, R2 is placed at the N-terminus of the fusion polypeptide, a signal sequence may desirably precede the receptor component. The receptor component(s) attached to the multimerizing component may further comprise a spacer component, for example, the GPG sequence of amino acids 229-231 of SEQ ID NO:7.

Fusion Partner and Multimerizing Components

[0035] The fusion partner is any component that enhances the functionality of the fusion polypeptide. Thus, for example, an fusion partner may enhance the biological activity of the fusion polypeptide, aid in its production and/or recovery, or enhance a pharmacological property or the pharmacokinetic profile of the fusion polypeptide by, for example, enhancing its serum half-life, tissue penetrability, lack of immungenicity, or stability. In preferred embodiments, the fusion partner is selected from the group consisting of a multimerizing component, a serum protein, or a molecule capable of binding a serum protein.

[0036] When the fusion partner is a serum protein or fragment thereof, it is selected from the group consisting of α-1-microglobulin, AGP-1, orosomuciod, α-1-acid glycoprotein, vitamin D binding protein (DBP), hemopexin, human serum albumin (hSA), transferrin, ferritin, afamin, haptoglobin, α-fetoprotein thyroglobulin, α-2-HS-glycoprotein, β-2-glycoprotein, hyaluronan-binding protein, syntaxin, C1R, C1q a chain, galectin3-Mac2 binding protein, fibrinogen, polymeric Ig receptor (PIGR), α-2-macroglobulin, urea transport protein, haptoglobin, IGFBPs, macrophage scavenger receptors, fibronectin, giantin, Fc, α-1-antichyromotrypsin, α-1-antitrypsin, antithrombin III, apolipoprotein A-I, apolipoprotein B, β-2-microglobulin, ceruloplasmin, complement component C3 or C4, CI esterase inhibitor, C-reactive protein, cystatin C, and protein C. In a more specific embodiment, fusion partner is selected from the group consisting of α-1-microglobulin, AGP-1, orosomuciod, α-1-acid glycoprotein, vitamin D binding protein (DBP), hemopexin, human serum albumin (hSA), afamin, and haptoglobin. The inclusion of a fusion partner component may extend the serum half-life of the fusion polypeptide of the invention when desired. See, for example, US Patent Nos. 6,423,512, 5,876,969, 6,593,295, and 6,548,653, herein specifically incorporated by

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reference in their entirety, for examples of serum albumin fusion polypeptides. hSA is widely distributed throughout the body, particularly in the intestinal and blood components, and has an important role in the maintenance of osmolarity and plasma volume. It is slowly cleared in the liver, and typically has an *in vivo* half-life of 14-20 days in humans (Waldmann et al. (1977) Albumin, Structure Function and Uses; Pergamon Press; pp. 255-275).

[0037] When a fusion partner is a molecule capable of binding a serum protein, the molecule may be a synthetic small molecule, a lipid or liposome, a nucleic acid, including a synthetic nucleic acid such as an aptomer, a peptide, or an oligosaccharide. The molecule may further be a protein, such as, for example, FcγR1, FcγR2, FcγR3, polymeric Ig receptor (PIGR), ScFv, and other antibody fragments specific for a serum protein.

[0038] When the fusion partner is a multimerizing component (MC), it is any natural or synthetic sequence capable of interacting with another MC to form a higher order structure, e.g., a dimer, a trimer, etc. Suitable MCs may include a leucine zipper, including leucine zipper domains derived from c-jun or c-fos; sequences derived from the constant regions of kappa or lambda light chains; synthetic sequences such as helix-loop-helix motifs (Müller et al. (1998) FEBS Lett. 432:45-49), coil-coil motifs, etc., or other generally accepted multimerizing domains known to the art. In some embodiments, the fusion component comprises an immunoglobulin-derived domain from, for example, human IgG, IgM or IgA. In specific embodiments, the immunoglobulin-derived domain may be selected from the group consisting of the Fc domain of IgG, the heavy chain of IgG, and the light chain of IgG. The Fc domain of IgG may be selected from the isotypes IgG1, IgG2, IgG3, and IgG4, as well as any allotype within each isotype group. In one example of the VEGF trap of the invention, the multimerizing component is an IgG4 Fc domain (SEQ ID NO:29).

Generation of Truncated VEGF Mini-Traps

[0039] In one embodiment of the trap of the invention, a truncated VEGF mini-trap comprising two or more fusion polypeptides of the invention, is generated by subjecting a parent trap having C-region-containing MCs to conditions under which one or more of the C-region-containing MCs is (are) cleaved. The resulting truncated mini-trap may be a full and partial cleavage product of a parent trap.

[0040] The C-region-containing MC may be any MC capable of interacting with another MC to form a higher order structure, e.g., a dimer or a trimer. The C-region may be created within an MC at any desired location. In light of the guidance provided in the examples below, one of skill in the art would be able to select a desired site for creation of a C-region based on the desired properties of the resulting truncated traps, e.g., molecular weight, monomeric or dimeric, etc.

[0041] In a specific embodiment, the C-region is a thrombin cleavage site (LVPRGS) (SEQID NO:6) inserted into an FcΔC1 domain following the N-terminal CPPC sequence (SEQ ID NO:1). In this embodiment, a full-sized parent VEGF trap construct is expressed in a cell as an Fc-tagged protein, thus allowing capture and purification by, for example, a Protein A column. Following formation of a dimer and covalent bonding between one or both of the cysteine residues of the CPPC sequence

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(SEQ ID NO:1), the dimer is exposed to thrombin under conditions which cleave one or both of the FcΔC1 domains such that truncated dimeric mini-traps are generated, having a molecular weight of approximately 50 kD – 90 kD, and has an affinity for VEGF comparable to that of the parent trap. The conditions of cleavage may be controlled by one of skill in the art to favor formation of the partial cleavage product or the fully cleaved product, the choice of cleavage conditions selected by desire for a particular product having specific properties such as molecular weight.

[0042] In a specific embodiment, the C-region is a thrombin cleavage site (LVPRGS) (SEQID NO:6) inserted into an FcΔC1 domain N-terminal to the CPPC sequence (SEQ ID NO:1). Following formation of a dimer and covalent bonding between one or both of the cysteine residues of the CPPC sequence (SEQ ID NO:1), the dimer is exposed to thrombin under conditions in which one or both of the FcΔC1 domain occur and truncated monomeric mini-traps are generated. The monomeric truncated mini-trap thus generated comprises a receptor component, and a small fragment of the Fc, and is approximately 25 kD in size and exhibits a reduced affinity for VEGF relative to the truncated dimeric trap and the full length parent trap. A similar monomeric trap produced as a recombinant protein has been shown to have a K_D of about 1 nM.

Generation of VEGF Mini-Traps

[0043] In one embodiment, the invention features VEGF mini-traps having one or more receptor component domains $(R1R2)_X$ and/or $R1R3)_Y$, wherein $X \geq 1$, $Y \geq 1$, and R1, R2, and R3 are as defined above, and optionally, a fusion partner which is preferably a MC domain which is an amino acid sequence between 1 to about 200 amino acids in length comprising at least one cysteine residue, wherein the at least one cysteine residue is capable of forming a disulfide bond with a cysteine residue present in the MC of another fusion polypeptide (cMC). The cMC may occur at the N-terminus or C-terminus of a fusion polypeptide, or between two receptor component domains. In one specific embodiment, cysteine is added to the C-terminus of a VEGF receptor component, e.g., $R1R2_C$, which allows the fusion polypeptide to form covalent dimers through formation of a covalent disulfide bond between the cysteine residue at the C-terminus of one fusion polypeptide and the cysteine residue at the C-terminus of another fusion polypeptide. In this exemplification, the mini-trap is a dimer of the fusion polypeptide shown in SEQ ID NO:2, wherein each fusion polypeptide (R1R2-cMC or $R1R2_C$) has a molecular weight of about 23.0 kD.

[0044] In another embodiment, the cMC is a sequence of 4 amino acids (XXXX) (SEQ ID NO:11) wherein X is any amino acid and the sequence comprises at least one cysteine residue. In a specific embodiment, the cMC is added to the C-terminus of a receptor component domain. In a more specific embodiment, the 4 amino acid sequence is ACGC (SEQ ID NO:4) and the cMC forms two disulfide bonds with the cysteine residues present in a second fusion polypeptide. As shown below (Table 2), both the exemplified mini-traps exhibit an affinity for VEGF comparable to the parent trap.

Therapetic Uses

[0045] The VEGF mini-traps of the invention are therapeutically useful for treating any disease or

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condition which is improved, ameliorated, inhibited or prevented by removal, inhibition, or reduction of VEGF. A non-exhaustive list of specific conditions improved by inhibition or reduction of VEGF include, clinical conditions that are characterized by excessive vascular endothelial cell proliferation, vascular permeability, edema or inflammation such as brain edema associated with injury, stroke or tumor; edema associated with inflammatory disorders such as psoriasis or arthritis, including rheumatoid arthritis; asthma; generalized edema associated with burns; ascites and pleural effusion associated with tumors, inflammation or trauma; chronic airway inflammation; capillary leak syndrome; sepsis; kidney disease associated with increased leakage of protein; and eye disorders such as age related macular degeneration and diabetic retinopathy.

[0046] The compositions of the invention are therapeutically useful for treating a wide variety of diseases associated with increased VEGF levels. For example, exaggerated Th2 inflammation and airway remodeling are characteristic in the pathogenesis of asthma (see, for example, Elias et al. (1999) J. Clin. Invest. 104:1001-6). Elevated VEGF levels have been detected in tissues and biologic samples from patients with asthma, which correlate directly with disease activity (Lee et al. (2001) J. Allergy Clin. Immunol. 107:1106-1108) and inversely with airway caliber and airway responsiveness. Further, VEGF has been postulated to contribute to asthmatic tissue edema.

[0047] Another disease associated with increased VEGF is pancreatic ductal adenocarcinoma (PDAC). This malignancy often exhibits enhanced foci of endothelial cell proliferation and frequently overexpresses VEGF (Ferrara (1999) J. Mol. Med. 77:527-543). PDAC is responsible for over 20% of deaths due to gastrointestinal malignancies, making it the fourth most common cause of cancer-related mortality in the U.S. and other industrialized countries. Experimental evidence supports an important role for VEGF in pancreatic cancer, thus a VEGF inhibitor has promise as a therapeutic to attenuate intrapancreatic tumor growth and regional and distal metastasis.

[0048] A smaller, non-glycosylated mini-trap expressed in *E. coli* (Example 4), a glycosylated mini-trap expressed in CHO cells (Example 5), or a receptor-based monomeric trap (Example 6) has optimized characteristics for local/intra-vitreal delivery, ie. a shorter serum half life for faster clearance and minimizing unwanted systemic exposure. In addition due to its smaller size, the mini-trap has the ability to penetrate through the inner-limiting membrane (ILM) in the eye, and diffuse through the vitreous to the retina/retinal pigment epithelial (RPE) layer which will help to treat retinal disease. Additionally, the mini-trap can be used for local administration for the treatment of ocular disease such as choroidal neovascularization, diabetic macular edema, proliferative diabetic retinopathy, corneal neovascularization/transplant rejection. Still further, the mini-trap can be used in any situation where transient (short-term) blocking of VEGF is required, e.g., to avoid chronic exposure to VEGF blockade, such as, for example, in the treatment of psoriasis.

[0049] A serious problem leading to failure following glaucoma surgery is early inflammation and angiogenesis, as well as too aggressive wound healing. Accordingly, the VEGF traps of the invention may be usefully employed is as an adjuvant to glaucoma surgery to prevent early hem- and lymphangiogenesis and macrophage recruitement to the filterig bleb after glaucoma surgery, and improve surgical outcome.

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Combination Therapies

[0050] In numerous embodiments, a VEGF trap may be administered in combination with one or more additional compounds or therapies, including a second VEGF trap molecule, a chemotherapeutic agent, surgery, catheter devices, and radiation. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a VEGF trap and one or more additional agents; as well as administration of a VEGF trap and one or more additional agent(s) in its own separate pharmaceutical dosage formulation. For example, a VEGF trap and a cytotoxic agent, a chemotherapeutic agent or a growth inhibitory agent can be administered to the patient together in a single dosage composition such as a combined formulation, or each agent can be administered in a separate dosage formulation. Where separate dosage formulations are used, the VEGF-specific fusion polypeptide of the invention and one or more additional agents can be administered concurrently, or at separately staggered times, i.e., sequentially.

[0051] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g. I^{131}, I^{125}, Y^{90} and Re^{186}), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

[0052] A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (Cytoxan®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®;

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razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (Taxol®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (Taxotere®; Aventis Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0053] A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially a cancer cell either *in vitro* or *in vivo*. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), Taxol ®, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C.

Methods of Administration

[0054] The invention provides methods of treatment comprising administering to a subject an effective amount of a VEGF trap of the invention. In a preferred aspect, the trap is substantially purified (*e.g.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably a mammal, and most preferably a human.

[0055] Various delivery systems are known and can be used to administer an agent of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction can be enteral or parenteral and include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, intraocular, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. Administration can be acute or chronic (e.g. daily, weekly, monthly, etc.) or in combination with other agents. Pulmonary administration can also be employed,

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e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0056] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome, in a controlled release system, or in a pump. In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see, for example, U.S. Patent No. 4,980,286), by direct injection, or by use of microparticle bombardment, or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see *e.g.*, Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0057] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, by injection, by means of a catheter, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, fibers, or commercial skin substitutes.

[0058] A composition useful in practicing the methods of the invention may be a liquid comprising an agent of the invention in solution, in suspension, or both. The term "solution/suspension" refers to a liquid composition where a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix. A liquid composition also includes a gel. The liquid composition may be aqueous or in the form of an ointment. Further, the composition can take the form of a solid article that can be inserted in the eye, such as for example between the eye and eyelid or in the conjunctival sac, where the VEGF trap is released. Release from such an article is usually to the cornea, either via the lacrimal fluid, or directly to the cornea itself, with which the solid article is generally in direct contact. Solid articles suitable for implantation in the eye are generally composed primarily of bioerodible or nonbioerodible polymers. An aqueous solution and/or suspension can be in the form of eye drops. A desired dosage of the active agent can be measured by administration of a known number of drops into the eye. For example, for a drop volume of 25 μl, administration of 1-6 drops will deliver 25-150 μl of the composition.

[0059] An aqueous suspension or solution/suspension useful for practicing the methods of the invention may contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers and water-insoluble polymers such as cross-linked carboxyl-containing polymers. An aqueous suspension or solution/suspension of the present invention is preferably viscous or muco-adhesive, or even more preferably, both viscous or mucoadhesive.

[0060] In another embodiment, the composition useful in practicing the methods of the invention is an *in situ* gellable aqueous composition. Such a composition comprises a gelling agent in a concentration effective to promote gelling upon contact with the eye or with lacrimal fluid. Suitable

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gelling agents include but are not limited to thermosetting polymers. The term "*in situ* gellable" as used herein is includes not only liquids of low viscosity that form gels upon contact with the eye or with lacrimal fluid, but also includes more viscous liquids such as semi-fluid and thixotropic gels that exhibit substantially increased viscosity or gel stiffness upon administration to the eye.

Diagnostic and Screening Methods

[0061] The VEGF traps of the invention may be used diagnostically and/or in screening methods. For example, the trap may be used to monitor levels of VEGF during a clinical study to evaluate treatment efficacy. In another embodiment, the methods and compositions of the present invention are used to screen individuals for entry into a clinical study to identify individuals having, for example, too high or too low a level of VEGF. The traps can be used in methods known in the art relating to the localization and activity of VEGF, *e.g.*, imaging, measuring levels thereof in appropriate physiological samples, in diagnostic methods, etc.

[0062] The traps of the invention may be used in *in vivo* and *in vitro* screening assay to quantify the amount of non-bound VEGF present, e.g., for example, in a screening method to identify test agents able to decrease the expression of VEGF. More genenerally, the traps of the invention may be used in any assay or process in which quantification and/or isolation of VEGF is desired.

Pharmaceutical Compositions

[0063] The present invention also provides pharmaceutical compositions comprising a VEGF mini-trap of the invention. Such compositions comprise a therapeutically effective amount of one or more mini-traps, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0064] The VEGF mini-trap of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

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[0065] Further more, aqueous compositions useful for practicing the methods of the invention have ophthalmically compatible pH and osmolality. One or more ophthalmically acceptable pH adjusting agents and/or buffering agents can be included in a composition of the invention, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, and sodium lactate; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases, and buffers are included in an amount required to maintain pH of the composition in an ophthalmically acceptable range. One or more ophthalmically acceptable salts can be included in the composition in an amount sufficient to bring osmolality of the composition into an ophthalmically acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions.

[0066] The amount of the trap that will be effective for its intended therapeutic use can be determined by standard clinical techniques based on the present description. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. Generally, suitable dosage ranges for intravenous administration are generally about 50-5000 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0067] For systemic administration, a therapeutically effective dose can be estimated initially from *in vitro* assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from *in vivo* data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

[0068] Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. In cases of local administration or selective uptake, the effective local concentration of the compounds may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

[0069] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

Cellular Transfection and Gene Therapy

[0070] The present invention encompasses the use of nucleic acids encoding the fusion polypeptides of the invention for transfection of cells *in vitro* and *in vivo*. These nucleic acids can be inserted into any of a number of well-known vectors for transfection of target cells and organisms. The nucleic acids are transfected into cells *ex vivo* and *in vivo*, through the interaction of the vector and the

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target cell. The compositions are administered (e.g., by injection into a muscle) to a subject in an amount sufficient to elicit a therapeutic response. An amount adequate to accomplish this is defined as "a therapeutically effective dose or amount."

[0071] In another aspect, the invention provides a method of reducing VEGF levels in a human or other animal comprising transfecting a cell with a nucleic acid encoding a fusion polypeptide of the invention, wherein the nucleic acid comprises an inducible promoter operably linked to the nucleic acid encoding the fusion polypeptide or mini-trap. For gene therapy procedures in the treatment or prevention of human disease, see for example, Van Brunt (1998) Biotechnology 6:1149-1154.

Kits

[0072] The invention also provides an article of manufacturing comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent comprises at least one VEGF trap composed of two or more fusion polypeptides of the invention, and wherein the packaging material comprises a label or package insert which indicates that the VEGF-specific fusion polypeptide can be used for treating a VEGF-mediated disease or condition.

Transgenic Animals

[0073] The invention includes transgenic non-human animals expressing a trap of the invention. A transgenic animal can be produced by introducing nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Any of the regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the transgene to particular cells. A transgenic non-human animal expressing a fusion polypeptide or mini-trap of the invention is useful in a variety of applications, including as a means of producing such a fusion polypeptide.. Further, the transgene may be placed under the control of an inducible promoter such that expression of the fusion polypeptide or mini-trap may be controlled by, for example, administration of a small molecule.

Specific Embodiments

[0074] In the experiments described below, smaller VEGF traps were generated and their ability to bind VEGF was investigated. Such mini-traps are preferably uses in specific applications. For example, certain conditions or diseases may be preferably treated with local administration of a VEGF trap to a specific organ, tissue, or cell, rather than by systemic administration. In one exemplification of the mini-traps of the invention, a smaller VEGF trap was generated by directed cleavage of a dimerized VEGF trap having a cleavage region (C-region) generated in a Fc domain (Example 2). The truncated trap exhibited comparable affinity for VEGF and half-life as the full-sized parent trap. Examples 3-5 describe construction of fusion polypeptides having a VEGF receptor component and a multimerizing component consisting of one or two cysteine residues. Affinity measurements showed that the non-glycosylated fusion polypeptides expressed in *E. coli* or

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the glycosylated polypeptides expressed in CHO cells had comparable binding affinity for VEGF as the full-sized parent trap. Example 6 further illustrates a monomeric VEGF trap consisting of $(R1R2)_2$ which is capable of binding and inhibiting VEGF. Example 7 describes the construction of a VEGF mini-trap (SEQ ID NO:26) exhibiting high affinity binding for VEGF comparable to the full length trap (SEQ ID NO:10).

[0075] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[0076] The following example is put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Construction of Flt1D2.Flk1D3.FcΔC1(a)

[0077] The construction of a parent VEGF trap, Flt1D2.Flk1D3.FcΔC1(a) (SEQ ID NOs:7-8), VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10), and Flt1D2.VEGFR3D3.FcΔC1(a) (SEQ ID NOs:12-13) is described in detail in PCT publication WO/0075319, herein specifically incorporated by reference in its entirety. Also described in WO/0075319 are methods of constructing and expressing nucleic acid constructs encoding VEGF traps, methods of detecting and measuring VEGF trap binding to VEGF, methods of determining the stoichiometry of VEGF binding by BIAcore analysis, and pharmacokinetic analyses.

Example 2: Thrombin-cleaved dimeric VEGF mini-trap

[0078] The VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10) construct was modified by insertion of a thrombin cleavage following the CPPC (SEQ ID NO:1) of the Fc domain. Purified VEGF trap (5 μg) was incubated with thrombin (Novagen) in 20 mM Tris-HCl, pH 8.4, 50 mM NaCl, 2.5 mM $CaCl_2$ for 16 hrs at 37° C. Controls included cleavage control protein (CCP) and parent VEGF trap protein incubated without thrombin. SDS-PAGE analysis (Tris-Glycine 4-20% gel; 5 μg protein per lane) verified correct cleavage (results not shown).

[0079] Affinity determination. The Kd of binding of each VEGF trap to hVEGF165 was determined as described in WO/0075319, for the parent VEGF trap, uncleaved VEGF trap containing a thrombin cleavage site ("uncleaved VEGF trap"), cleaved VEGF mini-trap and recombinant monomeric R1R2-myc myc his. More specifically, the ability of the traps to block $VEGF_{165}$-dependent receptor phosphorylation was determined using primary human endothelial cells (HUVECs). $VEGF_{165}$ was incubated in the presence of varying concentrations of the test traps, and the mixture was added to

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HUVECs to stimulate tyrosine phosphorylation of VEGFR2. At sub-stoichiometric concentrations of VEGF trap, unbound VEGF induced receptor phosphorylation. However, at a 1:1 molar ratio of greater of a VEGF trap to ligand, complete blocking of receptor signaling was observed, establishing that a single molecule of a trap dimer is capable of blocking a single molecule of human $VEGF_{165}$. Thus, the high binding affinity of the VEGF trap for VEGF results in formation of a complex that prevents VEGF from interaction with cell surface receptors. Equivalent results were obtained for identical phosphorylation inhibition experiments for the parent VEGF trap, uncleaved VEGF trap, and cleaved VEGF mini-trap The results are shown in Table 1.

TABLE 1

Trap	Kinetic Dissociation Rate (1/s)	$T_{1/2}$ (hr)
parent VEGF trap	$5.51 \times 10^{-5} \pm 0.94\%$	3.5
uncleaved VEGF trap	$4.93 \times 10^{-5} \pm 0.70\%$	3.9
cleaved VEGF mini-trap	$5.46 \times 10^{-5} \pm 0.62\%$	3.53
R1R2-myc myc his monomer	$6.74 \times 10^{-3} \pm 0.38\%$	0.028

Example 3. Construction of Plasmids Encoding VEGF Mini-Traps

[0080] VEGF mini-traps were constructed from a precursor of the parent VEGF trap, VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10), in which the three amino acids glycine-alanine-proline served as a linker between the Flk1 D3 and FcΔC1(a). This plasmid, pTE115 was used in the construction of the VEGF mini-traps because the linker DNA sequence included a Srf I restriction endonuclease recognition sequence that facilitated engineering the VEGF trap. In all other respects, the VEGF trap encoded by pTE115 is identical to that of the VEGF trap, VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10) described in detail in PCT publication WO/0075319.

[0081] Two VEGF mini-traps were constructed with multimerization domains consisting of either a single cysteine residue ($R1R2_C$) (SEQ ID NO:2) or the amino acids ACGC (SEQ ID NO:4) ($R1R2_{ACGC}$) (SEQ ID NO:5) added to the C-terminus of receptor components Flt1D2.Flk1D3. Both of these constructs are capable of forming homo-dimeric molecules stabilized by one ($R1R2_C$) or two ($R1R2_{ACGC}$) intermolecular disulfides.

[0082] The plasmid pTE517 was made by removing the 690 bp fragment generated by digestion of pTE115 DNA with Srf I and Not I and inserting the synthetic DNA fragment formed by annealing the oligos R1R2NC (SEQ ID NO:14) and R1R2CC (SEQ ID NO:15). The resulting plasmid encodes $R1R2_C$, which consists of the Flt1D2.Flk1D3 domains followed by a cysteine residue (SEQ ID NO:23). Similarly, the plasmid pTE518 was made by removing the 690 bp fragment generated by digestion of pTE115 DNA with Srf I and Not I, followed by ligation with the synthetic DNA fragment formed by annealing the oligos R1R2NACGC (SEQ ID NO:16) and R1R2CACGC (SEQ ID NO:17). The resulting plasmid encodes $R1R2_{ACGC}$, which consists of the Flt1D2.Flk1D3 domains followed by the amino acids ACGC (SEQ ID NO:25).

[0083] Plasmids were also constructed to direct the expression of these mini-traps in *E. coli*. The primers R1R2N-Nco1 (SEQ ID NO:18) and R1R2CNot1 (SEQ ID NO:19) were used to amplify a DNA fragment from pTE115 that encodes amino acids G30 to K231, relative to the parental VEGF trap (SEQ ID NO:10). Amplification of this sequence resulted in fusion of an initiating methionine

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codon at the 5' end and fusion of the codon for cysteine, followed by a stop codon, at the 3' end (SEQ ID NO:2). This DNA fragment was then cloned into the Nco I and Not I sites of the *E. coli* expression plasmid pRG663 to yield pRG1102 such that expression of $R1R2_C$ was dependent on transcription from the phage T7 Φ1.1 promoter. Induction of gene expression from pRG1102 results in accumulation of R1R2cys in the cytoplasm of the *E. coli* host strain RFJ238. Similarly, the primers R1R2N-Nco1 (SEQ ID NO:18) and R1R2ACGC-N ot1 (SEQ ID NO:20) were used to amplify a DNA fragment from pTE115 that encodes amino acids G30 to K231 (SEQ ID NO:10) resulting in fusion of an initiating methionine codon at the 5' end and fusion of codons for ACGC (SEQ ID NO:4), followed by a stop codon, at the 3' end (SEQ ID NO:5). This fragment was then cloned into the Nco I and Not I sites of the *E. coli* expression plasmid pRG663 to yield pRG1103 such that expression of $R1R2_{ACGC}$ was dependent on transcription from the phage T7 Φ1.1 promoter. Induction of gene expression from both pRG1102 and pRG1103 resulted in accumulation of $R1R2_C$ or $R1R2_{ACGC}$, respectively, in the cytoplasm of the *E. coli* host strain RFJ238.

Example 4. Purification and characterization of VEGF mini-traps from *E. coli*

[0084] Both $R1R2_C$ and $R1R2_{ACGC}$ were expressed as cytoplasmic proteins in *E. coli* and were purified by the same method. Induction of the phage T7 Φ1.1 promoter on either pRG1102 or pRG1103 in the *E. coli* K12 strain RFJ238 resulted in accumulation of the protein in the cytoplasm. After induction, cells were collected by centrifugation, resuspended in 50 mM Tris-HCl, pH 7.5, 20 mM EDTA, and lysed by passage through a Niro-Soavi cell homogenizer. Inclusion bodies were collected from lysed cells by centrifugation, washed once in distilled H_2O, then solubilized in 8 M guanidinium-HCl, 50 mM Tris-HCl, pH 8.5, 100 mM sodium sulfite,10 mM sodium tetrathionate and incubated at room temperature for 16 hours. Clarified supernatant was fractionated on an S300 column equilibrated with 6 M guanidinium-HCl, 50 mM Tris-HCl, pH 7.5. Fractions containing $R1R2_C$ were pooled and dialyzed against 6M Urea, 50 mM Tris-HCl, pH 7.5. Dialyzed protein was diluted to 2M Urea, 50 mM Tris-HCl, pH 8.5, 2 mM cysteine then stirred slowly for 7 days at 4°C. Refolded protein was dialyzed against 50 mM Tris-HCl, pH 7.5 then loaded onto an SP-sepharose column equilibrated with 50 mM Tris-HCl, pH 7.5 and eluted with a NaCl gradient from 0 to 1 M in 50 mM Tris-HCl, pH 7.5. Fractions containing $R1R2_C$ were pooled, concentrated, and loaded onto a Superdex 200 column equilibrated with 50 mM Tris-HCl, pH 7.5, 150 mM NaCl. Fractions containing mini-trap dimer were collected and pooled. The molecular weight of purified mini-trap was estimated to be about 46 kD by SDS-PAGE.

[0085] BIAcore assays were conducted (as described in WO/0075319) to determine trap affinity for VEGF, and the results showed that the $R1R2_C$ and $R1R2_{ACGC}$ mini-traps had VEGF affinity comparable to the full length VEGF trap (Table 2).

TABLE 2

Trap	Kinetic Dissociation Rate (1/s)	$T_{1/2}$ (hr)
VEGF trap	4.23×10^{-5}	4.53
$R1R2_C$	3.39×10^{-5}	5.68
$R1R2_{ACGC}$	3.41×10^{-5}	5.65

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Example 5. Expression of VEGF mini-traps in CHO K1

[0086] Expression of the VEGF mini-traps encoded by pTE517 and pTE518 is dependent on transcription from the human CMV-MIE promoter and results in secretion of the mini-traps into the culture medium when expressed in CHO cells. When expressed as secreted proteins in CHO K1, both mini-traps were found in the conditioned media and estimation of their molecular weight by SDS-PAGE suggested, as expected, that the proteins were glycosylated. Analysis by SDS-PAGE also indicated that the mini-traps were capable of forming homo-dimeric molecules stabilized by intermolecular disulfide(s) between the C-terminal cysteine(s). Specifically, the $R1R2_C$ mini-trap efficiently formed covalent dimers when expressed as a secreted protein in CHO cells.

Example 6. Construction and expression of a single chain VEGF mini-trap

[0087] A VEGF mini-trap was also constructed that did not require a multimerization domain (SEQ ID NO:24). This mini-trap was constructed by direct fusion of one Flt1D2.Flk1D3 domain (R1R2) (amino acids 30-231 of SEQ ID NO:24) to a second Flt1D2.Flk1D3 domain (R1R2) (amino acids 234-435 of SEQ ID NO:24) with a Gly-Pro linker between the tandem receptor domains (amino acids 232-233 of SEQ ID NO:24).

[0088] To construct a gene encoding tandem Flt1D2.Flk1D3 domains, a DNA fragment was synthesized (Blue Heron Biotechnology) that encoded one Flt1D2.Flk1D3 domain that minimized DNA homology with the Flt1D2.Flk1D3 domain-encoding DNA found in pTE115. This synthetic DNA fragment was cloned as a Srf I-Not I fragment into the Srf I-Not I sites of pTE115 to yield pTE570, which expresses the R1R2-R1R2 VEGF mini-trap from the CMV-MIE promoter. When this plasmid is transfected into CHO K1 cells the R1R2-R1R2 VEGF mini-trap accumulates in the culture medium.

Example 7. Construction and expression of a VEGF mini-trap

[0089] A VEGF mini-trap was constructed as described above, by direct fusion of one Flt1D2.Flk1D3 domain (R1R2) (amino acids 30-231 of SEQ ID NO:26) with a C-terminal nine amino acid sequence terminating in CPPC. When this plasmid is transfected into CHO K1 cells the VEGF mini-trap of SEQ ID NO:26 is secreted into the culture medium. Subsequent purification by non-reducing SDS-PAGE electrophoresis as well as native light-scattering analysis identified a trap molecule with molecular weight approximately 64 kDa. This molecular weight indicates that a covalent dimer was formed between two fusion polypeptides of SEQ ID NO:26. Similar experiments were conducted with plasmids encoding the fusion polypeptides of SEQ ID NOS:27 and 28, and similarly showed these molecules formed homodimeric traps. Affinity determinations for human VEGF-165 binding to EGF traps composed of dimers of SEQ ID NO:10 and SEQ ID NO:26 are shown in Table 3.

TABLE 3

VEGF Trap	ka (1/Ms)	kd (1/s)	KD (M)
SEQ ID NO:10	$2.73 \times 10^{+7}$	1.79×10^{-5}	6.55×10^{-13}
SEQ ID NO:26	$2.00 \times 10^{+7}$	6.56×10^{-6}	3.28×10^{-13}
SEQ ID NO:26	$2.61 \times 10^{+7}$	5.77×10^{-6}	2.21×10^{-13}

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We claim:

1. An isolated nucleic acid molecule encoding a fusion polypeptide consisting of components $(R1R2)_X$ or $(R1R3)_Y$, and a fusion partner (FP), wherein $X \geq 1$, $Y \geq 1$, R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 and R2 is Ig domain 3 of Flk-1, R3 is Ig domain 3 of Flt-4.

2. The isolated nucleic acid of claim 1, wherein the fusion partner (FP) is a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure.

3. The isolated nucleic acid of claim 3, wherein the MC is selected from the group consisting of (i) a multimerizing component comprising a cleavable region (C-region), (ii) a truncated multimerizing component, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain.

4. A fusion polypeptide encoded by the nucleic acid molecule of claims 1 to 3.

5. The fusion polypeptide of claim 4, having the amino acid sequence of SEQ ID NO:26, 27, or 28.

6. A replicable expression vector capable in a transformed host cell comprising the nucleic acid molecule of claims 1 to 3.

7. A method of producing a VEGF fusion polypeptide, comprising the steps of introducing into a suitable expression system the expression vector of claim 6, and effecting expression of the VEGF fusion polypeptide.

8. A vascular endothelial cell growth factor (VEGF) trap, comprising a multimer of two or more fusion polypeptides of claim 4.

9. The VEGF trap of claim 8, which is a dimer.

10. A dimeric VEGF trap comprising two fusion polypeptides comprising the amino acid sequence of SEQ ID NO:26, 27, or 28.

11. A pharmaceutical composition comprising the fusion polypeptide of claims 8 or 9, and a pharmaceutically acceptable carrier.

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12. A method of treating a disease or condition which is improved, ameliorated, or inhibited by removal or inhibition of vascular endothelial growth factor (VEGF), comprising administering the pharmaceutical composition of claim 11 to a subject in need thereof.

13. The method of claim 12, wherein the disease or condition is an ocular disease or condition.

14. The method of claim 13, wherein the ocular disease or condition is age related macular degeneration.

15. An isolated nucleic acid molecule encoding a fusion polypeptide consisting of receptor components $(R1R2)_X$ or $(R1R3)_Y$, and a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure, wherein $X \geq 1$, $Y \geq 1$, R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 and R2 is Ig domain 3 of Flk-1, R3 is Ig domain 3 of Flt-4, wherein the multimerizing component (MC) is selected from the group consisting of (i) a MC comprising a cleavable region (C-region), (ii) a truncated MC, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain.

16. The isolated nucleic acid molecule of claim 15, wherein the receptor components are $(R1R2)_X$ and the multimerizing component is an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue.

17. The isolated nucleic acid molecule of claim 16, wherein the receptor component is R1R2, X is 1, and the multimerizing component is an amino acid sequence 1-15 amino acids in length with 1-2 cysteine residues.

18. A fusion polypeptide capable of binding vascular endothelial growth factor (VEGF) encoded by the nucleic acid molecule of claims 15 to 17.

19. The fusion polypeptide of claim 18, comprising the amino acid sequence of SEQ ID NO:26, 27 or 28.

20. A fusion polypeptide consisting of receptor components $(R1R2)_X$ or $(R1R3)_Y$, and a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure, wherein $X \geq 1$, $Y \geq 1$, R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 and R2 is Ig domain 3 of Flk-1, R3 is Ig domain 3 of Flt-4, wherein the multimerizing component (MC) is selected from the group consisting of (i) a MC comprising a cleavable region (C-region), (ii) a truncated MC, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain.

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21. The fusion polypeptide of claim 20, wherein the receptor components are $(R1R2)_X$ and the multimerizing component is an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue.

22. The fusion polypeptide of claim 21, wherein the receptor component is R1R2, X is 1, and the multimerizing component is an amino acid sequence 1-15 amino acids in length with 1-2 cysteine residues.

23. A dimeric VEGF trap composed of two of the fusion polypeptides of claims 20 to 22.

24. An article of manufacturing comprising:

(a) packaging material; and

(b) a pharmaceutical agent contained within said packaging material;

wherein the pharmaceutical agent comprises at least one VEGF trap consisting of receptor components $(R1R2)_X$ or $(R1R3)_Y$, and a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure, wherein $X \geq 1$, $Y \geq 1$, and wherein the packaging material comprises a label or package insert which indicates that said VEGF-specific fusion polypeptide can be used for treating a VEGF-mediated disease or condition.

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Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
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Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            340                 345                 350
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
        355                 360                 365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    370                 375                 380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385                 390                 395                 400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                405                 410                 415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            420                 425                 430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        435                 440                 445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
<210> 9
<211> 1377
<212> DNA
<213> homo sapiens

<400> 9
atggtcagct actgggacac cggggtcctg ctgtgcgcgc tgctcagctg tctgcttctc 60
acaggatcta gttccggaag tgataccggt agacctttcg tagagatgta cagtgaaatc 120
cccgaaatta tacacatgac tgaaggaagg gagctcgtca ttccctgccg ggttacgtca 180
cctaacatca ctgttacttt aaaaaagttt ccacttgaca ctttgatccc tgatggaaaa 240
cgcataatct gggacagtag aaagggcttc atcatatcaa atgcaacgta caaagaaata 300
gggcttctga cctgtgaagc aacagtcaat gggcatttgt ataagacaaa ctatctcaca 360
catcgacaaa ccaatacaat catagatgtg gttctgagtc cgtctcatgg aattgaacta 420
tctgttggag aaaagcttgt cttaaattgt acagcaagaa ctgaactaaa tgtggggatt 480
gacttcaact gggaataccc ttcttcgaag catcagcata agaaacttgt aaaccgagac 540
ctaaaaaccc agtctgggag tgagatgaag aaatttttga gcaccttaac tatagatggt 600
```


Petitioner Fresenius Ex. 1002, 0082

```
gtaacccgga gtgaccaagg attgtacacc tgtgcagcat ccagtgggct gatgaccaag 660
aagaacagca catttgtcag ggtccatgaa aaggacaaaa ctcacacatg cccaccgtgc 720
ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac 780
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 840
gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 900
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 960
caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 1020
gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 1080
accctgcccc catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc 1140
aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 1200
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1260
ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1320
gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaatga    1377
```

<210> 10
<211> 458
<212> PRT
<213> homo sapiens

<400> 10

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Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                245                 250                 255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            260                 265                 270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    290                 295                 300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320
```


Petitioner Fresenius Ex. 1002, 0083

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            340                 345                 350
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
        355                 360                 365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    370                 375                 380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385                 390                 395                 400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                405                 410                 415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            420                 425                 430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        435                 440                 445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
```

<210> 11
<211> 4
<212> PRT
<213> homo sapiens

<220>
<221> VARIANT
<222> 1, 2, 3, 4
<223> Xaa = Any Amino Acid

<400> 11
Xaa Xaa Xaa Xaa
1

<210> 12
<211> 1444
<212> DNA
<213> homo sapiens

<400> 12

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aagcttgggc tgcaggtcga tcgactctag aggatcgatc cccgggcgag ctcgaattcg 60
caaccaccat ggtcagctac tgggacaccg gggtcctgct gtgcgcgctg ctcagctgtc 120
tgcttctcac aggatctagt tccggaggta gacctttcgt agagatgtac agtgaaatcc 180
ccgaaattat acacatgact gaaggaaggg agctcgtcat tccctgccgg gttacgtcac 240
ctaacatcac tgttacttta aaaaagtttc cacttgacac tttgatccct gatggaaaac 300
gcataatctg ggacagtaga aagggcttca tcatatcaaa tgcaacgtac aaagaaatag 360
ggcttctgac ctgtgaagca acagtcaatg ggcatttgta taagacaaac tatctcacac 420
atcgacaaac caatacaatc atagatatcc agctgttgcc caggaagtcg ctggagctgc 480
tggtagggga gaagctggtc ctcaactgca ccgtgtgggc tgagtttaac tcaggtgtca 540
cctttgactg ggactaccca gggaagcagg cagagcgggg taagtgggtg cccgagcgac 600
gctcccaaca gacccacaca gaactctcca gcatcctgac catccacaac gtcagccagc 660
acgacctggg ctcgtatgtg tgcaaggcca acaacggcat ccagcgattt cgggagagca 720
ccgaggtcat tgtgcatgaa aatggcccgg gcgacaaaac tcacacatgc ccaccgtgcc 780
cagcacctga actcctgggg ggaccgtcag tcttcctctt cccccaaaa cccaaggaca 840
ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg agccacgaag 900
accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat gccaagacaa 960
agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc accgtcctgc 1020
accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag 1080
cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca caggtgtaca 1140
ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc tgcctggtca 1200
aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag ccggagaaca 1260
```


Petitioner Fresenius Ex. 1002, 0084

actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc tatagcaagc 1320
tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg 1380
aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt aaatgagcgg 1440
ccgc 1444

<210> 13
<211> 455
<212> PRT
<213> homo sapiens

<400> 13
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Gly Arg Pro Phe Val Glu
20 25 30
Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu
35 40 45
Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu
50 55 60
Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile
65 70 75 80
Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu
85 90 95
Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys
100 105 110
Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Ile Gln
115 120 125
Leu Leu Pro Arg Lys Ser Leu Glu Leu Leu Val Gly Glu Lys Leu Val
130 135 140
Leu Asn Cys Thr Val Trp Ala Glu Phe Asn Ser Gly Val Thr Phe Asp
145 150 155 160
Trp Asp Tyr Pro Gly Lys Gln Ala Glu Arg Gly Lys Trp Val Pro Glu
165 170 175
Arg Arg Ser Gln Gln Thr His Thr Glu Leu Ser Ser Ile Leu Thr Ile
180 185 190
His Asn Val Ser Gln His Asp Leu Gly Ser Tyr Val Cys Lys Ala Asn
195 200 205
Asn Gly Ile Gln Arg Phe Arg Glu Ser Thr Glu Val Ile Val His Glu
210 215 220
Asn Gly Pro Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys

Petitioner Fresenius Ex. 1002, 0085

```
385                 390                 395                 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445
Leu Ser Leu Ser Pro Gly Lys
    450                 455
```

<210> 14
<211> 24
<212> DNA
<213> homo sapiens

<400> 14
gggctgttga gagagagaga gagc 24

<210> 15
<211> 28
<212> DNA
<213> homo sapiens

<400> 15
ggccgctctc tctctctctc aacagccc 28

<210> 16
<211> 23
<212> DNA
<213> homo sapiens
<400> 16
gggcgcatgc ggttgttgag agc 23

<210> 17
<211> 27
<212> DNA
<213> homo sapiens

<400> 17
ggccgctctc aacaaccgca tgcgccc 27

<210> 18
<211> 36
<212> DNA
<213> homo sapiens

<400> 18
gagagagacc atgggtagac ctttcgtaga gatgta 36

<210> 19
<211> 48
<212> DNA
<213> homo sapiens

<400> 19
agagaggcgg ccgctttatc aacacttttc atggaccctg acaaatgt 48

<210> 20
<211> 57
<212> DNA

Petitioner Fresenius Ex. 1002, 0086

<213> homo sapiens

<400> 20
agagaggcgg ccgctttatc aacaaccgca tgccttttca tggaccctga caaatgt 57

<210> 21
<211> 39
<212> DNA
<213> homo sapiens

<400> 21
agttccggaa gtgccatggg tagacctttc gtagagatg 39

<210> 22
<211> 44
<212> DNA
<213> homo sapiens

<400> 22
agagaggcgg ccgctgttat cacttctcgt gcacgcgcac gaag 44

<210> 23
<211> 235
<212> PRT
<213> homo sapiens

<400> 23
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
20 25 30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
35 40 45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
50 55 60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65 70 75 80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
85 90 95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
100 105 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
115 120 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
130 135 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145 150 155 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
165 170 175
Val Asn Thr Gln Ser Gly Ser Glu Met Lys Arg Asp Leu Lys Lys Phe
180 185 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
195 200 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
210 215 220
Phe Val Arg Val His Glu Lys Gly Pro Gly Cys
225 230 235

<210> 24
<211> 435

Petitioner Fresenius Ex. 1002, 0087

<212> PRT
<213> homo sapiens

<400> 24

```
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Gly Pro Gly Arg Pro Phe Val Glu Met
225                 230                 235                 240
Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu
                245                 250                 255
Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys
            260                 265                 270
Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp
        275                 280                 285
Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile
    290                 295                 300
Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr
305                 310                 315                 320
Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu
                325                 330                 335
Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu
            340                 345                 350
Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp
        355                 360                 365
Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg Asp
    370                 375                 380
Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu
385                 390                 395                 400
Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala
                405                 410                 415
Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg Val
            420                 425                 430
His Glu Lys
        435
```


Petitioner Fresenius Ex. 1002, 0088

<210> 25
<211> 238
<212> PRT
<213> homo sapiens

<400> 25
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
20 25 30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
35 40 45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
50 55 60
Val Thr Leu Lys Lys Phe Pro Leu Asn Thr Leu Ile Pro Asn Gly Lys
65 70 75 80
Ala Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
85 90 95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
100 105 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
115 120 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
130 135 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145 150 155 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
165 170 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
180 185 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
195 200 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
210 215 220
Phe Val Arg Val His Glu Lys Gly Pro Gly Ala Cys Gly Cys
225 230 235

<210> 26
<211> 240
<212> PRT
<213> homo sapiens

<400> 26
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
20 25 30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
35 40 45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
50 55 60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65 70 75 80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
85 90 95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
100 105 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
115 120 125

Petitioner Fresenius Ex. 1002, 0089

```
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240
```

<210> 27
<211> 240
<212> PRT
<213> homo sapiens

<400> 27

```
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Ser Pro Pro Cys
225                 230                 235                 240
```

<210> 28
<211> 237
<212> PRT
<213> homo sapiens

<400> 28

```
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
```


Petitioner Fresenius Ex. 1002, 0090

```
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys
225                 230                 235
```

<210> 29
<211> 434
<212> PRT
<213> homo sapiens

```
<400> 29
Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
 1                   5                  10                  15
Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
            20                  25                  30
Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
        35                  40                  45
Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
    50                  55                  60
Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
65                  70                  75                  80
Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
                85                  90                  95
Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile
            100                 105                 110
Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr
        115                 120                 125
Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys
    130                 135                 140
His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly
145                 150                 155                 160
Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr
                165                 170                 175
Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met
            180                 185                 190
Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys Glu Ser Lys
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      195                 200                 205
Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
    210                 215                 220
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
225                 230                 235                 240
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
                245                 250                 255
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
            260                 265                 270
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
        275                 280                 285
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
    290                 295                 300
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
305                 310                 315                 320
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
                325                 330                 335
Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
            340                 345                 350
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
        355                 360                 365
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
    370                 375                 380
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
385                 390                 395                 400
Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
                405                 410                 415
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
            420                 425                 430
Gly Lys
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 December 2004 (09.12.2004)

PCT

(10) International Publication Number
WO 2004/106378 A2

(51) International Patent Classification[7]: C07K 16/24, A61K 31/7088, C07K 19/00, 14/71

(21) International Application Number: PCT/US2004/012540

(22) International Filing Date: 23 April 2004 (23.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/473,734 28 May 2003 (28.05.2003) US
60/492,865 6 August 2003 (06.08.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF TREATING CORNEAL TRANSPLANT REJECTION

(57) Abstract: Methods of preventing, reducing, or treating corneal transplant rejection to improve transplant survival in a subject in need thereof comprising administering an agent capable of blocking or inhibiting vascular endothelial growth factor (VEGF) are provided. The methods are useful for inhibiting or preventing corneal transplant rejection in a human subject who is the recipient of a transplanted cornea.

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METHOD OF TREATING CORNEAL TRANSPLANT REJECTION

BACKGROUND

Field of the Invention

[0001] The field of the invention is related to methods of using VEGF antagonists to reduce, prevent, or treat corneal transplant rejection, thus improving long-term transplant survival.

Description of Related Art

[0002] It has previously been reported that topical application of an anti-VEGF neutralizing antibody suppresses acute allograft rejection in a rat corneal transplant model (Yatoh et al. (1998) Transplantation 66(11):1519-24). As the leading cause of human corneal transplant failure is transplant rejection, there is a need for a therapeutic for use in preventing corneal transplant rejection in humans who receive a corneal transplant.

BRIEF SUMMARY OF THE INVENTION

[0003] The invention is based in part on the finding that administration of an agent capable of blocking or inhibiting vascular endothelial growth factor (VEGF) prevents corneal transplant rejection. The experiments, described below, conducted in an animal model of corneal transplantation show that long-term transplant survival is promoted by blocking VEGF-mediated activity.

[0004] In a first aspect, the invention features a method of improving transplant survival in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that transplant survival is improved.

[0005] In specific embodiments, the agent capable of blocking, inhibiting, or ameliorating VEGF-mediated activity is a VEGF antagonist. The VEGF antagonist may be a polypeptide, an antibody, a small molecule, or a nucleic acid. More specifically, the VEGF antagonist includes a VEGF trap selected from the group consisting of acetylated Flt-1(1-3)-Fc, Flt-1(1-$3_{R->N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt-1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3D3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a). In a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF $trap_{R1R2}$) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2. The invention encompasses the use of a VEGF trap that is at least 90%, 95%, 98%, or at least 99%

homologous with the nucleotide sequence set forth in SEQ ID NO: 1 and/or the amino acid sequence set forth in SEQ ID NO:2.

[0006] In other embodiments, the agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity is a nucleic acid-based antagonist capable of interfering with the expression of VEGF. A specific example of this embodiment is one in which the nucleic acid-based antagonist is an aptamer, an siRNA, or an antisense molecule.

[0007] Administration of the agent may be by any method known in the art, including subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, oral, or topical routes of administration. Preferable, administration to the subject in need of the agent is topical administration to the eye or subconjunctival administration. Administration may occur prior to or following corneal transplantation, preferably following surgery. Administration may also include a second agent, such as an immunosuppressive agent.

[0008] The subject to be treated is preferably a human subject who has or will receive a corneal transplant.

[0009] In a related second aspect, the invention features the use of an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for improving transplant survival in a mammalian subject.

[0010] In a third aspect, the invention features a method of preventing corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that corneal transplant rejection is prevented.

[0011] In a related fourth aspect, the invention features the use of an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for the treatment of corneal transplant rejection in a mammalian subject.

[0012] In a fifth aspect, the invention features a method of reducing the incidence of corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that the incidence of corneal transplant rejection is reduced.

[0013] In a related sixth aspect, the invention features the use of an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for reducing the incidence of corneal transplant rejection in a mammalian subject receiving a corneal transplant.

[0014] In a seventh aspect, the invention features a pharmaceutical composition comprising a VEGF antagonist, for example the VEGF trap VEGFR1R2-FcΔC1(a), in a pharmaceutically

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acceptable carrier. Such pharmaceutical compositions may be liquid, gel, ointment, salve, slow release formulations or other formulations suitable for ophthalmic administration.

[0015] In an eighth aspect, the invention features an article of manufacture comprising packaging materials and a pharmaceutical agent contained within the packaging materials, wherein the pharmaceutical agent comprises at least one VEGF-specific fusion protein of the invention, and the packaging material comprises a label or package insert which indicates that the VEGF-specific fusion protein can be used for the treatment or prevention of corneal transplant rejection.

[0016] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0017] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0018] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

General Description

[0020] Experiments were undertaken to evaluate occurrence and time course of hem- and lymphangiogenesis after normal-risk corneal transplantation and to test whether pharmacologic strategies inhibiting both processes improve long-term graft survival. As described in the experimental section below, normal-risk allogeneic (C57BL/6 to BALB/c) and syngeneic (BALB/c to BALB/c) corneal transplantations were performed and occurrence and time course

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of hem- and lymphangiogenesis after keratoplasty was observed using double immunofluorescence of corneal flatmounts (with CD31 as panendothelial and LYVE-1 as lymphatic vascular endothelial specific marker). A molecular trap designed to eliminate VEGF-A ("VEGF $Trap_{R1R2}$"; 12.5 mg/kg) was tested for its ability to inhibit both processes after keratoplasty and to promote long-term graft survival (intraperitoneal injections on the day of surgery and 3, 7, and 14 days later). The results show that no blood or lymph vessels were detectable immediately after normal-risk transplantation in either donor or host cornea, but hem- and lymphangiogenesis were clearly visible at day 3 after transplantation. Both vessel types reached donor tissue at one week after allo- and similarly after syngeneic grafting. Early postoperative trapping of VEGF-A significantly reduced both hem- and lymphangiogenesis and significantly improved long-term graft survival (78% versus 40%; $p<0.05$). There is concurrent, VEGF-A-dependent hem- and lymphangiogenesis after normal-risk keratoplasty within the preoperatively avascular recipient bed. Inhibition of hem- and lymphangiogenesis (which mediate the efferent and afferent arms of an immune response) after normal-risk corneal transplantation improves long-term graft survival, establishing that early postoperative hem- and lymphangiogenesis are risk factors for graft rejection even in low-risk eyes.

Definitions

[0021] By the term "therapeutically effective dose" is meant a dose that produces the desired effect for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0022] By the term "blocker", "inhibitor", or "antagonist" is meant a substance that retards or prevents a chemical or physiological reaction or response. Common blockers or inhibitors include but are not limited to antisense molecules, antibodies, antagonists and their derivatives. More specifically, an example of a VEGF blocker or inhibitor is a VEGF receptor-based antagonist including, for example, an anti-VEGF antibody, or a VEGF trap such as VEGFR1R2-FcΔC1(a) (SEQ ID NOs:1-2). For a complete description of VEGF-receptor based antagonists including VEGFR1R2-FcΔC1(a), see PCT publication WO/00/75319, the contents of which is incorporated in its entirety herein by reference.

[0023] A "small molecule" is defined herein to have a molecular weight below about 500 Daltons, and may include chemical as well as peptide molecules.

VEGF Antagonists

[0024] In one aspect of the invention, VEGF-mediated activity is blocked or inhibited by the use

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of VEGF receptor-based blockers of VEGF-mediated activity. A non-limiting example of a VEGF receptor-based blocker includes, but is not limited to, VEGFR1R2-FcΔC1(a). Other suitable receptor-based blockers include acetylated Flt-1(1-3)-Fc, Flt-1(1-$3_{R->N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt-1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3D3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a). For a complete description of these and other VEGF-receptor-based blockers, including pegylated receptor-based blockers, see PCT Publication No. WO/00/75319, the contents of which is incorporated in its entirety herein by reference.

[0025] In addition to the VEGF receptor-based blockers described in PCT Publication No. WO/00/75319, variants and derivatives of such VEGF receptor-based blockers are also contemplated by the invention. The sequence of the variants or derivatives may differ by a change which is one or more additions, insertions, deletions and/or substitutions of one or more nucleotides of the sequence set forth in SEQ ID NO:1. Changes to a nucleotide sequence may result in an amino acid change at the protein level, or not, as determined by the genetic code. Thus, nucleic acid according to the present invention may include a sequence different from the sequence shown in SEQ ID NO:1, yet encode a polypeptide with the same amino acid sequence as SEQ ID NO: 2. On the other hand, the encoded polypeptide may comprise an amino acid sequence which differs by one or more amino acid residues from the amino acid sequence shown in SEQ ID NO:2. Nucleic acid encoding a polypeptide which is an amino acid sequence variant or derivative of the sequence shown in SEQ ID NO:2 is further provided by the present invention. Nucleic acid encoding such a polypeptide may show at the nucleotide sequence and/or encoded amino acid level greater than about 90%, 95%, 98%, or 99% homology with the coding sequence shown in SEQ ID NO:1 and/or the amino acid sequence shown in SEQ ID NO:2. For amino acid "homology", this may be understood to be similarity (according to the established principles of amino acid similarity, e.g. as determined using the algorithm GAP (Genetics Computer Group, Madison, Wis.)) or identity. GAP uses the Needleman and Wunsch algorithm to align two complete sequences that maximizes the number of matches and minimizes the number of gaps. Generally, the default parameters are used, with a gap creation penalty=12 and gap extension penalty=4.

[0026] Individual components of the VEGF-specific fusion proteins of the invention may be constructed by molecular biological methods known to the art with the instructions provided by the instant specification. These components are selected from a first cellular receptor protein, such as, for example, VEGFR1; a second cellular receptor protein, such as, for example, VEGFR2; a multimerizing component, such as an Fc.

[0027] Specific embodiments of the VEGF-specific fusion proteins useful in the methods of the invention comprise a multimerizing component which allows the fusion proteins to associate,

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e.g., as multimers, preferably dimers. Preferably, the multimerizing component comprises an immunoglobulin derived domain. Suitable multimerizing components are sequences encoding an immunoglobulin heavy chain hinge region (Takahashi et al. 1982 Cell 29:671-679); immunoglobulin gene sequences, and portions thereof.

[0028] The nucleic acid constructs encoding the fusion proteins useful in the methods of the invention are inserted into an expression vector by methods known to the art, wherein the nucleic acid molecule is operatively linked to an expression control sequence. Host-vector systems for the production of proteins comprising an expression vector introduced into a host cell suitable for expression of the protein are known in the art. The suitable host cell may be a bacterial cell such as *E. coli*, a yeast cell, such as *Pichia pastoris,* an insect cell, such as *Spodoptera frugiperda*, or a mammalian cell, such as a COS, CHO, 293, BHK or NS0 cell.

Antisense Nucleic Acids

[0029] In one aspect of the invention, VEGF-mediated activity is blocked or inhibited by the use of VEGF antisense nucleic acids. The present invention provides the therapeutic or prophylactic use of nucleic acids comprising at least six nucleotides that are antisense to a gene or cDNA encoding VEGF or a portion thereof. As used herein, a VEGF "antisense" nucleic acid refers to a nucleic acid capable of hybridizing by virtue of some sequence complementarity to a portion of an RNA (preferably mRNA) encoding VEGF. The antisense nucleic acid may be complementary to a coding and/or noncoding region of an mRNA encoding VEGF. Such antisense nucleic acids have utility as compounds that prevent VEGF expression, and can be used in the treatment or prevention of corneal transplant rejection. The antisense nucleic acids of the invention are double-stranded or single-stranded oligonucleotides, RNA or DNA or a modification or derivative thereof, and can be directly administered to a cell or produced intracellularly by transcription of exogenous, introduced sequences.

[0028] The VEGF antisense nucleic acids are of at least six nucleotides and are preferably oligonucleotides ranging from 6 to about 50 oligonucleotides. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 15 nucleotides, at least 100 nucleotides, or at least 200 nucleotides. The oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof and can be single-stranded or double-stranded. In addition, the antisense molecules may be polymers that are nucleic acid mimics, such as PNA, morpholino oligos, and LNA. Other types of antisence molecules include short double-stranded RNAs, known as siRNAs, and short hairpin RNAs, and long dsRNA (>50 bp but usually ≥500 bp).

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Short interfering RNAs

[0029] In another embodiment, VEGF-mediated activity is blocked by blocking VEGF expression. One method for inhibiting VEGF expression is the use of short interfering RNA (siRNA) through RNA interference (RNAi) or post-transcriptional gene silencing (PTGS) (see, for example, Ketting et al. (2001) Genes Develop. 15:2654-2659). siRNA molecules can target homologous mRNA molecules for destruction by cleaving the mRNA molecule within the region spanned by the siRNA molecule. Accordingly, siRNAs capable of targeting and cleaving homologous VEGF mRNA are useful for treating, reducing or preventing corneal transplant rejection.

Inhibitory Ribozymes

[0030] In aspect of the invention, corneal transplant rejection may be treated or prevented in a subject suffering from such disease by decreasing the level of VEGF activity by using ribozyme molecules designed to catalytically cleave gene mRNA transcripts encoding VEGF, preventing translation of target gene mRNA and, therefore, expression of the gene product.

[0031] Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by an endonucleolytic cleavage event. The composition of ribozyme molecules must include one or more sequences complementary to the target gene mRNA, and must include the well known catalytic sequence responsible for mRNA cleavage. For this sequence, see, *e.g.*, U.S. Patent No. 5,093,246. While ribozymes that cleave mRNA at site-specific recognition sequences can be used to destroy mRNAs encoding VEGF, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA has the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art. The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one that occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence where after cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that are present in the gene encoding VEGF.

Generation of Antibodies to VEGF Proteins

[0032] In another aspect of the invention, the invention may be practiced with an anti-VEGF

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antibody or antibody fragment capable of binding and blocking VEGF activity. Anti-VEGF antibodies are disclosed, for example, in US Patent No. 6,121,230, herein specifically incorporated by reference. The term "antibody" as used herein refers to a polypeptide comprising a framework region from an immunoglobulin gene or fragments thereof that specifically binds and recognizes an antigen. The recognized immunoglobulin genes include the kappa, lambda , alpha, gamma, delta, epsilon, and mu constant regions, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD, and IgE, respectively. Within each IgG class, there are different isotypes (eg. IgG_1, IgG_2, etc.). Typically, the antigen-binding region of an antibody will be the most critical in determining specificity and affinity of binding.

[0033] Antibodies exist as intact immunoglobulins, or as a number of well-characterized fragments produced by digestion with various peptidases. For example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab)'_2$, a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a disulfide bond. The $F(ab)'_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the $F(ab)'_2$ dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region. While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the terms antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (e.g., single chain Fv)(scFv) or those identified using phase display libraries (see, for example, McCafferty et al. (1990) Nature 348:552-554).

[0034] Methods for preparing antibodies are known to the art. See, for example, Kohler & Milstein (1975) Nature 256:495-497; Harlow & Lane (1988) Antibodies: a Laboratory Manual, Cold Spring Harbor Lab., Cold Spring Harbor, NY). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity. Techniques for the production of single chain antibodies or recombinant antibodies (US 4,946,778; US 4,816,567) can be adapted to produce antibodies used in the fusion proteins and methods of the instant invention. Also, transgenic mice, or other organisms such as other mammals, may be

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used to express human or humanized antibodies. Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens.

Antibody Screening and Selection

[0035] Screening and selection of preferred antibodies can be conducted by a variety of methods known to the art. Initial screening for the presence of monoclonal antibodies specific to a target antigen may be conducted through the use of ELISA-based methods, for example. A secondary screen is preferably conducted to identify and select a desired monoclonal antibody for use in construction of the multi-specific fusion proteins of the invention. Secondary screening may be conducted with any suitable method known to the art. One preferred method, termed "Biosensor Modification-Assisted Profiling" ("BiaMAP") is described in co-pending USSN 60/423,017 filed 01 Nov 2002, herein specifically incorporated by reference in its entirety. BiaMAP allows rapid identification of hybridoma clones producing monoclonal antibodies with desired characteristics. More specifically, monoclonal antibodies are sorted into distinct epitope-related groups based on evaluation of antibody:antigen interactions.

Treatment Population

[0036] A suitable subject for treatment by the method of the invention is a human who has received or will receive a corneal transplant. Corneal transplantation is the oldest, most successful and most commonly performed tissue transplantation, with nearly 40,000 transplantations a year alone in the US. When corneal grafts are placed into an avascular recipient bed (so-called normal-risk keratoplasty), 2-year graft survival rates approach 90% under cover of topical steroids, even without HLA-matching. This very successful outcome is attributed to corneal immune privilege, i.e. the phenomenon of suppressed corneal inflammation induced by an array of endogenous mechanisms downregulating alloimmune and inflammatory responses in the cornea and its bed. These mechanisms include the lack of both afferent lymphatic and efferent blood vessels in the normal-risk recipient cornea, lack of MHC II^+ antigen presenting cells (APCs), FASL-expression on corneal epithelium and endothelium, and the anterior chamber associated immune privilege (ACAID) directed at graft antigens etc. (Streilein et al. (1999) Transplant Proc. 31:1472-1475).

[0037] In contrast, survival rates of cornea grafts placed into vascularized, not immune-privileged recipient beds (so called high-risk keratoplasty) drop significantly to below 50% (even with local and systemic immune suppression). Pre-existing corneal stromal blood vessels have been identified as strong risk factors for immune rejection after corneal transplantation, both in

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the clinical setting as well as in the well-defined mouse model of corneal transplantation (Sano et al. (1995) Invest. Ophthalmol. Vis. Sci. 36:2176-85). Recently, in addition to blood vessels, biomicroscopically undetectable lymphatic vessels have been found in association with blood vessels in vascularized high-risk human corneas (Cursiefen et al. (2003) Cornea. 22:273-81) and it is likely that corneal lymphatic vessels enable effective access of donor and host APCs and antigenic material to regional lymph nodes where accelerated sensitisation to graft antigens occurs (Liu et al. (2002) J. Exp. Med. 195:259-68) even in the normal-risk setting (with a preoperatively avascular recipient bed), where mild corneal hemangiogenesis develops after keratoplasty. Outgrowth of new blood vessels from the limbal arcade towards the graft can be observed within the first postoperative year in about 50% of patients undergoing normal-risk keratoplasty, and in 10% of patients these new blood vessels even reach the interface or invade donor tissue (Cursiefen et al. (2001) Graefes Arch. clin. Exp. Ophthalmol. 39:514-21) at corneal suture sites, and then proceed centrally.

Methods of Administration

[0038] The invention provides methods of treatment comprising administering to a subject an effective amount of an agent of the invention. In a preferred aspect, the agent is substantially purified (*e.g.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, *e.g.,* such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0039] Various delivery systems are known and can be used to administer an active agent of the invention, *e.g.*, delivery systems suitable for topical administration, preferably topical administration directly to the eye, or subconjunctival administration, as well as other delivery systems such as those that utilize encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction are preferably topical or subconjunctival, but may be enteral or parenteral including but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, and oral routes. The active agents may be administered by any convenient route, for example by absorption through epithelial (e.g. topical administration to the eye) or mucocutaneous linings (*e.g.*, oral mucosa, intestinal mucosa, etc.) or infusion or bolus injection, and may be administered together with other biologically active agents. Administration can be systemic or local. Administration can be acute or chronic (*e.g.* daily, weekly, monthly, etc.) or in combination or alteration with other agents. Pulmonary

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administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0040] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533). In yet another embodiment, the active agent can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer (1990) *supra*). In another embodiment, polymeric materials can be used (see Howard et al. (1989) J. Neurosurg. 71:105). In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see, for example, U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see *e.g.*, Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0041] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by topical administration, subconjunctival administration, local infusion during surgery, *e.g.*, by injection, by means of a catheter, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, fibers, or commercial skin substitutes.

Cellular Transfection and Gene Therapy

[0042] The present invention encompasses the use of nucleic acids encoding the VEGF-specific fusion proteins of the invention for transfection of cells *in vitro* and *in vivo*. These nucleic acids can be inserted into any of a number of well-known vectors for transfection of target cells and organisms. The nucleic acids are transfected into cells *ex vivo* and *in vivo*, through the interaction of the vector and the target cell. Reintroduction of transfected cells may be accomplished by any method known to the art, including re-implantation of encapsulated cells. The compositions are administered (e.g., by injection into a muscle) to a subject in an amount sufficient to elicit a therapeutic response. An amount adequate to accomplish this is defined as "a therapeutically effective dose or amount."

[0043] In another aspect, the invention provides a method of treating or preventing corneal transplant rejection in a human comprising transfecting a cell with a nucleic acid encoding a

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VEGF-specific fusion protein of the invention, wherein the nucleic acid comprises an inducible promoter operably linked to the nucleic acid encoding the VEGF-specific fusion protein. For gene therapy procedures in the treatment or prevention of human disease, see for example, Van Brunt (1998) Biotechnology 6:1149-1154.

Pharmaceutical Compositions

[0044] Pharmaceutical compositions useful in the practice of the method of the invention include a therapeutically effective amount of an active agent, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0045] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, or intramuscular administration to human beings. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0046] The active agents of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those

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derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0047] The amount of the active agent of the invention that will be effective in the treatment or prevention of corneal transplant rejeciton can be determined by standard clinical techniques based on the present description. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each subject's circumstances. However, suitable dosage ranges for intravenous administration are generally about 50-5000 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0048] For systemic administration, a therapeutically effective dose can be estimated initially from *in vitro* assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from *in vivo* data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

[0049] Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. One having skill in the art will be able to optimize therapeutically effective local dosages witho ut undue experimentation.

[0050] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

Combination Therapies

[0051] In numerous embodiments, the VEGF blockers of the present invention may be administered in combination with one or more additional compounds or therapies or medical procedures. For example, suitable therapeutic agents for use in combination, either alternating or simultaneously, with the VEGF blockers may include topically administered immunosuppressive

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agents such as corticosteroids, dexamethasone, cyclosporin A, or anti-metabolic agents or systemically administered immunosuppressive agents such as corticosteroids, dexamethasone, cyclosporin A, FK506, or anti-metabolic agents, as well as other agents effective to treat, reduce, or prevent corneal transplant rejection (see Barker, NH, *et al.*, (2000) Clin Exp Opthal 28:357-360). Other suitable therapeutic agents for use in combination, either alternating or simultaneously, with the VEGF blockers of the subject invention may include blockers that can block other VEGF family members such as VEGF-C and VEGF-D.

Kits

[0052] The invention also provides an article of manufacturing comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent comprises at least one VEGF-specific fusion protein of the invention and wherein the packaging material comprises a label or package insert which indicates that the VEGF-specific fusion protein can be used for treating corneal transplant rejection.

[0053] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[0054] The following example is put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Inhibition of corneal lymphangiogenesis and angiogenesis after low-risk keratoplasty using VEGFR1R2-FcΔC1(a).

[0055] Mice and anesthesia. Six to 8 weeks old male C57BL/6 mice were used as donors and same-aged male BALB/c mice (Taconic, Germantown, NY) as recipients in the mouse model of normal-risk keratoplasty (Sonoda et al. (1992) Transplantation 54:694-704). For syngeneic transplantations, 6-8 weeks old male BALB/c mice were used both as donors as well as recipients. For the dose response studies, 8 weeks old male C57BL/6 mice were used. All animals were treated in accordance with the ARVO Statement for the Use of Animals in

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Ophthalmic and Vision Research. Mice were anesthetized using a mixture of ketamine and xylazine (120 mg/kg body weight and 20 mg/kg body weight respectively).

[0056] Dose response of VEGF Trap$_{R1R2}$. Five different doses of VEGF-Trap$_{R1R2}$ (SEQ ID NO:2) were tested in mice that received three interrupted intrastromal sutures (10-0 nylon, 50-μm-diameter, Sharpoint, Surgical Specialties Corporation, Reading, PA). Gentamicine and ophthalmic ointment were applied immediately after surgery. Following surgery (day 0), mice received a single subcutaneous injection of VEGF Trap$_{R1R2}$ (25 mg/kg, 12.5 mg/kg, 6.25 mg/kg, 2.5 mg/kg or 0.5 mg) or human Fc (12.5 mg/kg; control). Corneas were harvested on day 9 after suture placement, following an intravenous administration of an endothelial-specific fluorescein-conjugated lectin (*Lycopersicon esculentum*, Vector Laboratories, Burlingame, CA). The isolated corneas were flat-mounted on glass slides, and images of lectin-labeled vessels were captured using a Spot RT Digital camera (Diagnostic Instrument, Inc. Sterling Heights, MI) attached to a Nikon Microphot-FXA microscope (Nikon Inc. Garden City, NY). Scion Image 1.62c (Scion Corporation, Frederick, MD) was used to quantify the extent of corneal neovascularization.

[0057] Corneal transplantation in mice. Orthotopic corneal allografting in the mouse model of normal-risk keratoplasty was performed as described previously (Sonoda et al. (1992) *supra*). Donor corneas were excised by trephination using a 2.0 mm bore and cut with a curved vannas scissor. Until grafting, corneal tissue was placed in chilled phosphate-buffered saline. Recipients were anesthetized and the graft bed was prepared by trephining a 1.5 mm site in the central cornea of the right eye and discarding the excised cornea. The donor cornea was immediately applied to the bed and secured in place with 8 interrupted sutures (11-0 nylon, 70 μm diameter needles, Arosurgical, Newport Beach, CA). Antibiotic ointment (Oxymycin, Pharmafair, Hauppauge, NY) was placed on the corneal surface and the eyelids sutured with 8-0 suture (Sharpoint, Reading, PA). Recipients of grafts in which bleeding developed in the immediate postoperative period were discarded from further evaluation. All grafted eyes were examined after 72 hours, and grafts with technical difficulties (hyphema, cataract, infection, loss of anterior chamber) were excluded from further consideration. Tarsorraphy and corneal sutures were removed after 7 days and grafts were then examined at least twice a week until week 8 post transplantation by slit-lamp microscopy and scored for opacity. The survival experiment was performed twice and comprised 10 and 12 mice per experiment in both groups, respectively. Clinical scores of corneal grafts for opacity were as follows: 0= clear; +1=minimal, superficial (nonstromal) opacity; pupil margin and iris vessels readily visible through the cornea; +2= minimal, deep (stroma) opacity; pupil margins and iris vessels visible; +3= moderate stromal opacity; only pupil margin visible; +4= intense stromal opacity; only a portion of pupil margin

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visible; +5= maximum stromal opacity; anterior chamber not visible. Grafts with opacity scores of +2 or greater after 2 weeks were considered to have been rejected. Syngeneic transplantations were performed and evaluated in a similar manner.

[0058] Immunohistochemistry and morphometry of angiogenesis and lymphangiogenesis in the cornea. Briefly, corneal flat mounts were rinsed in PBS, fixed in acetone, rinsed in PBS, blocked in 2% bovine serum albumin, stained with FITC-conjugated CD31/PECAM-1 overnight (Santa Cruz Biotechnology, Santa Cruz, CA; 1:100), washed, blocked, stained with LYVE-1 (1:500; a lymphatic endothelium specific hyaluronic acid receptor (Cursiefen et al. (2002) Invest. Ophthalmol. Vis. Sci. 43:2127-35) washed, blocked, and stained with Cy3 (1:100; Jackson ImunoResearch Laboratories, West Grove, PA) and analyzed using a Zeiss Axiophot microscope. Digital pictures of the flat mounts were taken using Spot Image Analysis system. Then the area covered by $CD31^{+++}$/LYVE-1^{-} blood vessels and $CD31^{+}$/LYVE-1^{+++} lymph vessels was measured morphometrically on these flat-mounts using NIH Image software. The total corneal area was outlined using the innermost vessel of the limbal arcade as the border. The total area of blood versus lymphatic neovascularization was then normalized to the total corneal area and the percentage of the cornea covered by each vessel type calculated.

[0059] Neutralization of VEGF-A using VEGF $Trap_{R1R2}$. The VEGF $trap_{R1R2}$ (Regeneron Pharmaceuticals Inc, Tarrytown, NY (Holash et al. (2002) Proc. Natl. Acad. Sci. USA 99:11393-8, herein specifically incorporated by reference in its entirety) was used in the transplant survival experiment at a concentration of 12.5 mg/kg intraperitoneally (i.p.) at time of surgery (CHO hVEGFR1 [Ig domain 2] R2 [Ig domain 3]-Fc), and 3, 7, and 14 days after surgery. Human Fc-fragment given i.p. at same concentration and times was used in the control mice (sCHO h Fc).

[0060] Statistical analysis. Statistical significance was analyzed by Mann-Whitney's test. Differences were considered significant at $P < 0.05$. Each experiment was performed at least twice with similar results. Graphs were drawn using Graph Pad Prism, Version 3.02.

[0061] Results. Dose response of angiogenesis inhibition by VEGF $Trap_{R1R2}$. VEGF-$Trap_{R1R2}$ at doses of either 25 mg/kg or 12.5 mg/kg completely inhibited suture-induced inflammatory corneal neovascularization. In contrast, doses of 6.25mg/kg and 2.5mg/kg produced ~50% and ~20% inhibition of corneal neovascularization, respectively, while the lowest dose tested, 0.5 mg/kg, had a negligible effect (<5% inhibition). Therefore, for subsequent experiments a dose of 12.5 mg/kg VEGF $Trap_{R1R2}$ was chosen.

[0062] Rapid and parallel onset of hemangiogenesis and lymphangiogenesis *after* normal-risk allogeneic corneal transplantation. To determine whether the mild and temporary hemangiogenesis occurring *after* normal-risk keratoplasty is accompanied by lymphatic vessel outgrowth from the limbus into the normally alymphatic cornea, we studied the time course of

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ingrowth of both vessel types at days 0, 3, 7, 14, 21, and 28 *after* allogeneic keratoplasty (only accepted grafts). Immediately *after* surgery, blood and lymphatic vessels were not detectable either in the host or in donor tissue using biomicroscopy and immunohistochemistry on corneal flat mounts. But, at day 3 after allografting, both methods revealed new blood vessels growing into the cornea already 1/3 to halfway towards the graft interface. By day 7 these vessels had usually reached the donor tissue, but they rarely invaded the donor tissue itself. Analyzing flatmounts stained with LYVE-1 as a lymphatic vessel specific marker showed that $CD31^{+++}$/LYVE-1^{-} blood vessels were regularly accompanied by LYVE-1^{+++}/$CD31^{+}$ lymphatic vessels. Both vessel types reached the interface simultaneously at day 7. Thereafter, coincident with suture removal, both vessel types started to regress (if no immune rejection occurred; data not shown).

[0063] No difference in postkeratoplasty hem- and lymphangiogenesis between syngeneic and allogeneic corneal transplantation. To determine whether the simultaneous induction of hem- and lymphangiogenesis *after* normal-risk keratoplasty is primarily an effect of the surgical trauma, suturing and wound healing processes or secondary to early immunological rejection reactions, we compared speed and extent of both hem- and lymphangiogenesis occurring *after* keratoplasty between allogeneic (C57BL/6 into BALB/c) and syngeneic grafts (BALB/c into BALB/c) at day 3, 7, 14, 21, 28 after transplantation. In both groups, blood and lymphatic vessels grew out after keratoplasty and by day 3 reached about 1/3 to _ of the limbus-interface distance. At day 7 after syngeneic and allogeneic grafting both vessel types had reached the interface, before they started to regress thereafter. Furthermore, there was no significant difference in the hem- and lymphvascularized area, comparing syngeneic and allogeneic grafts at 3 days (allogeneic: hemvascularized area [HA] 25.2±4.1% and lymphvascularized area [LA] 22.2±9.4% versus syngeneic HA: 23±2.7% and LA 19.4±7.2%) and 7 days (allogeneic HA: 53.8±11.2% and LA: 37.9±6.2% versus syngeneic HA: 55.9±8.2% and LA: 38±22.7%) after surgery (n=8 mice per group per timepoint).

[0064] Neutralization of VEGF-A after normal-risk keratoplasty inhibits postoperative hemangiogenesis and lymphangiogenesis. Mice received either intraperitoneal injections of VEGF $Trap_{R1R2}$ (12.5 mg/kg) at surgery and 3 days later, or in the controls the Fc-protein in the same dosage. At day 3 and 7 after surgery, the extent of hem- and lymphangiogenesis was compared between these two groups (n=6 mice per group per timepoint). At day 3 and day 7 after surgery, the hemvascularized area was significantly smaller in trap-treated mice (day 3: 15.8±4.0%; day 7: 25.2±13.3%) compared to mice just receiving the Fc-fragment (day 3: 25.8±4.4%; day 7: 48.3±12.8%; $p<0.0001$). This was also true for the lymphvascularized area

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comparing Trap- (9.5±9.4%) and Fc-treated mice on day 3 (21.5±9.3%; $p<0.0001$). At day 7, the lymphvascularized area was smaller, but not significantly different in the Trap-group (28.7±20.3%) compared to the Fc-group (51.5±23.8%; $p=0.06$). In contrast to results obtained in corneal injury models neither hem- or lymphangiogenesis were completely inhibited by the VEGF $Trap_{R1R2}$ following corneal transplantation. However, the number of lymphatic vessels reaching the graft-host interface (10.6±0.6 versus 1.3±1.5 vessels) and the number of hours where the interface was filled with draining lymphatic vessels were much larger in the Fc-treated compared to the Trap-treated group (3±2 versus 0.2±0.3 hours; not significant due to small sample size) at day 7. This might indicate that lymphavascularized area per se is less decisive for host sensitisation than the contact area with donor tissue.

[0065] Partial inhibition of early postoperative hem- and lymphangiogenesis by trapping VEGF-A after normal-risk surgery improves long-term graft survival.

Since hem- and lymphangiogenesis occurring *after* normal-risk keratoplasty peaked around day 7, and regressed thereafter, and since both vascular processes could be significantly inhibited by early postoperative neutralization of VEGF-A, we determined whether inhibition of postkeratoplasty hem- and lymphangiogenesis during this interval improves graft survival. The long-term survival of C57BL/6 grafts placed into avascular BALB/c recipient beds was compared between mice receiving an i.p. injection of 12.5 mg/kg VEGF $Trap_{R1R2}$, or Fc-fragment alone, at surgery and 3, 7, and 14 days later. Trapping of VEGF-A postoperatively caused a significantly improved long-term graft survival at 8 weeks (78%), compared to grafts in eyes of Fc-treated controls (40%; $p=0.044$; $n=22$ in both groups).

[0066] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

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Claims

We claim,

1. Use of an first agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for treating or preventing corneal transplant rejection in a mammalian subject.

2. The use of claim 1, wherein the agent capable of blocking, inhibiting, or ameliorating VEGF-mediated activity is a VEGF antagonist.

3. The use of claim 2, wherein the VEGF antagonist is a polypeptide, an antibody, a small molecule, or a nucleic acid.

4. The use of claim 3, wherein the VEGF antagonist includes a VEGF trap selected from the group consisting of acetylated Flt-1(1-3)-Fc, Flt-1(1-$3_{R->N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt-1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3D3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a).

5. The use of claim 4, wherein the VEGF trap is VEGFR1R2-FcΔC1(a).

6. The use of claim 3, wherein the VEGF antagonist is a nucleic acid selected from the group consisting of aptamer, an siRNA, or an antisense molecule.

7. The use of claim 1, wherein administration is subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, oral, subconjunctival, or topical. Administration may also include a second agent, such as an immunosuppressive agent.

8. The use of claim 1, further comprising administering a second agent.

9. The use of claim 8, wherein the second agent is an immunosuppressive agent.

10. The use of claim 1, wherein the mammalian subject is a human.

11. The use of claim 10, wherein the human subject has received a corneal transplant.

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12. A method of reducing the incidence of corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that the incidence of corneal transplant rejection is reduced.

13. A method of treating corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that corneal transplant rejection is treated.

14. A pharmaceutical composition for prevention or treatment of corneal transplant rejection, comprising a vascular endothelial growth factor (VEGF) antagonist, and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, in the form of a liquid, gel, ointment, salve, or ophthalmic solution.

16. An article of manufacturing comprising:

(a) packaging material; and

(b) a pharmaceutical agent contained within the packaging material;

wherein the pharmaceutical agent comprises at least one VEGF-specific fusion protein of the invention and wherein the packaging material comprises a label or package insert which indicatess that the VEGF-specific fusion protein can be used to treat or prevent corneal transplant rejection in a mammalian subject.

SUBSTITUTE SHEET (RULE 26)

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The Schepens Eye Research Institute

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Electronic Acknowledgement Receipt

EFS ID:	40024530
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	16-JUL-2020
Filing Date:	12-OCT-2018
Time Stamp:	16:40:07
Application Type:	Utility under 35 USC 111(a)

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	0725US05_2020-07-16_Supp_IDS_trans_REGN-008CIPCON4.pdf	51820 d48f2adabdeb4e14d70b19773dbb7424b58434fc	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0725US05__2020-07-16_Supp_IDS_SB08A_REGN-008CIPCON4.pdf	64023 317e9f18b7e8bd572fd512f7d72cb130190d422d	no	5
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO2005000895A2.pdf	2338182 6363e90be1b6d4d24923286378ef404ecffe18c3	no	38
Warnings:					
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4	Foreign Reference	WO2004106378A2.pdf	1507654 b6c832b47fd56959cb880da99e6703a41bf742cc	no	23
Warnings:					
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5	Non Patent Literature	01_Benz_May_2007.pdf	46129 dff86fc070ae43858a162bc440b012b07665a2f9	no	2
Warnings:					
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6	Non Patent Literature	02_Do_May_2007.pdf	53639 d211e1d8d8063e474ab9ec77238f8a5a33fbdb06	no	2
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7	Non Patent Literature	03_Do_April_2009.pdf	47066 fd7e6416950ad2213097da0329a57a620e0666ce	no	2
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8	Non Patent Literature	04_Haller_April_2011.pdf	45545 6448e33f10ba36725ec030633267aa3d3133a9fd	no	2
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9	Non Patent Literature	05_Heier_April_2009.pdf	54469 4d1796d22d8862c22670a9a4c6ee29e2cffbac99	no	2
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10	Non Patent Literature	06_Heier_06-2011.pdf	402562 e8b2ec84c9b17d1057bfa2adb39c766db747a994	no	9
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11	Non Patent Literature	07-Heier_09-2011.pdf	31584 15391ae1a1e480c841fd2036de4dfdf7c1ddbd63	no	1
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12	Non Patent Literature	08_NCT00320775_2006-2011.pdf	1030862 f54e321e4d54c284543306b48388eb667d11d5ec	no	70
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13	Non Patent Literature	09_NCT00320775_2015.pdf	166014 b8b1693d8b4b3e738f3ff58c71a33c84ddf3de48	no	10
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14	Non Patent Literature	10_NCT00320788_2006-2011.pdf	1057353 5d52daa9713864354b281cc78676b4c20f378023	no	71
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15	Non Patent Literature	11_NCT00320788_2012.pdf	292436 caf8ed62780436c916ce5349682ef9800be64ba5	no	31
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16	Non Patent Literature	12_NCT00320814_2006-2011.pdf	565177 23acdc433c5f955442dacee7bac57e5c638654ca	no	30
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17	Non Patent Literature	13_NCT00509795_2007-2011.pdf	2602890 c6d8c231fc813a8b2669d47703c413892a68576e	no	318
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18	Non Patent Literature	14_NCT00509795_2012.pdf	1310807 2c09b0e7757a632fd4d161c021f006b14dd79d0e	no	200
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19	Non Patent Literature	15_NCT00527423_2007-2011.pdf	1018702 65d0686f0cfb0b04a106f45c706c3a53b119cb9b	no	64
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21	Non Patent Literature	17_NCT00637377_2008-2011.pdf	5617214 8aa5dc78ca7f38f0d940184519f1a5cbb2eb3427	no	667
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22	Non Patent Literature	18_NCT00637377_2012-2014.pdf	1866914 792b27b9bd3cc26e03f127fb7c7f1921dfaacdfa	no	289
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23	Non Patent Literature	19_NCT00789477_2008-2011.pdf	1979158 137fc01d547e7c160e94d4201107cb5694804f96	no	135
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25	Non Patent Literature	21_NCT00943072_2009-2011.pdf	1376368 75107823e44478105f7ee0f6f9702ec800cf8a45	no	98
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26	Non Patent Literature	22_NCT00943072_2012-2013.pdf	608635 d374bdcb944b6e0319cd2d4e4a282dfbbfedc06c	no	64
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27	Non Patent Literature	23_Major_April_2010.pdf	47042 7d6526cf1ea617db63bf6916ea89af0e5e7c3b9d	no	2
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28	Non Patent Literature	24_Nguyen_April_2011.pdf	47769 53199468f42d5607062332b5bff6f18111ec77d6	no	2
Warnings:					
Information:					
29	Non Patent Literature	25_Nguyen_May_2006.pdf	53195 1d36ad44555e658968d4db7321a487b04f8663ba	no	2
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30	Non Patent Literature	26_20080227_REGENERON_PHARMACEUTICALS_INC_10-K_2_27.pdf	4401063 efcfc2877ac780300b7b2ccf650693f6561cd21c	no	356
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31	Non Patent Literature	27_20090226_REGENERON_PHARMACEUTICALS_INC_10-K_2_26.pdf	2215659 307c1eab4433f9f3206c01d1402a65e366b312ae	no	154
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32	Non Patent Literature	28_20110217_REGENERON_PHARMACEUTICALS_INC_10-K_2_17.pdf	2160163 109c80000aec77ed0a6720806ec6b594c75d7ffe	no	140
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33	Non Patent Literature	29_20060508_REGENERON_PHARMACEUTICALS_INC_10-Q_5_8.pdf	782001 b96b3314981058716fb91ce50f9a40d6c5a88f97	no	55
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34	Non Patent Literature	30_20060808_Regeneron_10-Q.pdf	877073 6cf6aece8fcecda40bb3b9fb5138649930 6f2d91	no	62
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35	Non Patent Literature	31_20061106_REGENERON_PHARMACEUTICALS_INC_10-Q_11_6.pdf	2058625 f68aeb73dbb29d2f29ef97c6ea5a6cfeb3c5106a	no	174
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36	Non Patent Literature	32_20070504_REGENERON_PHARMACEUTICALS_INC_10-Q_5_4.pdf	1163823 2abbef802132edbc86b12510f49f8f81ccba7cb4	no	92
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37	Non Patent Literature	33_20070803_REGENERON_PHARMACEUTICALS_INC_10-Q_8_3.pdf	938799 f19ec4b03013f5f3b41424887f37672ad2e26331	no	66
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38	Non Patent Literature	34_20090430_REGENERON_PHARMACEUTICALS_INC_10-Q_4_30.pdf	1262748 64632b48b21ea7789c60d93cd35101c4149910c9	no	87
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39	Non Patent Literature	35_20091103_REGENERON_PHARMACEUTICALS_INC_10-Q_11_3.pdf	1103949 aa3c296cb48c93420a9a1790b221d111a815e2d0	no	68
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40	Non Patent Literature	36_20100429_REGENERON_PHARMACEUTICALS_INC_10-Q_4_29.pdf	936521 aa50813d2bb1222e3968feb64585a1a802420f95	no	55
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41	Non Patent Literature	37_20100728_REGENERON_PHARMACEUTICALS_INC_10-Q_7_28.pdf	1077694 6ec041c9177b3634f12b2c16701cb8648277d6c7	no	68
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45	Non Patent Literature	41_20111027_REGENERON_PHARMACEUTICALS_INC_10-Q_10_27.pdf	1525349 d0c5f6304a774eec3a3476331522df931f0a6910	no	105
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46	Non Patent Literature	42_20060502_REGENERON_PHARMACEUTICALS_INC_8-K_5_2.pdf	192447 310adeeaab905983bf2100aec1e2165d5fbbd40f	no	9
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47	Non Patent Literature	43_20060505_REGENERON_PHARMACEUTICALS_INC_8-K_5_.pdf	203031 e0f886a457b06e9b7f97607528fff2ed6f520228	no	12
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51	Non Patent Literature	47_20071001_REGENERON_PHARMACEUTICALS_INC_8-K_10_1.pdf	193071 2e454cbdef9dd2884160a8fb42eda404a105c92a	no	9
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54	Non Patent Literature	50_20081104_REGENERON_PHARMACEUTICALS_INC_8-K_11_4.pdf	253271 77e93d891ebeacae9e58a2cacabbb2fd6cb2d355	no	15
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58	Non Patent Literature	54_20101220_REGENERON_PHARMACEUTICALS_INC_8-K_12_20.pdf	223974 89081cdf82be61fc78b9ef3d9927fa0690ebdff0	no	11
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60	Non Patent Literature	56_20110427_REGENERON_PHARMACEUTICALS_INC_8-K_4_27.pdf	222046 f69072260a594cc28178ded2d598798f2cd0e83f	no	9
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			Total Files Size (in bytes):	77103693	

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.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT		
	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicant submits herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature are also enclosed.

The publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicant would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by

any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 16 July 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 07/01/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
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REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
07/01/2020	ELECTRONIC

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

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

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

docket@bozpat.com

CORRECTED ***Notice of Allowability***	**Application No.** 16/159,282	**Applicant(s)** Yancopoulos, George D.	
	Examiner JON M LOCKARD	**Art Unit** 1647	**AIA (FITF) 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 IDS filed 31 March 2020.
   ☐ 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 32-42 (renumbered as claims 1-11, respectively) . 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 _____.
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 _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Notice of Pre-AIA or AIA Status

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

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 31 March 2020 was filed after the mailing date of the Non-Final rejection on 01 October 2019. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

EXAMINER'S COMMENT

3. The information disclosure statement (IDS) filed 31 March 2020 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax 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.

/Christine J Saoud/
Primary Examiner, Art Unit 1647

/J.L/
Examiner, Art Unit 1647
June 24, 2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7070959	2006-07-04	Papadopoulos	
	2	8092803	2012-01-10	Furfine et al.	
	3	10406226	2019-09-10	Dix et al.	
	4	10464992	2019-11-05	Furfine et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2019/0388539	2019-12-26	Dix et al.	
	2	2020/0017572	2020-01-16	Furfine et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Anti-VEGF 2019: The State of the Art" Review of Ophthalmology (published August 5, 2019)	
	2	CHATZIRALLI et al. "Intravitreal aflibercept for neovascular age-related macular degeneration in patients aged 90 years or older: 2-year visual acuity outcomes" Eye (2018) 32:1523-1529	
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	4	COOPER et al., "Increased Renal Expression of Vascular Endothelial Growth Factor (VEGF) and Its Receptor VEGFR-2 in Experimental Diabetes" Diabetes (1999) 48:2229-2239	
	5	CROLL et al., "VEGF-mediated inflammation precedes angiogenesis in adult brain" Experimental Neurology (2004) 187:388-402	
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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 citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 03/31/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	FERRARA, N. "Vascular Endothelial Growth Factor: Molecular and Biological Aspects" Advances in Organ Biology (1999) pp. 1-30	
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	11	FLYVBJERG et al., "Amelioration of Long-Term Renal Changes in Obese Type 2 Diabetic Mice by a Neutralizing Vascular Endothelial Growth Factor Antibody" Diabetes (October 2002) 51:3090-3094	
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	14	MITCHELL, Edith P. "Targeted Therapy for Metastatic Colorectal Cancer: Role of Aflibercept" Clinical Colorectal Cancer (2013) 12(2):73-85	
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	20	THURSTON, Gavin "Complementary actions of VEGF and Angiopoietin-1 on blood vessel growth and leakage" J. Anat. (2002) 200:575-580	
	21	XIA et al., "Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis" Blood (July 1, 2003) 102(1):161-168	

Examiner Signature	/JON M LOCKARD/	Date Considered	06/24/2020

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	Bayer Investor News, "VEGF Trap-Eye: New Data Confirm Successes in the Treatment of Age-related Macular Degeneration" (September 28, 2008)	
	2	Regeneron Press Release "Positive Interim Phase 2 Data Reported For VEGF Trap-Eye In Age-Related Macular Degeneration" (March 27, 2007)	
	3	Regeneron Press Release "VEGF TRAP-Eye Phase 2 Wet AMD Results Reported At Arvo Annual Meeting" (May 9, 2007)	
	4	Regeneron Press Release "Regeneron Reports Second Quarter Financial And Operating Results" (August 1, 2007)	
	5	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer Healthcare Initiate Phase 3 Global Development Program for VEGF Trap-Eye In Wet Age-Related Macular Degeneration (AMD)" (August 2, 2007)	
	6	Regeneron Press Release "Regeneron Announces Positive Primary Endpoint Results From A Phase 2 Study Of VEGF Trap-Eye In Age-Related Macular Degeneration" (October 1, 2007)	
	7	Regeneron Press Release "Regeneron Reports Fourth Quarter And Full Year 2007 Financial And Operating Results" (February 27, 2008)	
	8	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration" (April 28, 2008)	
	9	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer HealthCare Announce VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2 Study in Patients with Age-related Macular Degeneration" (August 19, 2008)	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
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				First Named Inventor	George D. Yancopoulos
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				Examiner Name	Jon McClelland Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

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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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	10	Regeneron Pharmaceuticals, Inc. "Regeneron Reports Full Year and Fourth Quarter 2008 Financial and Operating Results" (February 26, 2009)	
	11	Regeneron Pharmaceuticals, Inc. "Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion" (April 30, 2009)	
	12	Regeneron Press Release "First Patient Enrolled In Regeneron And Bayer Healthcare VEGF Trap-Eye Phase 3 Program In Central Retinal Vein Occlusion" (July 23, 2009)	
	13	Regeneron Press Release "Regeneron Schedules November 22, 2010 Teleconference And Webcast To Discuss Results Of Two Phase 3 Studies With VEGF Trap-Eye In Wet Age-Related Macular Degeneration" (November 19, 2010)	
	14	Regeneron Press Release "Regeneron And Bayer Start Phase 3 Trial To Extend Ophthalmology Research & Development Program For VEGF Trap-Eye In Asia" (January 18, 2011)	
	15	Regeneron Press Release "Regeneron To Webcast Investor Briefing On VEGF Trap-Eye Clinical Program On Sunday, February 13th At 9 Am Et" (February 9, 2011)	
	16	Regeneron Press Release "Regeneron Submits Biologics License Application To FDA For VEGF Trap-Eye For Treatment Of Wet Age-Related Macular Degeneration" (February 22, 2011)	
	17	Regeneron Press Release "Regeneron And Bayer Announce Start Of Phase 3 Clinical Program In Diabetic Macular Edema" (April 8, 2011)	
	18	Regeneron Pharmaceuticals, Inc., "FDA Grants Priority Review for VEGF Trap-Eye for the Treatment of Wet Age-Related Macular Degeneration" (April 18, 2011)	
	19	Regeneron Press Release "VEGF Trap-Eye Submitted for EU Marketing Authorization for Treatment of Wet Age-Related Macular Degeneration (June 7, 2011)"	
	20	Regeneron Pharmaceuticals, Inc., "Regeneron Announces EYLEA™ (aflibercept ophthalmic solution) Receives Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee" (June 17, 2011)	
	21	Regeneron Press Release "Regeneron Announces Clinical Presentations at ASRS 2011 Annual Meeting" (August 17, 2011)	
	22	Regeneron Pharmaceuticals, Inc., "Regeneron Announces FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration: CORRECTED (November 18, 2011)	
	23	Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer Initiate Phase 3 Clinical Program for the Treatment of Wet Age-Related Macular Degeneration in China" (November 28, 2011)	
	24	Regeneron Pharmaceuticals, Inc., "Two Year Results of Phase 3 Studies with EYLEA™ (aflibercept) Injection in wet AMD Show Sustained Improvement in Visual Acuity" (December 5, 2011)	

Examiner Signature		Date Considered	

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Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1ST REQUEST	1801	1	1300	1300
		Total in USD ($)		**1300**

Electronic Acknowledgement Receipt

EFS ID:	39875398
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	30-JUN-2020
Filing Date:	12-OCT-2018
Time Stamp:	17:44:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1300
RAM confirmation Number	E20206TH44495830
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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 Continued Examination (RCE)	0725US05_2020-06-30_RCE_Transmittal.pdf	1352000 fbe72c4d1a7162a2001ef7e2acffdbcdcded8709	no	3
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Information:					
2		0725US05_2020-06-30_Pre_Amend.pdf	38519 590e8dc52c4bfe45e18b7ff08f2bab9ac8bf3398	yes	5

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	5

Warnings:					
Information:					
3	Transmittal Letter	0725US05_2020-06-30_Supp_IDS_trans_REGN-008CIPCON4.pdf	50766 7cc95ccb01a190f408ac5f92e2ddbbb31794d95e	no	2
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Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	0725US05__2020-06-30_Supp_IDS_SB08A_REGN-008CIPCON4.pdf	36089 5d83e275b04c9ec6f11044b9f482ac6739f27d5f	no	2
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5	Non Patent Literature	BayerNews_20080928_0448_en.pdf	127802 6d6478579d4b400aca428b8b3a577d4030031a53	no	5
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6	Non Patent Literature	REGN_Press_Release_Mar_27_2007.pdf	1360202 986d7edd7cdd3899ced99c0603f9540b36f32357	no	2
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7	Non Patent Literature	REGN_Press_Release_May_9_2007.pdf	1348579 4aea4c46411524118a56a126ad8880d5628dc9d1	no	2
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11	Non Patent Literature	REGN_Press_Release_Feb_27_2008.pdf	3789068 585e6714db309793c0e0f1d5dd74666c3615a379	no	6
Warnings:					
Information:					

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13	Non Patent Literature	REGN_Press_Release_Aug_19_2008.pdf	23293 5d13932b21799c081aff58b6fa4fc0a8e6b4b825	no	2
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Information:					
14	Non Patent Literature	REGN_Press_Release_Feb_26_2009.pdf	3449787 c5f91432559098f3ad1fb2789fde8c0fd873e91e	no	5
Warnings:					
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16	Non Patent Literature	REGN_Press_Release_Jul_23_2009.pdf	1070186 5d38c7318355bbb4bd99263a4d5c178ce9c0eb36	no	2
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17	Non Patent Literature	REGN_Press_Release_Nov_19_2010.pdf	350695 b241755a11b1083bf843f27bbf27849ece1d60a6	no	1
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18	Non Patent Literature	REGN_Press_Release_Jan_18_2011.pdf	1765835 834d1807fb38ebe24b62e6859d6c78251db8b218	no	3
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19	Non Patent Literature	REGN_Press_Release_Feb_9_2011.pdf	1371797 aab4ca6426678222de6ccf81389495a08d533ce5	no	2
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20	Non Patent Literature	REGN_Press_Release_Feb_22_2011.pdf	110830 1c15ab6a0cda244ad867d79f5839abc72511f8963	no	6
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21	Non Patent Literature	REGN_Press_Release_Apr_8_2011.pdf	1480611 a13f642ce8b29401bd55e0d61db1de29d171f413	no	2
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23	Non Patent Literature	REGN_Press_Release_Jun_7_2011.pdf	1463628 41e6c89cfa55d29dff0736ab0e82cebfbec32dea	no	2
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24	Non Patent Literature	REGN_Press_Release_Jun_17_2011.pdf	19498 afef5a7b39b651100449db5b31c908297f673434	no	2
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26	Non Patent Literature	REGN_Press_Release_Nov_18_2011.pdf	19527 8864153c02303fe0f6969e05c4cf59b74582f9f3	no	2
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Information:					
27	Non Patent Literature	REGN_Press_Release_Nov_28_2011.pdf	27840 42379aa75f28abacc9ffca7fea7a138a3fcd374f	no	3
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Information:					
28	Non Patent Literature	REGN_Press_Release_Dec_5_2011.pdf	32377 cc45cb0792fb752a70ed96149f7f07e1638ad13f	no	3
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Information:					
29	Fee Worksheet (SB06)	fee-info.pdf	30829 1b6543069ce24d87dc4f008d806b9820ce874237	no	2
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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.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16159282	Filing Date	2018-10-12	Docket Number (if applicable)	REGN-008CIPCON4	Art Unit	1647
First Named Inventor	George D. Yancopoulos			Examiner Name	Jon Lockard		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☑ Enclosed

- ☑ Amendment/Reply
- ☑ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☑ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 500815

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

✓ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Signature of Registered U.S. Patent Practitioner			
Signature	/Karl Bozicevic, Reg. No. 28,807/	Date (YYYY-MM-DD)	2020-06-30
Name	Karl Bozicevic	Registration Number	28807

This collection of information is required by 37 CFR 1.114. 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.

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

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronically filed		
PRELIMINARY AMENDMENT UNDER 37 C.F.R. §1.115	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
	Examiner Name	Jon McClelland Lockard
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This Preliminary Amendment is being submitted concurrently with a Request for Continued Examination (RCE). In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

1. - 31. (**Canceled**)

32. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by

one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.

33. (Previously Presented) The method of claim 32, wherein the VEGF antagonist is aflibercept.

34. (Previously Presented) The method of claim 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

35. (Previously Presented) The method of claim 34, wherein the intraocular administration is intravitreal administration.

36. (Previously Presented) The method of claim 35, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

37. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

38. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

Petitioner Fresenius Ex. 1002, 0148

39. (Previously Presented) The method of claim 36, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

40. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.

41. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.

42. (Previously Presented) The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.

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REMARKS

FORMAL MATTERS

Claims 32-42 are pending in this application

Claims 1-31 were previously cancelled.

No claims are amended.

No new matter is added.

ALLOWED CLAIMS

The claims that are pending here and shown above are identical to the claims that were allowed in the Notice of Allowance dated April 1, 2020.

This request for continued examination is filed for the purpose of citing additional publications in an IDS and thereby fully complying with Applicant's duty of disclosure.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2*

Applicant hereby advises the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2017 as U.S. Patent No. 9,669,069.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,681.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which a Request for Continued Examination was filed on June 30, 2020.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/397,267, filed April 29, 2019 for which an Office Action was mailed on May 12, 2020.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

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*This Statement is not an admission that any of the listed patents/applications are relevant to the instant claims.

CONCLUSION

Applicant submits that all the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 30 June 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

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Petitioner Fresenius Ex. 1002, 0151

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 30 June 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
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Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/159,282	Filing Date 10/12/2018	☐ 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 $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	06/30/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 11	Minus	** 22	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/LISA THOMAS/
*** 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.	

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

96387 7590 04/01/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/01/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	07/01/2020

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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

Petitioner Fresenius Ex. 1002, 0155

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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)

96387 7590 04/01/2020
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	07/01/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Petitioner Fresenius Ex. 1002, 0156

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.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 04/01/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/01/2020

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.

Petitioner Fresenius Ex. 1002, 0157

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 30 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. 16/159,282	Applicant(s) Yancopoulos, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

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

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

1. ☑ This communication is responsive to the Amendments filed 23 January 202 and 16 March 2020.
   ☐ 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 32-42 (renumbered as claims 1-11, respectively) . 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 _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 20200325.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Notice of Pre-AIA or AIA Status

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

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on 23 January 2020, 27 January 2020 and 21 February 2020 have been considered by the examiner.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

3. The Amendments filed 23 January 2020 and 16 March 2020 have been received and entered in full. Claim 32 has been amended, and claims 21-31 have been cancelled. Therefore, claims 32-42 are pending and the subject of this Office Action.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

5. The rejection of claims 21-31 under pre-AIA 35 U.S.C. 102(b) as set forth at pp. 3-4 of the previous Office action (mailed 01 October 2019) is moot in view of Applicant's cancellation of said claims.

6. The rejection of claims 32-42 under pre-AIA 35 U.S.C. 102(b) as set forth at pp. 2-3 of the previous Office action (01 October 2019) is withdrawn after further consideration in response to Applicant's persuasive arguments as they pertain to the disclosure of the Regeneron Press Release

Publication. There are 3 separate studies disclosed in the Press Release, and none of them teach or fairly suggest the dosing regimen recited in the instant claims.

Summary

7. Claims 32-42 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax 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.

/Christine J Saoud/
Primary Examiner, Art Unit 1647

/J.L/
Examiner, Art Unit 1647
March 25, 2020

Examiner-Initiated Interview Summary	**Application No.** 16/159,282	**Applicant(s)** Yancopoulos, George D.	
	Examiner JON M LOCKARD	**Art Unit** 1647	**AIA (FITF) Status** No

All participants (applicant, applicant's representative, PTO personnel):

(1) JON M. LOCKARD. (3) _____.

(2) KARL BOZICEVIC. (4) _____.

Date of Interview: 06 March 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☑ 102 ☐ 103 ☐ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1-32.

Identification of prior art discussed: Regeneron Press Release.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The Examiner called to discuss the amendment filed 23 January 2020 and the rejections of record. Applicant's attorney indicated that a supplemental response might possibly be filed. An agreement was not reached..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JON M LOCKARD/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	179	F	2013-01-01
C07K	/	16	/	22	I	2013-01-01
C07K	/	14	/	71	I	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2319	/	32	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/JON M LOCKARD/ Examiner, Art Unit 1647	25 March 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	27 March 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200325

Petitioner Fresenius Ex. 1002, 0164

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JON M LOCKARD/ Examiner, Art Unit 1647	25 March 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	27 March 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Petitioner Fresenius Ex. 1002, 0165

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JON M LOCKARD/ Examiner, Art Unit 1647	25 March 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	11	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	27 March 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20200325

Petitioner Fresenius Ex. 1002, 0166

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	NONE	03/29/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/29/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/29/2019	JML
PALM: Inventor search.	03/29/2019	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	09/25/2019	JML
PALM: Inventor search.	09/25/2019	JML

Petitioner Fresenius Ex. 1002, 0167

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	EAST (USPAT): See attached search history.	03/25/2020	JML
	PALM: Inventor search.	03/25/2020	JML

Petitioner Fresenius Ex. 1002, 0168

Inventor Information for 16/159282

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Grz

Search Another: Application # [ ] Search **or Patent #** [ ] Search **or International Registration #** [ ] Search

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Receipt date: 01/27/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

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	1					
	2					

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	16/055,847 – Third Party Submissions dated May 1, 2019	
	2	BROWN, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 120(10):2013-22 (October 2013)	
	3	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion: six-month primary end point results of a phase III study." Ophthalmology, 117(6):1102-1112 (June 2010)	
	4	DIXON et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" Expert Opin. Investig. Drugs, 18(10):1573-1580 (2009)	
	5	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 119(8):1658-65 (2012)	
	6	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, Issue 42, (June 2010) available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
	7	GOMEZ-MANZANO, "VEGF Trap induces antiglioma effect at different stages of disease." Neuro-Oncology, 10:940-945 (December 2008)	
	8	HEIER, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies." Ophthalmology, 123(11):2376-2385 (November 2016)	

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

Receipt date: 01/27/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973) (NOTE: May correspond to "Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**" which was cited in the Third Party Observations dated 05/01/19)	
	10	KAISER, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema." Br. J. Ophthalmol, 93(2):135-36 (February 2009)	
	11	MARGOLIS, "Hemorrhagic Recurrence Of Neovascular Age-Related Macular Degeneration Not Predicted By Spectral Domain Optical Coherence Tomography." Retinal Cases & Brief Reports, 4:1-4 (2010)	
	12	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 2003)	
	13	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCIE Study" Ophthalmology, 118(5)831-839 (2010)	
	14	SCHNICHELS, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." Br. J. Ophthalmol., 97:917-923 (2013)	
	15	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, 32(8):1556-1562 (August 2009)	
	16	SPAIDE, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." Am J Ophthalmology, 143(4):679-680 (April 2007)	
	17	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR] NOTE:** May correspond to **"**Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973)" cited by the Examiner in the Office Action dated 12/10/19 in USSN 16/055,847	
	18	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143:13-16 (October 1, 2010)	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/25/2020

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

Receipt date: 01/23/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	Yancopoulos, George D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS

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	2					

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
/J.L/	1	GUTIERREZ et al., "Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to retinal vein occlusion" Clin. Ophthalmol., 2(4):787,791 (2008)	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/25/2020

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EAST Search History

EAST Search History (Interference)

/J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2483	(flt1 or vegfr1 or (vegf adj r1)) same (flk1 or kdr or vegfr2 or (vegf adj r2))	USPAT	OR	ON	2020/03/25 23:22
L2	163	l1 same ((chimer$ or fusion) with vegf)	USPAT	OR	ON	2020/03/25 23:23
L3	823	(l1 l2) and ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2020/03/25 23:23
L4	823	l1 and ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2020/03/25 23:24
L5	66	l2 and ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2020/03/25 23:24
L6	155	yancopoulos-g$.in.	USPAT	OR	ON	2020/03/25 23:24
L7	30	l1 and l6	USPAT	OR	ON	2020/03/25 23:25
L8	7	l7 and (eye ocular macular).clm.	USPAT	OR	ON	2020/03/25 23:25

3/25/2020 11:25:28 PM
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Petitioner Fresenius Ex. 1002, 0173

Receipt date: 02/21/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	4	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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U.S. PATENT APPLICATION PUBLICATIONS

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	1					
	2					

NON PATENT LITERATURE DOCUMENTS

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	2	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01252011_27433.1)	
	3	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01262012_27428.1)	
	4	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01302013_27423.1)	

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 02/21/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	4	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	5	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02092010_27442.1)	
	6	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02202012_27427.1)	
	7	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_03162010_27441.1)	
	8	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04082011_27432.1)	
	9	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04162010_27440.1)	
	10	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_06232011_27431.1)	
	11	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_07222010_27439.1)	
	12	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08252010_27438.1)	
	13	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08262010_27437.1)	

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				Examiner Name	Jon M. Lockard
Sheet	3	of	4	Attorney Docket Number	REGN-008CIPCON4

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	14	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09082010_27436.1)	
	15	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09192011_27430.1)	
	16	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10042010_27435.1)	
	17	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10232012_27426.1)	
	18	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10272013_27422.1)	
	19	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11012010_27434.1)	
	20	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11132009_27444.1)	
	21	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11292011_27429.1)	
	22	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12182012_27425.1)	

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				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	4	of	4	Attorney Docket Number	REGN-008CIPCON4

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	23	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12212010_27443.1)	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/25/2020

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7070959	2006-07-04	Papadopoulos	
	2	8092803	2012-01-10	Furfine et al.	
	3	10406226	2019-09-10	Dix et al.	
	4	10464992	2019-11-05	Furfine et al.	

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2019/0388539	2019-12-26	Dix et al.	
	2	2020/0017572	2020-01-16	Furfine et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Anti-VEGF 2019: The State of the Art" Review of Ophthalmology (published August 5, 2019)	
	2	CHATZIRALLI et al. "Intravitreal aflibercept for neovascular age-related macular degeneration in patients aged 90 years or older: 2-year visual acuity outcomes" Eye (2018) 32:1523-1529	
	3	CHUNG et al. "Ziv-aflibercept: A novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer" Am J Heath-Syst Pharm (November 1, 2013) 70:1887-1896	
	4	COOPER et al., "Increased Renal Expression of Vascular Endothelial Growth Factor (VEGF) and Its Receptor VEGFR-2 in Experimental Diabetes" Diabetes (1999) 48:2229-2239	
	5	CROLL et al., "VEGF-mediated inflammation precedes angiogenesis in adult brain" Experimental Neurology (2004) 187:388-402	
	6	DeVRIESE et al., "Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes" J. Am. Soc. Nephrol (2001) 12:993-1000	
	7	EREMINA et al., "Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases" Journal of Clinical Investigation (March 2003) 111(5):707-716	
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Examiner Signature		Date Considered	

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				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

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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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	FERRARA, N. "Vascular Endothelial Growth Factor: Molecular and Biological Aspects" Advances in Organ Biology (1999) pp. 1-30	
	10	FERRARA et al., "Clinical applications of angiogenic growth factors and their inhibitors" Nature Medicine (December 1999) 5(12):1359-1364	
	11	FLYVBJERG et al., "Amelioration of Long-Term Renal Changes in Obese Type 2 Diabetic Mice by a Neutralizing Vascular Endothelial Growth Factor Antibody" Diabetes (October 2002) 51:3090-3094	
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	13	KOROBELNIK et al., "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion" American Academy of Ophthalmology (2014) 121(1):202-208	
	14	MITCHELL, Edith P. "Targeted Therapy for Metastatic Colorectal Cancer: Role of Aflibercept" Clinical Colorectal Cancer (2013) 12(2):73-85	
	15	NOGUERA-TROISE et al., "Blockade of D114 inhibits tumour growth by promoting non-productive angiogenesis" Nature (December 2006) 444:1032-1037	
	16	RUDGE et al., "VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade" PNAS (November 20, 2007) 104(47):18363-18370	
	17	SCHMIDT-ERFURTH et al., "Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration" Ophthalmology (2014) 121:193-201	
	18	SEMERARO et al., "Aflibercept in wet AMD: specific role and optimal use" Drug Design, Development and Therapy (August 2, 2013) 7:711-722	
	19	TANNOCK et al., "Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomized trial" Lancet Oncol (2013) 14:760-768	
	20	THURSTON, Gavin "Complementary actions of VEGF and Angiopoietin-1 on blood vessel growth and leakage" J. Anat. (2002) 200:575-580	
	21	XIA et al., "Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis" Blood (July 1, 2003) 102(1):161-168	

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Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	39027620
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	31-MAR-2020
Filing Date:	12-OCT-2018
Time Stamp:	20:15:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	E20203UK16083546
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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	Transmittal Letter	0725US05_2020-03-31_Supp_IDS_trans_REGN-008CIPCON4.pdf	50812 2a6b0abf9567592bf61f4ea411d46db748f55b6e	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0725US05__2020-03-31_Supp_IDS_SB08A_REGN-008CIPCON4.pdf	36424 adc8c45fff1f3cec2f127c98ea1ce5e979e750ea	no	2
Warnings:					
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3	Non Patent Literature	Anti-VEGF_2019.pdf	3877709 38be305da8c8aa0c9220de7e694de59f835d769c	no	10
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Information:					
4	Non Patent Literature	Chatziralli_2018.pdf	1099422 fa8ce24228ee66646858acc7a38e7903fd5b157f	no	7
Warnings:					
Information:					
5	Non Patent Literature	Chung_2013.pdf	218908 041564f7a01739052957d3e9faf294746cc30266	no	10
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Information:					
6	Non Patent Literature	Cooper_1999.pdf	1217098 bcf4c7b7a55190f3168a8ea18183e7372994f2d8	no	11
Warnings:					

Information:					
7	Non Patent Literature	Croll_2004.pdf	2647465 622951c3c1068cf513951f9878c58568c890ab4d	no	15
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Information:					
8	Non Patent Literature	DeVriese_2001.pdf	472800 315d7ee33b1ea94e70b3c2865ed739fbffbb6c83	no	8
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Information:					
9	Non Patent Literature	Eremina_2001.pdf	4088162 24fe6cadc852d68ab47d929eac59854d2373a3ed	no	10
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Information:					
10	Non Patent Literature	Eriksson_and_Alitalo.pdf	2081053 0a8d888a86fb2a6feed4a4cde01201eaff906a68	no	17
Warnings:					
Information:					
11	Non Patent Literature	Ferrara.pdf	3622466 ee47a2652aae7189cbb40aa871921d0fb894747e	no	30
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Information:					
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Information:					
20	Non Patent Literature	Semeraro_2013.pdf	239051 9c73e3927d9432e267858cf261f42789ddf8 ca9a	no	12
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Information:					

21	Non Patent Literature	Tannock_2013.pdf	264317 7699deca5f6f643b791e1b7f84a8b8705e664be1	no	9
Warnings:					
Information:					
22	Non Patent Literature	Thurston_2002.pdf	430961 cd5fea4cd11d72c0b3f1cd4c029ea57ddd818398	no	6
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Information:					
23	Non Patent Literature	Xia_Blood_2013.pdf	2098399 07488287a13cc7c26c9adf9542d1998a9a491e29	no	8
Warnings:					
Information:					
24	Fee Worksheet (SB06)	fee-info.pdf	30897 e2a22ed3bcc1d17598ed36d9c751e2bc4e7cb369	no	2
Warnings:					
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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 31 March 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/159,282	Filing Date 10/12/2018	☐ 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 $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	03/16/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 11	Minus	** 22	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TINA J BARDEN/
*** 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.	

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.

Electronically filed 3/16/2020		
SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. §1.111 AND INTERVIEW SUMMARY	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
	Examiner Name	Jon McClelland Lockard
Address to: Mail Stop AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This is a supplemental amendment further to applicant's amendment filed on January 23, 2020.

In addition, this is an Interview Summary reflecting the Examiner initiated telephone interview of March 6, 2020.

In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

1. - 31. (**Canceled**)

32. (**Currently Amended**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is **Flk1**~~Flt1~~, and a multimerizing component.

33. (Previously Presented) The method of claim 32, wherein the VEGF antagonist is aflibercept.

34. (Previously Presented) The method of claim 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

35. (Previously Presented) The method of claim 34, wherein the intraocular administration is intravitreal administration.

36. (Previously Presented) The method of claim 35, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

37. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

38. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

Petitioner Fresenius Ex. 1002, 0191

39. (Previously Presented) The method of claim 36, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

40. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.

41. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.

42. (Previously Presented) The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.

Petitioner Fresenius Ex. 1002, 0192

REMARKS

Formal Matters

Claims 32-42 are now pending in this application

Claims 1-21 were previously cancelled.

Claims 21-31 are cancelled by this Supplemental Amendment without prejudice. Applicant will pursue subject matter encompassed by these claims within a yet to be filed application.

Claim 32 is amended.

No new matter is added.

INTERVIEW SUMMARY

Applicant appreciates the Examiner initiated telephone interview of March 6, 2020.

During the interview, the pending claims in the response filed by applicants on January 23, 2020 were discussed.

During the interview, the Examiner requested further clarification with respect to specific claim elements of the pending independent claims with respect to the Press Release having an indicated date of September 14, 2009. The undersigned attorney indicated that he would refer to the client and provide further clarification.

CLARIFICATION ON DISTINCTIONS

Initially, Applicant points out that the "Press Release" which, on its face, displays a date of September 14, 2009, has not been shown to be prior art and the Applicant does not concede to such. In addition, Applicant notes that the cited reference neither describes nor enables the current claims.

Claims 21-31 have been cancelled without prejudice and the following comments focus on the patentability of claims 32-42 relative to the Press Release. To the extent possible, Applicant wishes to expedite prosecution of this application. To that end, it is believed that, by focusing on a single set of claims and showing distinctions between the invention encompassed by those claims and the Press Release, the application can be readily seen as allowable.

Claims 32-42 relate to a method requiring tertiary dosing administered 12 weeks after the immediately preceding dose. There is a single appearance of the words "12 weeks" within the fourth paragraph of the Press Release. However, this paragraph is referring to a " flexible, criteria-based extended PRN regimen with a dose administered at least every 12 weeks, but not more often than every four weeks". As explained in our January 23, 2020 Response, this is not a disclosure of a regimen

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having 12-week tertiary dosing as specified in the claims. Mere mention of a prospective possibility of dosing at 12 weeks does not specifically indicate or teach towards a method where 12-week dosing would be undertaken, let alone successful.

REQUESTED INTERVIEW

It is Applicant's belief that by clarifying issues via the cancellation of claims 21-31 and providing the above explanation with respect to claims 32-42, the case will be seen as in condition for allowance. However, if the Examiner requires further clarification, Applicant respectfully requests an opportunity for an additional interview to discuss distinguishing features between the claimed invention and the cited references.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2*

Applicant hereby advises the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2017 as U.S. Patent No. 9,669,069.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,681.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which an Interview Summary was filed on March 12, 2020.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/397,267, filed April 29, 2019.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

*This Statement is not an admission that any of the listed patents/applications are relevant to the instant claims.

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CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 16, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

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Facsimile: (650) 327-3231

Petitioner Fresenius Ex. 1002, 0195

Electronic Acknowledgement Receipt

EFS ID:	38872205
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	16-MAR-2020
Filing Date:	12-OCT-2018
Time Stamp:	13:43:54
Application Type:	Utility under 35 USC 111(a)

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		REGN-008CIPCON4_0725-US05_2020-03-16_Suppl_Amend_Intv_Summ.pdf	43341 5eaf4fa14e1e0be2bb373a486057dabfe2944105	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	6
Warnings:			
Information:			
	Total Files Size (in bytes):	43341	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	4	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01182013_27424.1)	
	2	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01252011_27433.1)	
	3	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01262012_27428.1)	
	4	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01302013_27423.1)	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	4	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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	5	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02092010_27442.1)	
	6	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02202012_27427.1)	
	7	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_03162010_27441.1)	
	8	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04082011_27432.1)	
	9	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04162010_27440.1)	
	10	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_06232011_27431.1)	
	11	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_07222010_27439.1)	
	12	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08252010_27438.1)	
	13	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08262010_27437.1)	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	3	of	4	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	14	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09082010_27436.1)	
	15	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09192011_27430.1)	
	16	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10042010_27435.1)	
	17	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10232012_27426.1)	
	18	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10272013_27422.1)	
	19	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11012010_27434.1)	
	20	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11132009_27444.1)	
	21	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11292011_27429.1)	
	22	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12182012_27425.1)	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	4	of	4	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	23	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12212010_27443.1)	

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.

Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	38658165
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	21-FEB-2020
Filing Date:	12-OCT-2018
Time Stamp:	15:33:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	E20202KF33511926
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	0725US05_2020-02-21_Supp_IDS_trans_REGN-008CIPCON4.pdf	50801 538fefce8204b859636c1ddd0fd00db21336b06e	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0725US05__2020-02-21_Supp_IDS_SB08A.pdf	42693 5becee681b9bcf91441c236381f96005c20a1f32	no	4
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Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	NCT01012973_01182013_27424_1a.pdf	387850 3611596cbf2c3151497ab7f1023827335e74dfd0	no	38
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Information:					
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Information:					
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Information:					
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Warnings:					

Information:					
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Warnings:					
Information:					
8	Non Patent Literature	NCT01012973_02202012_27427_1a.pdf	205076 0b34980c7a0f3e5e341d6b0c58b7346829ae9b16	no	11
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Information:					
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Information:					
10	Non Patent Literature	NCT01012973_04082011_27432_1a.pdf	202854 2b6eaff33edab7147db38435285f46f2b6befc80	no	10
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Information:					
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Information:					
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Warnings:					
Information:					

14	Non Patent Literature	NCT01012973_08252010_27438_1a.pdf	207066 582fe282007a1d7a122b245830b5a0cef56595e9	no	12
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Information:					
15	Non Patent Literature	NCT01012973_08262010_27437_1a.pdf	203139 fa7f94b3e8de7bb3ef65f3adac4d9145c4736123	no	10
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Information:					
16	Non Patent Literature	NCT01012973_09082010_27436_1a.pdf	202787 10f24e5ee4809b91556b3959a04af8002920bbf1	no	10
Warnings:					
Information:					
17	Non Patent Literature	NCT01012973_09192011_27430_1a.pdf	202833 f8c01baf26e9d562dae1246e3590022a470d2e8e	no	10
Warnings:					
Information:					
18	Non Patent Literature	NCT01012973_10042010_27435_1a.pdf	202793 947ae692be386b88631fedf064a2933898a81924	no	10
Warnings:					
Information:					
19	Non Patent Literature	NCT01012973_10232012_27426_1a.pdf	387280 baa1f57c36ac7107700b3484197711e18792a8c9	no	38
Warnings:					
Information:					
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Information:					

21	Non Patent Literature	NCT01012973_11012010_27434_1a.pdf	202609 419a169b77875f93570ffb485e599399b6d350d5	no	10
Warnings:					
Information:					
22	Non Patent Literature	NCT01012973_11132009_27444_1a.pdf	205352 2014c1892ab17afd7ae36889f0cbf4f35d3a8e28	no	12
Warnings:					
Information:					
23	Non Patent Literature	NCT01012973_11292011_27429_1a.pdf	202738 1e20bf11575dd80b56a6cc6d51744682dc430bd4	no	10
Warnings:					
Information:					
24	Non Patent Literature	NCT01012973_12182012_27425_1a.pdf	387906 1b275ad8ebcdd13b7008bbb387c8d249babeabd7	no	38
Warnings:					
Information:					
25	Non Patent Literature	NCT01012973_12212010_27443_1a.pdf	205393 69eca39829ebf95d6eadd663cc3719a86ca210b9	no	12
Warnings:					
Information:					
26	Fee Worksheet (SB06)	fee-info.pdf	30896 854588f73f025ca73624412a821a890113246f7b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	5751147	

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.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 21 February 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	16/055,847 – Third Party Submissions dated May 1, 2019	
	2	BROWN, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 120(10):2013-22 (October 2013)	
	3	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion: six-month primary end point results of a phase III study." Ophthalmology, 117(6):1102-1112 (June 2010)	
	4	DIXON et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" Expert Opin. Investig. Drugs, 18(10):1573-1580 (2009)	
	5	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 119(8):1658-65 (2012)	
	6	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, Issue 42, (June 2010) available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
	7	GOMEZ-MANZANO, "VEGF Trap induces antiglioma effect at different stages of disease." Neuro-Oncology, 10:940-945 (December 2008)	
	8	HEIER, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies." Ophthalmology, 123(11):2376-2385 (November 2016)	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973) (NOTE: May correspond to "Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**" which was cited in the Third Party Observations dated 05/01/19)	
	10	KAISER, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema." Br. J. Ophthalmol, 93(2):135-36 (February 2009)	
	11	MARGOLIS, "Hemorrhagic Recurrence Of Neovascular Age-Related Macular Degeneration Not Predicted By Spectral Domain Optical Coherence Tomography." Retinal Cases & Brief Reports, 4:1-4 (2010)	
	12	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 2003)	
	13	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCIE Study" Ophthalmology, 118(5)831-839 (2010)	
	14	SCHNICHELS, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." Br. J. Ophthalmol., 97:917-923 (2013)	
	15	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, 32(8):1556-1562 (August 2009)	
	16	SPAIDE, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." Am J Ophthalmology, 143(4):679-680 (April 2007)	
	17	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR] NOTE:** May correspond to **"**Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973)" cited by the Examiner in the Office Action dated 12/10/19 in USSN 16/055,847	
	18	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143:13-16 (October 1, 2010)	

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.

Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	38406081
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	27-JAN-2020
Filing Date:	12-OCT-2018
Time Stamp:	14:23:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	E20201QE23469168
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	0725US05_2020-01-27_Supp_IDS_trans_REGN-008CIPCON4.pdf	51298 c7512faab60f0cbb6b3cff7417a087d874cafab7	no	2
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Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0725US05__2020-01-27_Supp_IDS_SB08A.pdf	39301 7aebd0d4209d319d24aaa2d2289a97ded67cc976	no	2
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This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	16055847_third_party_observations_2019-05-01.pdf	409136 9a090cea6b91331b4bd0905bfb9aa84cf8ef8872	no	22
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Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	30896 1e2c338dd4fecfbca7dcf670d846c401547a83ae	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	1356924

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

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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.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such.

A listing of the documents is shown on enclosed Form PTO/SB/08A. All documents with the exception of documents (1), (9) and (10) in the non-patent literature were previously submitted and copies are not enclosed. These documents are being relisted on the PTO/SB/08A form to complete the NPL cite from the originally submitted version, for example, article submitted while "In Press".

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by

any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON3.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 27 January 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	Yancopoulos, George D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	GUTIERREZ et al., "Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to retinal vein occlusion" Clin. Ophthalmol., 2(4):787,791 (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.

Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
			Total in USD ($)	**200**

Electronic Acknowledgement Receipt

EFS ID:	38382518
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	23-JAN-2020
Filing Date:	12-OCT-2018
Time Stamp:	18:23:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$200
RAM confirmation Number	E20201MI23346957
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-008CIPCON4_amend_oa_2020-01-23.pdf	63193 c28b066a19b50fa3577715921750ee7b3bf25860	yes	9

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	9

Warnings:

Information:

2	Transmittal Letter	REGN-008CIPCON4_2020-01-23_Supp_IDS_trans.pdf	50854 ccfdc2651097ae7d3e74e1d77d73bd3800fa7756	no	2

Warnings:

Information:

3	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON4_2020-01-23_Supp_IDS_SB08A.pdf	23154 714326c369dff1f4fc7fbf725dbb48d8f61da5b6	no	1

Warnings:

Information:

This is not an USPTO supplied IDS fillable form

4	Non Patent Literature	Gutierrez_Clin_ophthalmol_2008.pdf	575541 34d52f2bfddcbd7b0a273c6b63255f1933b1629b	no	6

Warnings:

Information:

5	Fee Worksheet (SB06)	fee-info.pdf	31090 b2ca3580dda8cadaaf6a4817ca2a5497fad88b0b	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	743832

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.

Electronically filed 1/23/2020		
AMENDMENT UNDER 37 C.F.R. §1.111	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
Address to:	Filing Date	October 12, 2018
Mail Stop AF	Group Art Unit	1647
Commissioner for Patents	Examiner Name	Jon McClelland Lockard
P.O. Box 1450	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	
Alexandria, VA 22313-1450		

Sir:

This amendment is responsive to the Office Action dated October 1, 2019, for which a three-month period for response was given. A petition and petition fee for a one month extension of time is requested herewtih making this response timely filed on or before February 1, 2020. Accordingly, this response is timely filed.

In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

1. - 20. (**Canceled**)

21. (**Currently Amended**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes ~~**VEGF receptor, and a multimerizing component.**~~ as assessed by a physician or other qualified medical professional;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component**: and**

wherein the angiogenic eye disorder is age-related macular degeneration, retinal vein occlusion (RVO), central retinal vein occlusion, macular edema following CRVO, branch retinal vein occlusion (BRVO), diabetic macular edema (DME), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy or diabetic retinopathy.

22. (Previously Presented) The method of claim 21, wherein the VEGF antagonist is aflibercept.

23. (Previously Presented) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

24. (Previously Presented) The method of claim 23, wherein the intraocular administration is intravitreal administration.

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25. (Previously Presented) The method of claim 24, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

26. (Previously Presented) The method of claim 25, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

27. (Previously Presented) The method of claim 25, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

28. (**Canceled**)

29. (**Currently Amended**) The method of claim **[[**28**]]**<u>**25**</u> wherein the angiogenic eye disorder is age related macular degeneration.

30. (**Currently Amended**) The method of claim **[[**28**]]**<u>**25**</u> wherein the angiogenic eye disorder is diabetic retinopathy.

31. (**Currently Amended**) The method of claim **[[**28**]]**<u>**25**</u>, wherein the angiogenic eye disorder is diabetic macular edema.

32. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flt1, and a multimerizing component.

33. (Previously Presented) The method of claim 32, wherein the VEGF antagonist is

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aflibercept.

34. (Previously Presented) The method of claim 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

35. (Previously Presented) The method of claim 34, wherein the intraocular administration is intravitreal administration.

36. (Previously Presented) The method of claim 35, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

37. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

38. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

39. (Previously Presented) The method of claim 36, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

40. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.

41. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.

42. (Previously Presented) The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.

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REMARKS

Formal Matters

Claims 21-27 and 29-42 are now pending in this application

Original claims and claim 28 have been cancelled without prejudice.

Claims 21, and 29-31 have been amended.

The amendments to claim 21 are supported within the originally filed specification such as in paragraph [0026] and in previously pending now canceled claim 28.

The amendments to claims 29, 30 and 31 are formal in nature and necessitated by the cancellation of claim 28.

No new matter is added.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which a non-final Office Action was mailed December 10, 2019.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

Claim 21 Objection

Claim 21 was objected to due to the insertion of a clerical error relating to the "VEGF receptor and a multimerizing component." The term has been deleted thereby rendering the rejection moot.

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35 U.S.C. §102 Rejection

Claims 21-31 were rejected under 35 U.S.C. §102 as anticipated by Dixon et al.

The rejection is traversed as applied and as it might be applied to the presently pending claims.

Dixon does not disclose the PRN dosing as claimed and as such claims 21-31 are not anticipated by Dixon et al.

The Examiner stated that the disclosure in §§2.6.1 and 2.6.1 of Dixon *et al.* anticipated the claims which related to treatment of an angiogenic eye disorder by administering VEGF Trap every 4 weeks, then *pro re nata* (PRN) (q4w→PRN). We disagree. The claims are not anticipated by Dixon *et al.*, because the cited art does not disclose every element of the amended claims.

The Examiner was mistaken in stating that Section 2.6.1 discussed PRN dosing. Rather, the discussion in this section related to a Phase I trial of "intravenous aflibercept" and a trial wherein "The first part was a sequential cohort dose escalation study" and "In the second part, 30 patients received a single intravitreal injection of either 0.5 or 4 mg of VEGF Trap-Eye and were followed for 8 weeks". Neither of these discussions relate to PRN dosing.

Section 2.6.2 did not disclose treatment of age-related macular degeneration, retinal vein occlusion (RVO), central retinal vein occlusion, macular edema following CRVO, branch retinal vein occlusion (BRVO), diabetic macular edema (DME), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy or diabetic retinopathy. This section discussed a trial wherein "The mean age of the group was 78.2 years and all angiographic subtypes of CNV were represented at baseline". CNV was defined in the Introduction section of Dixon *et al.* as "subfoveal choroidal neovascularization".

Thus, Dixon *et al.* does not anticipate because not every element of the amended claims was disclosed. The Applicants submit that the claims are in condition for passage to allowance and earnestly solicit such action.

Claims 32-42 Rejection

Claims 32-42 were rejected under 35 U.S.C. §102 as anticipated by a press release dated September of 2009.

The rejection is traversed as applied and as it might be applied to the presently pending claims. The reference does not disclose tertiary dosing administered 12 weeks after the immediately preceding

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dose. Accordingly, the press release does not anticipate the claims and the rejection should be withdrawn.

The Examiner alleged that the September 14, 2009 Press Release (Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)) (hereinafter "Press Release") disclosed treatment of patients with VEGF Trap every 4 weeks (q4w), for one year, followed by a flexible PRN treatment regimen with doses given at least every 12 weeks but no more often than every 4 weeks. The Examiner's argument appears to suggest that the claims were inherently anticipated by the Press Release insofar as the upper limit of PRN dosing frequency, which followed the q4w component, was set at 12 weeks. The claims, however, are novel over the Press Release. The Press Release fell short of teaching the q12w dosing component.

First, the Press Release did not explicitly disclose a dosing regimen having a 12 week dosing (q12w) component. A practitioner of ordinary skill in the art would not have understood a PRN dosing regimen with 4 and 12 week limits as encompassing a q12w regimen.

Furthermore, the q12w dosing component was also not inherently disclosed in the Press Release. Though the Press Release discussed a PRN dosing regimen wherein a dose interval may extend out as far as 12 weeks, the dosages administered to patients were not necessarily this infrequent. For this reason, the Press Release was insufficient as an inherently anticipating reference.

> As pointed out in the MPEP 2112(IV),
>
> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461,1464 (Bd. Pat. App. & Inter. 1990)
> (emphasis added)

A similar issue was raised before the PTAB in *Eli Lilly Co v. LA Med. Res. Inst.*, IPR2014-00693 (2014). In this case, a dosing regimen was found novel over a patent application alleged to inherently anticipated the claims. Briefly, the claims related to treating penile tissue fibrosis or corporeal tissue fibrosis by administering a continuous long term regimen of up to 1.5 mg/kg/day of a PDE5 inhibitor for not less than 45 days. The cited art taught administering a PDE5 inhibitor "preferably daily for three or more days" and that treatment should continue as long as the patient suffers from erectile dysfunction (ED). Expert opinion stated that this could

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mean treatment for months, if not longer. The cited art further discussed a study where patients were treated "daily" for 8 or 12 weeks, but administrations were only given about 30-70% of the time. The petitioner argued that these disclosures were sufficient to anticipate the claims.

The PTAB rejected this argument pointing out that this was not sufficient to demonstrate continuous administration for at least 45 days as required by the claims. The Board pointed out that though patients may suffer from erectile dysfunction for months or longer, this "was not sufficient to demonstrate . . . an inherent description of continuous administration for at least 45 days as required by claim 1". *Eli Lilly*, p. 9. In other words, though treatment for as long as the patient suffers from ED (months or longer) may encompass 45 days, it did not necessarily encompass 45 days. The PTAB's decision, finding no anticipation, was affirmed by the Court of Appeals for the Federal Circuit. *Eli Lilly & Co. v. Los Angeles Biomed. Res. Inst at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073 (Fed. Cir. 2017).

The Press Release did not disclose each and every element of the claims and, so, the claims are novel over this art. The Applicants submit that the claims are in condition for passage to allowance and earnestly solicit such action.

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CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 23, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

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Petitioner Fresenius Ex. 1002, 0235

Electronically Filed 1/23/2020

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature where required are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☐ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☒ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 23, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/159,282	Filing Date 10/12/2018	☐ 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 $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	01/23/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 22	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/APRIL L. WALKER/
*** 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.	

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.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 10/01/2019

Regeneron - Bozicevic, Field & Francis
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REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
10/01/2019	ELECTRONIC

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

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

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

docket@bozpat.com

Office Action Summary	Application No. 16/159,282	Applicant(s) Yancopoulos, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 28 June 2019, 14 August 2019 and 15 August 2019.

☐ 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) 21-42 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) 21-42 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/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The Amendments filed 28 June 2019, 14 August 2019 and 15 August 2019 have been received and entered in full. Claims 21, 23, 28, 32-36 and 39 have been amended. Therefore, claims 21-42 are pending and the subject of this Office Action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 19 June 2019 and 18 September 2019 have been considered by the examiner.

5. The Third Party Submission under 37 CFR 1.290 has been considered by the Examiner.

Withdrawn Objections and/or Rejections

6. The objection to the Specification as set forth at pg. 2 of the previous Office action (mailed 03 April 2019) is withdrawn in view of Applicant's amendment to the Title (filed 28 June 2019).

7. The rejection of claims 21-42 on the ground of nonstatutory obviousness-type double patenting as set forth at pp. 3-8 of the previous Office action (mailed 03 April 2019) is withdrawn in view of Applicant's submission of a Terminal Disclaimer (pertaining to U.S. Patent Nos. 9,254,338, 9,669,069 and 10,130,681), and in view of Applicant's persuasive arguments as they

pertain to the rejection over U.S. Patent Nos. 7,303,746, 7,303,747, 7,306,799 and 7,521,049 (filed 28 June 2019).

Maintained and/or New Objections and/or Rejections

Claim Objections

8. Claim 21 is objected to because of the following informalities: the recitation of "VEGF receptor, and a multimerizing component" should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim(s) 21-31 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Dixon et al. (Expert Opin. Investig. Drugs 18(10):1573-1580; published Oct. 2009; cited by Applicant).

11. Dixon et al. teaches methods for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, and diabetic macular edema (See §2.6.1 and 2.6.2 at pp. 1575-1576) with the VEGF antagonist aflibercept. Dixon et al. teaches that patients received intraocular/intravitreal monthly doses of 0.5mg or 2mg for 12 weeks (0, 4, 8, 12) followed by treatment of the same dose on a PRN basis. Therefore, Dixon et al. teaches a treatment protocol of (1) a single dose of 0.5mg or 2mg at week 0, followed by 3 secondary

doses in 4-week intervals (week 4, 8 and 12); followed by tertiary doses on a PRN basis. Dixon et al. further teaches criteria for PRN basis, including visual (ETDRS letters) or anatomical (retinal thickness by OCT) outcomes (See §2.6.2 at pg. 1576). The VEGF antagonist disclosed by Dixon et al. is aflibercept, a VEGF trap which comprises immunoglobin-like (Ig) domain 2 of Flt1, Ig domain of 3 Flk1, and IgG Fc fragment as a multimerizing component (See §2.2 and §2.3 at pg. 1575).

12. Thus, the reference of Dixon et al. meets all the limitations of claims 21-31.

13. Claim(s) 32-42 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Regeneron Press Release; dated September 2009; cited by Applicant).

14. Regeneron teaches methods for treating an angiogenic eye disorder, including neovascular age-related macular degeneration with the VEGF antagonist VEGF-Trap-Eye. Regeneron also teaches VEGF Trap Eye for the treatment of diabetic macular edema and central retinal vein occlusion (See pg. 1). Regeneron teaches that patients received intraocular/intravitreal doses of 0.5mg or 2g VEGF Tap-Eye at 4-week intervals in the first year, followed by continual treatment for another year on a flexible, PRN regiment, with a dose administered at least every 12 weeks, but not more often that every 4 weeks. Therefore, Regeneron teaches treatment of AMD patients with (1) a single dose of 0.5mg or 2mg, followed by (2) secondary doses at 4-week intervals for a year, followed by (3) treatment for another year based on a flexible PRN schedule, which would include at least one tertiary dose at 12 weeks from the immediately preceding dose. The VEGF antagonist disclosed by Regeneron is VEGF Trap-Eye, which is a VEGF trap which is a VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor. As disclosed in Dixon et al. (referenced

supra), VEGF Trap Eye comprises immunoglobin-like (IG) domain 2 of Flt1, Ig domain 3 of Flk1, and IgG Fc fragment as a multimerizing component (See §2.2 and §2.3 at pg. 1575).

15. Thus, the reference of Regeneron meets all the limitations of claims 32-42.

Summary

16. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax 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.

/JON M LOCKARD/
Examiner, Art Unit 1647
September 26, 2019

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	NONE	03/29/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/29/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/29/2019	JML
PALM: Inventor search.	03/29/2019	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	09/25/2019	JML
PALM: Inventor search.	09/25/2019	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Petitioner Fresenius Ex. 1002, 0246

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

1	James A. Dixon et al., Expert Opin. Investig. Drugs (2009) 18(10):1573-1580	☐	☐
2	Regeneron Press Release dated September 14, 2009	☐	☐

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

Signature	/Michael Berry/		
Name/Print	Michael Berry	Registration Number (if applicable)	

Examiner Signature	/JON M LOCKARD/	Date Considered	09/25/2019

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 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. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Receipt date: 09/18/2019

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	Yancopoulos, George D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	**2008/0220004**	2008-09-11	Wiegand et al.	
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	BARBAZETTO, "DOSING REGIMEN AND THE FREQUENCY OF MACULAR HEMORRHAGES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH RANIBIZUMAB." Retina, 30:9, 1376-85, 2010	
	2	Bayer Investor News, "Bayer and Regeneron Start additional Phase 3 Study for VEGF Trap=Eye in Wet Age-related Macular Degeneration." May 8, 2008	
	3	BOYER, "A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration." Opthalmology, 116:9, 1731-39, September 2009.	
	4	BROWN, "Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration." N Engl J Med 355:14, 1432-44, October 5, 2006	
	5	BROWN, "Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration." Ophthalmology, 118:6, 1089-97, June 2011.	
	6	BROWN, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 2013.	
	7	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion." Ophthalmology, 2010.	
	8	CAMPOCHIARO, "Sustained Benefits from Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a phase III Study." Ophthalmology, 188:10, 2041-49, October 2011.	
	9	CSAKY, "Safety Implications of Vascular Endothelial Growh Factor Blockade for Subjects Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Therapies." Am. J. Ophthalmology, 148:5, 647-56, November 2009.	

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 09/18/2019

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	10	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 2012.	
	11	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, June 2010, available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
	12	ENGELBERT, "LONG-TERM FOLLOW-UP FOR TYPE 1 (SUBRETINAL PIGMENT EPITHELIUM) NEOVASCULARIZATION USING A MODIFIED 'TREAT AND EXTEND' DOSING REGIMENT OF INTRAVITREAL ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY." Retina, 30:9, 1368-75, 2010	
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	15	FUNG, "An Optical Coherence Tomography-Guided, Variable Dosing Regiment with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration." Am J Ophthalmology 143:4, 566-83, April 2007	
	16	GALE, "Complementary and Coordinated Roles of the VEGFs and Angiopoietins during Normal and Pathologic Vascular Formation." Cold Spring Harbor Symposia on Quantitative Biology, Volume LXVIL, pp. 267-73, 2002.	
	17	GARCIA-QUINTANILLA, "Pharmacokinetics of Intravitreal Anti-VEGF Drugs in Age-Related Macular Degeneration." Pharmaceutics, 11:365, 2019.	
	18	GOMEZ-MANZANO, "VEGF Trap induces antiglioma effect at different stages of disease." Society for Neuro-Oncology, December 2008.	
	19	GRAGOUDAS, "Pegaptanib for Neovascular Age-Related Macular Degeneration." N Engl J Med 351:27, 2805-16, December 30, 2004	
	20	HEIER, "Intravitreal Aflibercept for Diabetic Macular Edema." Ophthalmology, 2016.	
	21	Ho et al., Slides entitled CLEAR IT 2 One-Year Key Results, Retina Society 2008	
	22	KAISER, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema." Br. J. Ophthalmol, 93:2, 135-36, February 2009.	
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	24	LALWANI, "All About PrONTO: Study Yielded Good Results in AMD With Treatment Guided by OCT." Retina Today, May 2007	
	25	LALWANI, 'A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-related Macular Degeneration: Year 2 of the PrONTO Study." Am J Ophthalmology, 148:1, 43-58, July 2009.	
	26	LEVINE, "MACULAR HEMORRHAGE IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION AFTER STABILIZATION WITH ANTIANGIOGENIC THERAPY." Retina, 29:8, 1074-79, 2009.	

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	27	MARGOLIS, "HEMORRHAGIC RECURRENCE OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION NOT PREDICTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY." Retinal Cases & Brief Reports, 4:1, 2010	
	28	MASSIN, "Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study*)." Diabetes Care, 33:11, 2399-405, November 2010.	
	29	MITCHELL, "The RESTORE Study, Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema." Ophthalmology, 188:4, 615-25, April 2011.	
	30	NGUYEN, "Ranibizumab for Diabetic Macular Edema, Results from 2 Phase III Randomized Trials: RISE and RIDE." Ophthalmology, 119:4, 789-801, April 2012.	
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	32	Regeneron Press Release, "VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients With Diabetic Macular Edema." February 18, 2010	
	33	ROSENFELD, "Ranibizumab for Neovascular Age-Related Macular Degeneration." N Engl J Med, 355:14, 1419-31, October 5, 2006.	
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	35	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration." Ophthalmology, 2010.	
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	39	YANCOPOULOS, "Vascular-specific growth factors and blood vessel formation." Nature 407:242-48, September 14, 2000.	
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	41	YUNG, "moving Toward the Next Steps in Angiogenesis Therapy?" Society for Neuro-Oncology, 10:939, 2008	

Examiner Signature	/JON M LOCKARD/	Date Considered	09/25/2019

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Inventor Information for 16/159282

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Grz

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Petitioner Fresenius Ex. 1002, 0253

EAST Search History

EAST Search History (Prior Art) /J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	7578	(flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L2	1918	L1 and ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L3	781	L1 same ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L4	7397	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L5	399	L4 with ((chimer$ or fusion) with vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L6	2348	(L4 L5) and ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L7	349	(L3 L5) and ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L8	21	(L3 L5) same ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L9	460	yancopoulos-g$.in.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L10	49	L7 and L9	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46
L11	17	L10 and (eye ocular macular).clm.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/09/25 16:46

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Petitioner Fresenius Ex. 1002, 0254

Receipt date: 06/19/2019

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7303746	2007-12-04	Wiegand	
	2	7303748	2007-12-04	Wiegand	
	3	7306799	2007-12-11	Wiegand	
	4	9254338	2016-02-09	Yancopoulos	
	5	9669069	2017-06-06	Yancopoulos	
	6	10130681	2018-11-20	Yancopoulos	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2006/047325	2006-03-04	Genentech, Inc.		
	2	WO 2012/097019	2012-07-19	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	BROWNING et al. "Aflibercept for age-related macular degeneration: a game-changer or quiet addition?" American Journal of Ophthalmology, Vol. 154(2):222-226 (08/01/2012)	
	2	CAMPOCHIARO et al. "Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator" Molecular Therapy, 16(4):791-799 (2008)	
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	8	KARIA, Niral, "Retinal vein occlusion: pathophysiology and treatment options" Clinical Ophthalmology, 4:809-816 (2010)	

Examiner Signature		Date Considered	

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

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	23	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**	

Examiner Signature	/JON M LOCKARD/	Date Considered	09/25/2019

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Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON4

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	1	**2008/0220004**	2008-09-11	Wiegand et al.	
	2				

FOREIGN PATENT DOCUMENTS

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				First Named Inventor	Yancopoulos, George D.
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	11	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, June 2010, available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
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	27	MARGOLIS, "HEMORRHAGIC RECURRENCE OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION NOT PREDICTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY." Retinal Cases & Brief Reports, 4:1, 2010	
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Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	37202638
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	18-SEP-2019
Filing Date:	12-OCT-2018
Time Stamp:	15:26:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	E20199HF26377714
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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	Transmittal Letter	REGN-008CIPCON4_2091-09-18_Supp_IDS_trans.pdf	52264 571da79e8273088ccb2497f87e29b4f491c6544a	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON4_2019-09-18_IDS_SB08A.pdf	49094 fa7b474fdc66580a5f9fef6578273c137be2085b	no	3
Warnings:					
Information:					
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3	Fee Worksheet (SB06)	fee-info.pdf	30896 e46fad2d359d010e408b3a10300ee768021c4a86	no	2
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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.

Electronically Filed 9/18/2019

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature where required are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

All of the references identified herein were disclosed in parent application serial number 16/055,847, and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by

any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 18, 2019

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
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Electronically filed 8/15/2019		
SECOND SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. §1.111	Attorney Docket No.	REGN-008CIPCON4
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	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This second supplemental amendment is further to the Supplemental Amendment filed on August 14, 2019 and further to the Amendment Filed June 28, 2019, and is responsive to the Non-Final Office Action dated April 3, 2019, for which a three-month period for response was given. In view of the previously filed response, no extension of time is believed to be necessary. However, if the patent office determines the need for an extension, applicants petition for any required extension and authorize the cost of such petition to be charged to our deposit account 500815.

Amendments to the Claims are shown on page 2 of this document.

Remarks/Arguments begin on page 5 of this document.

AMENDMENTS TO THE CLAIMS

1. - 20. (**Canceled**)

21. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient
a single initial dose of a VEGF antagonist, followed by
one or more secondary doses of the VEGF antagonist, followed by
one or more tertiary doses of the VEGF antagonist;
wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes
VEGF receptor, and a multimerizing component.
as assessed by a physician or other qualified medical professional;
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.

22. (Previously Presented) The method of claim 21, wherein the VEGF antagonist is aflibercept.

23. (Previously Presented) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

24. (Previously Presented) The method of claim 23, wherein the intraocular administration is intravitreal administration.

25. (Previously Presented) The method of claim 24, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

26. (Previously Presented) The method of claim 25, wherein all doses of the VEGF

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antagonist comprise 0.5 mg of the VEGF antagonist.

27. (Previously Presented) The method of claim 25, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

28. (**Currently Amended**) The method of claim **25**~~27~~, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

29. (Previously Presented) The method of claim 28 wherein the angiogenic eye disorder is age related macular degeneration.

30. (Previously Presented) The method of claim 28 wherein the angiogenic eye disorder is diabetic retinopathy.

31. (Previously Presented) The method of claim 28, wherein the angiogenic eye disorder is diabetic macular edema.

32. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient
a single initial dose of a VEGF antagonist, followed by
one or more secondary doses of the VEGF antagonist, followed by
one or more tertiary doses of the VEGF antagonist;
wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising
an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flt1, and a multimerizing component.

33. (Previously Presented) The method of claim 32, wherein the VEGF antagonist is

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aflibercept.

34. (Previously Presented) The method of claim 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

35. (Previously Presented) The method of claim 34, wherein the intraocular administration is intravitreal administration.

36. (Previously Presented) The method of claim 35, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

37. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

38. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

39. (**Currently Amended**) The method of claim **<u>36</u>**~~38~~, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

40. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.

41. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.

42. (Previously Presented) The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.

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REMARKS

Formal Matters

Claims 21-42 are now pending in this application

Claims 1-20 were previously cancelled without prejudice.

Claims 28 and 39 are amended to correct an error in claim dependency.

No claims are added.

No new matter is added.

Double Patenting Rejection

All the claims were rejected on the grounds of non-statutory obviousness type-double patenting.

The claims were rejected over seven different patents. Applicants respond hereby dividing the patents into two groups.

The first group includes U.S. Patents 7,303,746; 7,303,747; 7,306,799; and 7,521,049.

The second group includes U.S. Patents 9,254,338; 9,669,069; and 10,130,681.

Terminal Disclaimers

With respect to the patents in the second group which includes issued U.S. Patents 9,254,338; 9,669,069; and 10,130,681, Applicants do not acquiesce to the validity of the rejection. However, purely to expedite prosecution, applicants have attached hereto a Terminal Disclaimer with respect to these three patents thereby rendering the rejections moot with respect to these three patents.

Non-Obviousness

With respect to the four patents in the first group, applicants request that the rejection be reconsidered and withdrawn based on the following arguments.

DOUBLE PATENTING REJECTIONS – '746; '747; '799; AND '049 PATENTS

There are four additional obviousness type double patenting rejections.

In section 8 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-5 of issued U.S. Patent 7,303,746.

In section 9 of the Office Action, claims 1-3, 6-8, 13, 14, and 18-21 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-6 of issued U.S. Patent 7,303,747.

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In section 10 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-11 of issued U.S. Patent 7,306,799.

In section 11 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 were rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-15 of issued U.S. Patent 7,521,049.

The rejections in sections 8, 9, 10 and 11 are traversed for the reasons indicated below and as further supported by the attached **Heir et al.** publication.

NON-OBVIOUSNESS RESPONSE

None of the '746, '747, '799 or '049 patents disclose the treatment protocol of the pending claims. Thus, based on the working examples set forth in the present application, along with the endorsement of the present invention as set out in the attached peer reviewed publication, as well as the facts and reasoning provided below, the rejection should be reconsidered and withdrawn.

At the time of the invention the standard of care for the treatment of the neovascular (or wet) form of age-related macular degeneration (AMD) was to administer an antibody formulation (ranibizumab) by injection to the eye once per month (see the attached Heier et al. paper).

This treatment protocol is (1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event.

Due to all the above factors (1-5) there was a need in the art for alternative treatment protocols whereby the treatment would be carried out with less inconvenience and reduced safety risks to the patient. However, until the present invention once a month treatment remained the standard of care.

There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month. However, notwithstanding that position, any *prima facie* case of obviousness is overcome by the showing of improved unexpected results. Thus, while the rejection is citing case law (In re Aller) which

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supports the position that where the general conditions of a claim are disclosed within the prior art, it is not inventive to discover optimal ranges, the Examiner is aware that this case law is not applicable to situations where improved unexpected results are shown (MPEP 2145). Such results have been obtained and are described in the working examples of the present application and in the attached publication, portions of which are referred to below.

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

The attached Heier et al. paper published in December of 2012, and as such is not prior art with respect to the present application claiming priority to November 21, 2011.

The Heier et al. paper shows results of a protocol of the type claimed on over 2,400 patients. The protocols summarized in the Heier *et al.* paper correspond to those in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or "VEGF Trap."[1] The Heier et al. results suggest that by administering the VEGF antagonist in accordance with a dosage regimen as claimed in independent claims 21 and 32, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible. This provides enormous benefits to patients, reduces health care cost, reduces the pain and suffering of the patient, as well as the inconvenience to the patient and their family, and as such provides a major step forward in the treatment of patients suffering from angiogenic eye disorders, which is worthy of patent protection.

The attached Heier et al. article is a peer reviewed article published in "Ophthalmology" which describes the aforementioned clinical trial as follows:

> "Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4 and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were

[1] Aflibercept is a VEGF receptor-based chimeric molecule as defined in **claim 33**.

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assigned to treatment groups on the basis of predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system."

In the "primary end point analysis" section of the paper, it is indicated that the proportion of patients maintaining vision was similar among all test groups and this is dramatically shown within Figure 2. Thus, the results show that the test groups which were compared with groups receiving monthly dosing surprisingly did not obtain an inferior result. As such, the PRN treatment protocol as encompassed by the presently pending independent claim 21; and the 12 week dosing of claim 32 achieves results which would be surprisingly as good or better than the results obtained with monthly treatment.

Within the "Discussion" section of the Heier et al. paper, it is noted that the group dosed every two months achieved a visual acuity score within 0.3 letters of the group treated on a monthly basis. See also the results summarized in Table 1, page 15, of the present application. Thus, it is indicated that the group which received the drug far less frequently than the monthly dosing arm achieved remarkably similar improvements without requiring the monthly monitoring and visits to the health care provider. Similar remarkable results are shown in Example 5 of the present application, which illustrates an administration regimen encompassed by claim 1 (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered as needed (PRN)) for the effective treatment of diabetic macular edema (DME). As noted at paragraph [0065] of the present specification: "the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity."

An acknowledgement of the unexpected results of the administration regimen of the present invention is echoed in the Heier et al. paper, which points out that less frequent injections should also provide an ocular safety benefit, and that using fewer injections may substantially decrease the cumulative population risk of certain adverse events which can have a considerable impact considering the millions of injections given each year. For example, Heier et al. states on page 2546, middle left column that:

"The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that

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> remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians."

Moreover, the final paragraph of the Heier et al. paper reads as follows:

> "In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events."

Based on the above, it is clear that the claimed treatment protocol provides enormous advantages to patients. Further, in view of the disadvantages of carrying out the treatment on a once per month basis, there was a need in the art for alternative treatment protocols. However, this did not occur until the present invention and as such, the claimed treatment protocol is inventive above and beyond the inventions claimed within the patents cited in the obviousness type double patenting rejection. In view of such, those rejections should be reconsidered and withdrawn.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

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The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which no actions have been mailed.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a non-final Office Action was mailed April 3, 2019.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

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Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: August 15, 2019 By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

Enclosures:
1) Terminal Disclaimer (submitted on June 28, 2019)
2) Heir et al. (submitted on June 28, 2019)

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Electronic Acknowledgement Receipt

EFS ID:	36884479
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	15-AUG-2019
Filing Date:	12-OCT-2018
Time Stamp:	13:48:29
Application Type:	Utility under 35 USC 111(a)

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		REGN-008CIPCON4_2019-08-15_second_supp_amend.pdf	77420 4a3ddcf08422be90fee86280e1173ce5ea6c8683	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	11
Warnings:			
Information:			
	Total Files Size (in bytes):	77420	

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.

Electronically filed 8/14/2019		
SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. §1.111	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
Address to: Mail Stop AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1647
	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This supplemental amendment is further to the Amendment Filed June 28, 2019, and is responsive to the Non-Final Office Action dated April 3, 2019, for which a three-month period for response was given. In view of the previously filed response, no extension of time is believed to be necessary. However, if the patent office determines the need for an extension, applicants petition for any required extension and authorize the cost of such petition to be charged to our deposit account 500815.

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one or more tertiary doses of the VEGF antagonist;
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VEGF receptor, and a multimerizing component.
as assessed by a physician or other qualified medical professional;
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor **which is Flt1** and Ig domain 3 of a second VEGF receptor **which is Flk1**, and a multimerizing component.

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26. (Previously Presented) The method of claim 25, wherein all doses of the VEGF

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antagonist comprise 0.5 mg of the VEGF antagonist.

27. (Previously Presented) The method of claim 25, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

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wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising
an immunoglobin-like (Ig) domain 2 of a first VEGF receptor **which is Flt1** and Ig domain 3 of a second VEGF receptor **which is Flt1**, and a multimerizing component.

33. (**Currently Amended**) The method of claim 32, wherein the VEGF antagonist is

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aflibercept.

34. (**Currently Amended**) The method of claim **32**~~33~~, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

35. (Previously Presented) The method of claim 34, wherein the intraocular administration is intravitreal administration.

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REMARKS

Formal Matters

Claims 21-42 are now pending in this application

Claims 1-20 were previously cancelled without prejudice.

Claims 21 and 32 are amended to clarify the VEGF as supported in paragraph [0024].

Claims 23 and 34 are amended to correct an error in claim dependency.

No claims are added.

No new matter is added.

Double Patenting Rejection

All the claims were rejected on the grounds of non-statutory obviousness type-double patenting.

The claims were rejected over seven different patents. Applicants respond hereby dividing the patents into two groups.

The first group includes U.S. Patents 7,303,746; 7,303,747; 7,306,799; and 7,521,049.

The second group includes U.S. Patents 9,254,338; 9,669,069; and 10,130,681.

Terminal Disclaimers

With respect to the patents in the second group which includes issued U.S. Patents 9,254,338; 9,669,069; and 10,130,681, Applicants do not acquiesce to the validity of the rejection. However, purely to expedite prosecution, applicants have attached hereto a Terminal Disclaimer with respect to these three patents thereby rendering the rejections moot with respect to these three patents.

Non-Obviousness

With respect to the four patents in the first group, applicants request that the rejection be reconsidered and withdrawn based on the following arguments.

DOUBLE PATENTING REJECTIONS – '746; '747; '799; AND '049 PATENTS

There are four additional obviousness type double patenting rejections.

In section 8 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-5 of issued U.S. Patent 7,303,746.

In section 9 of the Office Action, claims 1-3, 6-8, 13, 14, and 18-21 were rejected on the grounds

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of non-statutory obviousness-type double patenting over claims 1-6 of issued U.S. Patent 7,303,747.

In section 10 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-11 of issued U.S. Patent 7,306,799.

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The rejections in sections 8, 9, 10 and 11 are traversed for the reasons indicated below and as further supported by the attached **Heir et al.** publication.

NON-OBVIOUSNESS RESPONSE

None of the '746, '747, '799 or '049 patents disclose the treatment protocol of the pending claims. Thus, based on the working examples set forth in the present application, along with the endorsement of the present invention as set out in the attached peer reviewed publication, as well as the facts and reasoning provided below, the rejection should be reconsidered and withdrawn.

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There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month. However, notwithstanding that position, any *prima facie* case of obviousness is overcome by the

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showing of improved unexpected results. Thus, while the rejection is citing case law (In re Aller) which supports the position that where the general conditions of a claim are disclosed within the prior art, it is not inventive to discover optimal ranges, the Examiner is aware that this case law is not applicable to situations where improved unexpected results are shown (MPEP 2145). Such results have been obtained and are described in the working examples of the present application and in the attached publication, portions of which are referred to below.

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

The attached Heier et al. paper published in December of 2012, and as such is not prior art with respect to the present application claiming priority to November 21, 2011.

The Heier et al. paper shows results of a protocol of the type claimed on over 2,400 patients. The protocols summarized in the Heier *et al.* paper correspond to those in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or "VEGF Trap."[1] The Heier et al. results suggest that by administering the VEGF antagonist in accordance with a dosage regimen as claimed in independent claims 21 and 32, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible. This provides enormous benefits to patients, reduces health care cost, reduces the pain and suffering of the patient, as well as the inconvenience to the patient and their family, and as such provides a major step forward in the treatment of patients suffering from angiogenic eye disorders, which is worthy of patent protection.

The attached Heier et al. article is a peer reviewed article published in "Ophthalmology" which describes the aforementioned clinical trial as follows:

> "Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4 and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or

[1] Aflibercept is a VEGF receptor-based chimeric molecule as defined in **claim 33**.

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0.5mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system."

In the "primary end point analysis" section of the paper, it is indicated that the proportion of patients maintaining vision was similar among all test groups and this is dramatically shown within Figure 2. Thus, the results show that the test groups which were compared with groups receiving monthly dosing surprisingly did not obtain an inferior result. As such, the PRN treatment protocol as encompassed by the presently pending independent claim 21; and the 12 week dosing of claim 32 achieves results which would be surprisingly as good or better than the results obtained with monthly treatment.

Within the "Discussion" section of the Heier et al. paper, it is noted that the group dosed every two months achieved a visual acuity score within 0.3 letters of the group treated on a monthly basis. See also the results summarized in Table 1, page 15, of the present application. Thus, it is indicated that the group which received the drug far less frequently than the monthly dosing arm achieved remarkably similar improvements without requiring the monthly monitoring and visits to the health care provider. Similar remarkable results are shown in Example 5 of the present application, which illustrates an administration regimen encompassed by claim 1 (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered as needed (PRN)) for the effective treatment of diabetic macular edema (DME). As noted at paragraph [0065] of the present specification: "the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity."

An acknowledgement of the unexpected results of the administration regimen of the present invention is echoed in the Heier et al. paper, which points out that less frequent injections should also provide an ocular safety benefit, and that using fewer injections may substantially decrease the cumulative population risk of certain adverse events which can have a considerable impact considering the millions of injections given each year. For example, Heier et al. states on page 2546, middle left column that:

"The demonstration that monthly aflibercept provides similar efficacy and safety as the

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> current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians."

Moreover, the final paragraph of the Heier et al. paper reads as follows:

> "In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events."

Based on the above, it is clear that the claimed treatment protocol provides enormous advantages to patients. Further, in view of the disadvantages of carrying out the treatment on a once per month basis, there was a need in the art for alternative treatment protocols. However, this did not occur until the present invention and as such, the claimed treatment protocol is inventive above and beyond the inventions claimed within the patents cited in the obviousness type double patenting rejection. In view of such, those rejections should be reconsidered and withdrawn.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No.

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14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which no actions have been mailed.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a non-final Office Action was mailed April 3, 2019.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

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Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: August 14, 2019

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

Enclosures:
1) Terminal Disclaimer (submitted on June 28, 2019)
2) Heir et al. (submitted on June 28, 2019)

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Petitioner Fresenius Ex. 1002, 0289

Electronic Acknowledgement Receipt

EFS ID:	36873296
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	14-AUG-2019
Filing Date:	12-OCT-2018
Time Stamp:	16:46:01
Application Type:	Utility under 35 USC 111(a)

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		REGN-008CIPCON4_2019-08-14_supp_amend.pdf	77543 f3cf3a2194a00f6e5709aadccec3dc83052e314a	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	11
Warnings:			
Information:			
	Total Files Size (in bytes):	77543	

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.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 16/159,282 *	16/159,282	Yancopoulos, George D.	
	Examiner	Art Unit	
	LOCKARD, JON MCCLELLAND	1647	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 28 June 2019	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
/CRYSTAL QUEEN/
Technology Center: PLRC
Telephone:

PTO/SB/26 (08-11)
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.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) **REGN-008CIPCON4**

In re Application of: **Yancopoulos, George D.**

Application **16/159,282**

Filed: **October 12, 2018**

For: **Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders**

The owner, **Regeneron Pharmaceuticals, Inc.**, of **100%** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** Nos. **9,254,338; 9,669,069;** and **10,130,681** as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patents** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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

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

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

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 Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 28,807

/Karl Bozicevic, Reg. No. 28,807/ — Signature

June 28, 2019 — Date

Karl Bozicevic, Reg. No. 28,807 — Typed or printed name

650-833-7735 — Telephone Number

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

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

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

This collection of information is required by 37 CFR 1.321. 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.**

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

Electronically filed 6/28/2019		
AMENDMENT UNDER 37 C.F.R. §1.111	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
Address to:	Filing Date	October 12, 2018
Mail Stop AF	Group Art Unit	1647
Commissioner for Patents	Examiner Name	Jon McClelland Lockard
P.O. Box 1450	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	
Alexandria, VA 22313-1450		

Sir:

This amendment is responsive to the Non-Final Office Action dated April 3, 2019, for which a three-month period for response was given, making this response timely filed on or before July 3, 2019.

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

Amendments to the Claims are shown on page 3 of this document.

Remarks/Arguments begin on page 6 of this document.

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph **[0001]** of the specification as shown below

[0001] This application is a **continuation of U.S. Patent Application Serial No. 15/471,506 filed March 28, 2017, now U.S. Patent No. 10,130,681 issued November 20, 2018, which is a continuation of U.S. Patent Application Serial No. 14/972,560 filed December 17, 2015, now U.S. Patent No. 9,669,069 issued June 6, 2017, which is a continuation of U.S. Patent Application Serial No. 13/940,370 filed July 12, 2013, now U.S. Patent 9,254,338 issued February 9, 2016, which is a** continuation-in-part of International Patent Application No. PCT/US2012/020855, filed on January 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on January 13, 2011, 61/434,836, filed on January 21, 2011, and 61/561,957, filed on November 21, 2011, the contents of which are hereby incorporated by reference in their entireties.

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AMENDMENTS TO THE CLAIMS

1. - 20. (**Canceled**)

21. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient
a single initial dose of a VEGF antagonist, followed by
one or more secondary doses of the VEGF antagonist, followed by
one or more tertiary doses of the VEGF antagonist;
wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional;
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

22. (Previously Presented) The method of claim 21, wherein the VEGF antagonist is aflibercept.

23. (Previously Presented) The method of claim 22, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

24. (Previously Presented) The method of claim 23, wherein the intraocular administration is intravitreal administration.

25. (Previously Presented) The method of claim 24, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

26. (Previously Presented) The method of claim 25, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

27. (Previously Presented) The method of claim 25, wherein all doses of the VEGF

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antagonist comprise 2 mg of the VEGF antagonist.

28. (Previously Presented) The method of claim 27, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

29. (Previously Presented) The method of claim 28 wherein the angiogenic eye disorder is age related macular degeneration.

30. (Previously Presented) The method of claim 28 wherein the angiogenic eye disorder is diabetic retinopathy.

31. (Previously Presented) The method of claim 28, wherein the angiogenic eye disorder is diabetic macular edema.

32. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient
a single initial dose of a VEGF antagonist, followed by
one or more secondary doses of the VEGF antagonist, followed by
one or more tertiary doses of the VEGF antagonist;
wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising
an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

33. (**Currently Amended**) The method of claim **32**~~22~~, wherein the VEGF antagonist is aflibercept.

34. (**Currently Amended**) The method of claim **33**~~23~~, wherein all doses of the VEGF

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antagonist are administered to the patient by intraocular administration.

35. (**Currently Amended**) The method of claim **34**~~24~~, wherein the intraocular administration is intravitreal administration.

36. (**Currently Amended**) The method of claim **35**~~25~~, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

37. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

38. (Previously Presented) The method of claim 36, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

39. (Previously Presented) The method of claim 38, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

40. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.

41. (Previously Presented) The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.

42. (Previously Presented) The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.

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REMARKS

Formal Matters

Claims 21-42 are now pending in this application

Claims 1-20 were previously cancelled without prejudice.

Claims 33-36 are amended to correct an error in claim dependency.

No claims are added.

No new matter is added.

Double Patenting Rejection

All the claims were rejected on the grounds of non-statutory obviousness type-double patenting.

The claims were rejected over seven different patents. Applicants respond hereby dividing the patents into two groups.

The first group includes U.S. Patents 7,303,746; 7,303,747; 7,306,799; and 7,521,049.

The second group includes U.S. Patents 9,254,338; 9,669,069; and 10,130,681.

Terminal Disclaimers

With respect to the patents in the second group which includes issued U.S. Patents 9,254,338; 9,669,069; and 10,130,681, Applicants do not acquiesce to the validity of the rejection. However, purely to expedite prosecution, applicants have attached hereto a Terminal Disclaimer with respect to these three patents thereby rendering the rejections moot with respect to these three patents.

Non-Obviousness

With respect to the four patents in the first group, applicants request that the rejection be reconsidered and withdrawn based on the following arguments.

DOUBLE PATENTING REJECTIONS – '746; '747; '799; AND '049 PATENTS

There are four additional obviousness type double patenting rejections.

In section 8 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-5 of issued U.S. Patent 7,303,746.

In section 9 of the Office Action, claims 1-3, 6-8, 13, 14, and 18-21 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-6 of issued U.S. Patent 7,303,747.

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In section 10 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-11 of issued U.S. Patent 7,306,799.

In section 11 of the Office Action, claims 1-3, 6-8, 13, 14 and 18-21 were rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-15 of issued U.S. Patent 7,521,049.

The rejections in sections 8, 9, 10 and 11 are traversed for the reasons indicated below and as further supported by the attached **Heir et al.** publication.

NON-OBVIOUSNESS RESPONSE

None of the '746, '747, '799 or '049 patents disclose the treatment protocol of the pending claims. Thus, based on the working examples set forth in the present application, along with the endorsement of the present invention as set out in the attached peer reviewed publication, as well as the facts and reasoning provided below, the rejection should be reconsidered and withdrawn.

At the time of the invention the standard of care for the treatment of the neovascular (or wet) form of age-related macular degeneration (AMD) was to administer an antibody formulation (ranibizumab) by injection to the eye once per month (see the attached Heier et al. paper).

This treatment protocol is (1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event.

Due to all the above factors (1-5) there was a need in the art for alternative treatment protocols whereby the treatment would be carried out with less inconvenience and reduced safety risks to the patient. However, until the present invention once a month treatment remained the standard of care.

There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month. However, notwithstanding that position, any *prima facie* case of obviousness is overcome by the showing of improved unexpected results. Thus, while the rejection is citing case law (In re Aller) which

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supports the position that where the general conditions of a claim are disclosed within the prior art, it is not inventive to discover optimal ranges, the Examiner is aware that this case law is not applicable to situations where improved unexpected results are shown (MPEP 2145). Such results have been obtained and are described in the working examples of the present application and in the attached publication, portions of which are referred to below.

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

The attached Heier et al. paper published in December of 2012, and as such is not prior art with respect to the present application claiming priority to November 21, 2011.

The Heier et al. paper shows results of a protocol of the type claimed on over 2,400 patients. The protocols summarized in the Heier *et al.* paper correspond to those in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or "VEGF Trap."[1] The Heier et al. results suggest that by administering the VEGF antagonist in accordance with a dosage regimen as claimed in independent claims 21 and 32, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible. This provides enormous benefits to patients, reduces health care cost, reduces the pain and suffering of the patient, as well as the inconvenience to the patient and their family, and as such provides a major step forward in the treatment of patients suffering from angiogenic eye disorders, which is worthy of patent protection.

The attached Heier et al. article is a peer reviewed article published in "Ophthalmology" which describes the aforementioned clinical trial as follows:

> "Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4 and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were

[1] Aflibercept is a VEGF receptor-based chimeric molecule as defined in **claim 33**.

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assigned to treatment groups on the basis of predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system."

In the "primary end point analysis" section of the paper, it is indicated that the proportion of patients maintaining vision was similar among all test groups and this is dramatically shown within Figure 2. Thus, the results show that the test groups which were compared with groups receiving monthly dosing surprisingly did not obtain an inferior result. As such, the PRN treatment protocol as encompassed by the presently pending independent claim 21; and the 12 week dosing of claim 32 achieves results which would be surprisingly as good or better than the results obtained with monthly treatment.

Within the "Discussion" section of the Heier et al. paper, it is noted that the group dosed every two months achieved a visual acuity score within 0.3 letters of the group treated on a monthly basis. See also the results summarized in Table 1, page 15, of the present application. Thus, it is indicated that the group which received the drug far less frequently than the monthly dosing arm achieved remarkably similar improvements without requiring the monthly monitoring and visits to the health care provider. Similar remarkable results are shown in Example 5 of the present application, which illustrates an administration regimen encompassed by claim 1 (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered as needed (PRN)) for the effective treatment of diabetic macular edema (DME). As noted at paragraph [0065] of the present specification: "the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity."

An acknowledgement of the unexpected results of the administration regimen of the present invention is echoed in the Heier et al. paper, which points out that less frequent injections should also provide an ocular safety benefit, and that using fewer injections may substantially decrease the cumulative population risk of certain adverse events which can have a considerable impact considering the millions of injections given each year. For example, Heier et al. states on page 2546, middle left column that:

"The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that

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> remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians."

Moreover, the final paragraph of the Heier et al. paper reads as follows:

> "In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events."

Based on the above, it is clear that the claimed treatment protocol provides enormous advantages to patients. Further, in view of the disadvantages of carrying out the treatment on a once per month basis, there was a need in the art for alternative treatment protocols. However, this did not occur until the present invention and as such, the claimed treatment protocol is inventive above and beyond the inventions claimed within the patents cited in the obviousness type double patenting rejection. In view of such, those rejections should be reconsidered and withdrawn.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

Petitioner Fresenius Ex. 1002, 0303

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018 for which no actions have been mailed.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a non-final Office Action was mailed April 3, 2019.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

Petitioner Fresenius Ex. 1002, 0304

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 28, 2019

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

Enclosures:
1) Terminal Disclaimer
2) Heir et al.

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Petitioner Fresenius Ex. 1002, 0305

Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Savanna Fuentes
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt

EFS ID:	36445011
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	28-JUN-2019
Filing Date:	12-OCT-2018
Time Stamp:	14:43:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	070119INTEFSW14435500
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	REGN-008CIPCON4_Terminal_Disclaimer.pdf	24945 f04d09fe8eef60fcddf35e157a9c4d844994fc75	no	1
Warnings:					
Information:					
2	Non Patent Literature	Heier_2012.pdf	714624 e4142a2e2bb06b1ad89fce84878c9b42f4c69a0d	no	12
Warnings:					
Information:					
3		REGN-008CIPCON4_2019-06-28_amend.pdf	79465 5ada2123f3583d08bbb0d519241984da661f0cf0	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	12

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30513 2aa32144bae235b730a0f17d7a50adb623c360c2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	849547		

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
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/159,282	Filing Date 10/12/2018	☐ 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 $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	06/28/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 22	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/APRIL L. WALKER/
*** 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.	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7303746	2007-12-04	Wiegand	
	2	7303748	2007-12-04	Wiegand	
	3	7306799	2007-12-11	Wiegand	
	4	9254338	2016-02-09	Yancopoulos	
	5	9669069	2017-06-06	Yancopoulos	
	6	10130681	2018-11-20	Yancopoulos	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2006/047325	2006-03-04	Genentech, Inc.		
	2	WO 2012/097019	2012-07-19	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	BROWNING et al. "Aflibercept for age-related macular degeneration: a game-changer or quiet addition?" American Journal of Ophthalmology, Vol. 154(2):222-226 (08/01/2012)	
	2	CAMPOCHIARO et al. "Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator" Molecular Therapy, 16(4):791-799 (2008)	
	3	CAO, "A Subretinal Matrigel Rat Choroidal Neovascularization (CNV) Model and Inhibition of CNV and Associated Inflammation and Fibrosis by VEGF Trap" Investigative Ophthalmology & Visual Science, 51(11):6009- 6017 (11/2010)	
	4	EICHTEN, "Rapid decrease in tumor perfusion following VEGF blockade predicts long-term tumor growth inhibition in preclinical tumor models" Angiogenesis, 16:429-441 (2013)	
	5	HO, "VEGF Trap-Eye in Wet AMD - CLEAR-IT 2: One-Year OCT and FA Outcomes" CLEAR-IT 2 Study Group, pp 1-24 (09/28/2008)	
	6	HOLASH, "VEGF-Trap: A VEGF blocker with potent antitumor effects" PNAS 99(17)11393-11398 (8/20/2002)	
	7	HOLASH, "Inhibitors of growth factor receptors, signaling pathways and angiogenesis as therapeutic molecular agents." Cancer Metastasis 25:243-252 (2006)	
	8	KARIA, Niral, "Retinal vein occlusion: pathophysiology and treatment options" Clinical Ophthalmology, 4:809-816 (2010)	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	KUO, "Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer" PNAS 98(8):4605-4610 (04/10/2001)	
	10	Lucentis Label Title, 7 pages, 30/06/2010 **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**	
	11	OHR, "Aflibercept in wet age-related macular degeneration: a perspective review" Ther. Adv. Chronic Dis., 3(4):153-161 (2012)	
	12	PAPADPPOULOS, "Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab" Angiogenesis, 15:171-185 (2012)	
	13	REGILLO et al., "Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: OIER Study Year 1" American Journal of Ophthalmology, 145(2):239-248 (2008)	
	14	SCHNICHELS, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." Br. J. Opthalmol. (05/17/2013)	
	15	SHARMA and S. AND KAISER, P. K., Update on VEGF TRAP-Eye Clinical Trials and Retinal. Physician, 2010, Nov/Dec, p.1-6, <URL: https://www.retinalphysician.com/issues/2010/nov-dec/update-on-vegf-trap-eye-clinical-trials>	
	16	STEWART et al., "Predicted biological activity of intravitreal VEGF Trap" British Journal of Ophthalmology, 2008, vol.92, no.5, p.667-668	
	17	STEWART, "Aflibercept" Nature Reviews: Drug Discovery 11:269-270 (04/01/2012)	
	18	THURSTON, "Vascular endothelial growth factor and other signaling pathways in developmental and pathologic angiogenesis." International Journal of Hematology 80:7-20 (2004)	
	19	WACHSBERGER, "VEGF trap in combination with radiotherapy improves tumor control in u87 glioblastoma." Int. J. Radiation Oncology Biol Phys. 67(5):1526-1537 (2007)	
	20	ADSIS R&D Profile "Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye." Drugs R D, 9(4):261-269 (2008)	
	21	N/A "Materials from June 2011 FDA Committee Mtg" (06/17/2011)	
	22	N/A "Materials from Dec 2011 FDA Committee Mtg"(12/01/2011)	
	23	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**	

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.

Electronic Patent Application Fee Transmittal

Application Number:	16159282
Filing Date:	12-Oct-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	36351153
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	19-JUN-2019
Filing Date:	12-OCT-2018
Time Stamp:	17:32:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	062019INTEFSW17333000
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-008CIPCON4_2091-06-19_Supp_IDS_trans.pdf	52251 34564158542d7e3e815c1624800f1b88fdde47bc	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON4_2019-06-19_Supp_IDS_SB08A.pdf	40192 57cb81a6f12c727636754ba1e5676e63a17efc6f	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Karia_2010.pdf	1111161 9b01a58ac047d6da4342f005232e032570c9b592	no	8
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30896 1b9e5e0397f5fcab08b5bb9a569ee5580fb7b223	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1234500		

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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.

Electronically Filed 6/19/2019

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	George D. Yancopoulos
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature where required are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

All of the references identified herein were disclosed in parent application serial number 16/055/847, and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by

any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 19, 2019

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 05/31/2019

Regeneron - Bozicevic, Field & Francis
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REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/31/2019	ELECTRONIC

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

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

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

docket@bozpat.com

Petitioner Fresenius Ex. 1002, 0321

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/159,282	10/12/2018	Yancopoulos, George D.	REGN-008CIPCON4

	EXAMINER	
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065	MARIANNE C SEIDEL	
	ART UNIT	PAPER
	1600	20190529

DATE MAILED: _____

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

Commissioner for Patents

The third-party submission under 37 CFR 1.290 filed on 5/28/19 for the instant application has been determined to be compliant with 35 U.S.C. 122(e) and 37 CFR 1.290 and is being entered in the application. Please allow a few days for the submission to be visible in the Patent Application Information Retrieval (PAIR) system.

/MARIANNE C SEIDEL/
Quality Assurance Specialist, Art Unit 1600

PTO-90C (Rev.04-03)

Concise Description of Relevance

VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration

James A. Dixon et al. *Expert Opin. Investig. Drugs* (**2009**) 18(10):1573-1580 (hereafter "Dixon")

Dixon is prior art under pre-AIA §102(b) because it published more than one year before the earliest effective filing date (January 13, 2011) of U.S. Application No. 16/159,282 (hereafter "the '282 application).

U.S. Application No. 16/159,282	Relevant disclosure in Dixon
21. A method for treating an angiogenic eye disorder in a patient, said method comprising	**Dixon** is related to clinical trial results of treating neovascular age-related macular degeneration (wet AMD) with VEGF Trap-eye. Wet AMD is an angiogenic eye disorder. *See e.g.*, ***Background/p. 1573***, disclosing that aflibercept (VEGF Trap-eye) is a promising therapy for AMD by interrupting angiogenesis. *See also* the definition of "angiogenic eye disorder" in the '282 application (para. [0004]).
sequentially administering to the patient a single **initial dose** of a VEGF antagonist, followed by one or more **secondary doses** of the VEGF antagonist, followed by **one or more tertiary doses** of the VEGF antagonist;	Phase II trial ***(§2.6.2, p. 1576***) teaches that patients with CNV (subfoveal choroidal neovascularization), a subtype of AMD, received monthly dose of 0.5mg or 2mg for 12 weeks (0, 4, 8, 12) followed by treatment of the same dose on a PRN basis. Thus, DIXON teaches AMD patients being treated by (1) a **single initial dose** of 0.5mg or 2mg at **week 0**, followed by **3 secondary doses** in 4-week intervals (*i.e.*, on **week 4, 8 and 12 after the initial dose**); followed by **tertiary doses** on **PRN basis**. **Dixon** further teaches criteria for re-dosing, including basis on visual (ETDRS letters) or anatomical (retinal thickness by OCT).
wherein each secondary dose is administered **4 weeks after the immediately preceding dose**; and	
wherein each **tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional**;	
wherein the **VEGF antagonist** is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF	VEGF Trap-eye is a VEGF antagonist having key binding domains of human VEGFR-1 and -2 combined with a human

receptor, and a multimerizing component.	IgG Fc fragment. (***§2.2, p 1575***)
22. The method of claim 21, wherein the VEGF antagonist is **aflibercept**.	VEGF Trap-eye is chemically identical to aflibercept. (***§2.3, p 1575***)
23. The method of claim 22, wherein all doses of the VEGF antagonist are administered to the patient by **intraocular** administration.	Phase II trial (***§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in one eye (*i.e.*, intraocular administration). **Dixon** teaches intravitreal injection throughout.
24. The method of claim 23, wherein the intraocular administration is **intravitreal** administration.	Phase II trial (***§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in one eye (*i.e.*, intraocular administration). **Dixon** teaches intravitreal injection throughout.
25. The method of claim 24, wherein all doses of the VEGF antagonist comprise from about **0.5 mg** to about **2 mg** of the VEGF antagonist.	Phase II trial (***§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in 0.5mg or 2mg per dose.
28. The method of claim 27, wherein the angiogenic eye disorder is selected from the group consisting of: **age related macular degeneration**, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.	AMD is an angiogenic eye disorder.
29. The method of claim 28 wherein the angiogenic eye disorder is age related macular degeneration.	AMD is an angiogenic eye disorder.
30. The method of claim 28 wherein the angiogenic eye disorder is diabetic retinopathy.	VEGF Trap-Eye was used to treat diabetic retinopathy (***§2.6.1, p1575, the third paragraph***).
31. The method of claim 28, wherein the angiogenic eye disorder is diabetic macular edema.	VEGF Trap-Eye was used to treat diabetic macular edema (***§2.6.1, p1575, the fourth paragraph***).

Concise Description of Relevance

Enrollment Completed in Regeneron and Bayer HealthCare Two Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)

Regeneron Press Release dated **September 14, 2009** (hereafter "**Regeneron**")

https://newsroom.regeneron.com/static-files/661111b9-3da3-459b-b0da-c74f00ab4b32

Regeneron is prior art under pre-AIA §102(b) because it published more than one year before the earliest effective filing date (January 13, 2011) of U.S. Application No. 16/159,282 (hereafter "the '282 application."

U.S. Application No. 16/159,282	Relevant disclosure in Regeneron (with evidentiary support from Dixon)
32. A method for treating an angiogenic eye disorder in a patient, said method comprising	**Regeneron** discloses the VIEW Program, which included Phase 3 studies for treating neovascular age-related macular degeneration (wet AMD). Wet AMD is a known angiogenic eye disorder. *See also* definition of "angiogenic eye disorder" in the '282 application (para. [0004]).
sequentially administering to the patient a **single initial dose** of a VEGF antagonist, followed by **one or more secondary doses** of the VEGF antagonist, followed by **one or more tertiary doses** of the VEGF antagonist;	The VIEW Program teaches patients with wet AMD are to receive regular doses of 0.5mg or 2mg VEGF Trap-eye at 4-week intervals in the first year, followed by continued treatment for another year on a flexible, criteria-based extended PRN regimen with a dose administered ***at least every 12 weeks***, but not more often than every four weeks. Thus, **Regeneron** teaches AMD patients being treated by (1) a ***single initial dose*** of 0.5mg or 2mg, followed by (2) ***secondary doses at 4-week intervals*** for a year, followed by (3) treatment for another year based on a flexible schedule, which would include ***at least one tertiary dose at 12-week*** from the immediately preceding dose. *See also*, Example 4 of the '282 application, which tracks closely to the VIEW program. Example 4 provides the written support for the dosing regimen recited in claim 32.
wherein each secondary dose is administered **4 weeks** after the immediately preceding dose; and	
wherein each tertiary dose is administered **12 weeks** after the immediately preceding dose;	
wherein the VEGF antagonist is a receptor-	VEGF Trap-eye is an anti-VEGF agent, a soluble

based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.	VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PIGF). *See* "About VEGF Trap-Eye; *see also* evidentiary support in **Dixon**.
33. The method of claim 22*, wherein the VEGF antagonist is **aflibercept**. * *It appears that claim 32 was intended.*	VEGF Trap-eye is chemically identical to aflibercept. *See also* evidentiary support in **Dixon (*§2.3, p 1575*)**.
34. The method of claim 23*, wherein all doses of the VEGF antagonist are administered to the patient by **intraocular** administration. * *It appears that claim 33 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye "on maintaining and improving vision when dosed as an ***intravitreal*** injection…" *See* the first paragraph. Intravitreal injection is a type of intraocular administration.
35. The method of claim 23*, wherein the intraocular administration is **intravitreal** administration. * *It appears that claim 33 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye "on maintaining and improving vision when dosed as an ***intravitreal*** injection…" *See* the first paragraph of page 1.
36. The method of claim 25*, wherein all doses of the VEGF antagonist comprise from about **0.5 mg** to about **2 mg** of the VEGF antagonist. * *It appears that claim 35 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye of two dosing strengths (0.5mg and 2mg) administered on regular schedules. *See* paragraph 1 and paragraph 4 on page 1.
37. The method of claim 36, wherein all doses of the VEGF antagonist comprise **0.5 mg** of the VEGF antagonist.	
38. The method of claim 36, wherein all doses of the VEGF antagonist comprise **2 mg** of the VEGF antagonist.	
39. The method of claim 36, wherein the angiogenic eye disorder is selected from the group consisting of: **age related macular degeneration**, diabetic retinopathy, **diabetic macular edema**, **central retinal vein occlusion**, branch retinal vein occlusion, and	**Regeneron** teaches that VEGF Trap-eye is used for treating eye diseases, including wet AMD, diabetic macular edema (DME), and Central Retinal Vein Occlusion (CRVO). *See* the second paragraph on page 1.

corneal neovascularization.	
40. The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.	**Regeneron** teaches treating AMD throughout.
41. The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.	**Regeneron** teaches that the primary endpoint is evaluated using the standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart for visual acuity, suggesting that an effective therapy for treating AMD could also be used to treat diabetic retinopathy.
42. The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.	**Regeneron** teaches VEGF Trap-eye is also for treatment of diabetic macular edema. *See* the second paragraph on page 2.

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	16159282

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance

U.S. PATENT APPLICATION PUBLICATION

Cite No	Publication Number	Concise Description of Relevance

FOREIGN PATENT DOCUMENTS		
CiteNo	**Foreign Document Number**	**Concise Description of Relevance**

NON-PATENT PUBLICATIONS		
Cite No	**Reference**	**Concise Description of Relevance**
1	Regeneron Press Release dated September 14, 2009	See Attached

2	James A. Dixon et al., Expert Opin. Investig. Drugs (2009) 18(10):1573-1580	See Attached

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

1	James A. Dixon et al., Expert Opin. Investig. Drugs (2009) 18(10):1573-1580	☐	☐
2	Regeneron Press Release dated September 14, 2009	☐	☐

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

Signature	/Michael Berry/		
Name/Print	Michael Berry	Registration Number (if applicable)	

Examiner Signature		Date Considered	

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 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. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Petitioner Fresenius Ex. 1002, 0333

Electronic Acknowledgement Receipt

EFS ID:	36133892
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	
First Named Inventor/Applicant Name:	
Correspondence Address:	-
Filer:	Michael Berry
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	28-MAY-2019
Filing Date:	
Time Stamp:	18:48:57
Application Type:	

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	Non Patent Literature	Expert_Opinion_2009_Dixon.PDF	309524 2c3c83ba00e8ab387c5811f4e8a8cd525b78e5c8	no	8
Warnings:					
Information:					
2	Non Patent Literature	REGN_News_2009_9_14_General_Releases.PDF	19451 e3bd0705cfeb86d02dd060253ce18d308faa9985	no	2
Warnings:					
Information:					
3	Concise Description of Relevance	Concise_Description_of_Relevance_Dixon.pdf	126013 799231529e1c7dc8e3ca6157997f40484631c099	no	2
Warnings:					
Information:					
4	Concise Description of Relevance	Concise_Description_of_Relevance_Regeneron.pdf	129770 e0e1d202349cb183cbcc9d2d4a02388680c27991	no	3
Warnings:					
Information:					
5	Concise Description of Relevance	Concise-description-generated.pdf	29880 ae58db77ab1df26a286651d7edc3d47bd40693a5	no	3
Warnings:					
Information:					
6	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	42846 a9a51a283af49cfe20e69f4f802c10f06a583271	no	3
Warnings:					
Information:					
7	Request for Notification of Non-compliant Third-Party Submission	Third-party-notification-request.pdf	19739 7952fd2c976baa92be77b598e0026bbcd475d8a4	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	677223

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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docket@bozpat.com

Office Action Summary	Application No. 16/159,282	Applicant(s) Yancopoulos, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 12 October 2018.

☐ 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) 21-42 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) 21-42 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 12 October 2018 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/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed on 12 October 2018 has been entered in full. Claims 1-20 have been cancelled, and claims 21-42 have been added. Therefore, claims 21-42 are pending and the subject of this Office Action.

Information Disclosure Statement

3. The information disclosure statement (IDS) filed 12 December 2018 has been considered by the examiner.

Specification

4. The disclosure is objected to because of the following informalities: An updated status of the parent nonprovisional application should be included in the first sentence of the specification. Appropriate correction is suggested.

Double Patenting

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

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

6. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

7. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

8. Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 7,303,746. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '746 patent are drawn to methods for treating retinal neovascularization (an angiogenic eye

disorder), comprising administering a fusion polypeptide which comprises the amino acid sequence of SEQ ID NO:16, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component. While the '746 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

9. Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 7,303,747. Although the conflicting claims are not identical as they differ in scope, they are not patentably distinct from each other because claims 1-6 of the '747 patent are drawn to methods for treating or ameliorating an angiogenic eye disorder, including choroidal neovascularization, vascular leak, or retinal edema, comprising administering a fusion polypeptide capable of binding endothelial growth factor (VEGF) to a patient in need thereof, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO:6, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component. While the '747 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

10. Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,306,799. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-6 of the '799 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration and diabetic retinopathy, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:6, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component. While the '799 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

11. Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 7,521,049. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15 of the '049 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:23, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component. While the

'049 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

12. Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 9,254,338. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-26 of the '338 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component. While the '338 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

13. Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,669,069. Although the conflicting

claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the '069 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component. While the '069 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

14. Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 10,130,681. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the '681 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component.

While the '681 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

Summary

15. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon M. Lockard whose telephone number is (571) 272-2717. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama, can be reached on (571) 272-2911. The fax 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.

/JON M LOCKARD/
Examiner, Art Unit 1647
March 29, 2019

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/159,282	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	NONE	03/29/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/29/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/29/2019	JML
PALM: Inventor search.	03/29/2019	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Petitioner Fresenius Ex. 1002, 0347

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(FILE 'HOME' ENTERED AT 11:29:57 ON 29 MAR 2019)

FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 11:30:09 ON 29 MAR 2019

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L1          4335 S (FLT1 OR VEGFR1 OR (VEGF (W) R1)) (S) ((FLK1 OR KDR OR VEGFR2
L2            19 S L1 (S) ((CHIMER? OR FUSION) (S) VEGF)
L3            11 DUP REM L2 (8 DUPLICATES REMOVED)
L4          1722 S VEGF (W) TRAP
L5             0 S L3 (P) ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DISORDER)
L6             0 S L3 AND ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DISORDER)
L7             7 S L3 AND (EYE OR OCULAR OR RETINA? OR MACULAR)
L8           636 S L4 (P) (EYE OR OCULAR OR RETINA? OR MACULAR)
L9           392 S L4 (S) (EYE OR OCULAR OR RETINA? OR MACULAR)
                 E YANCOPOULOS G/AU
L10         1329 S E3 OR E7 OR E8
L11          100 S L4 AND L10
L12           31 S L11 AND (EYE OR OCULAR OR RETINA? OR MACULAR)
L13           38 S L7 OR L12
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EAST Search History

EAST Search History (Prior Art) /J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	7239	(flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:01
L2	1825	l1 and ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:08
L3	732	l1 same ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:08
L4	7071	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:08
L5	375	l4 with ((chimer$ or fusion) with vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:08
L6	2236	(l4 l5) and ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:08
L7	323	(l3 l5) and ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:09
L8	20	(l3 l5) same ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:09
L9	446	yancopoulos-g$.in.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:09
L10	47	l7 and l9	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:09
L11	16	l10 and (eye ocular macular).clm.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/29 11:10

3/ 29/ 2019 11:10:30 AM
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CONFIRMATION NO. 8618

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/159,282	10/12/2018 RULE	424	1647	REGN-008CIPCON4

APPLICANTS

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

INVENTORS

George D. Yancopoulos, Yorktown Heights, NY;

**** CONTINUING DATA ***************************

This application is a CON of 15/471,506 03/28/2017 PAT 10130681
which is a CON of 14/972,560 12/17/2015 PAT 9669069
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

10/23/2018

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JON MCCLELLAND LOCKARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	1	22	2

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UNITED STATES

TITLE

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

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Petitioner Fresenius Ex. 1002, 0350

Inventor Information for 16/159282

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Grz

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Petitioner Fresenius Ex. 1002, 0351

Receipt date: 12/10/2018

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7396664	2008-07-08	Daly et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	20050163798	2005-07-28	Papadopoulos et al.	
	2	20050260203	2005-11-24	Wiegand et al.	
	3	20060058234	2006-03-16	Daly et al.	
	4	20060172944	2006-08-03	Wiegand et al.	
	5	20070190058	2007-08-16	Shams	
	6	20030171320	2003-09-11	Guyer	

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Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	2	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		
	3	WO 2008/063932	2008-05-29	Genentech, Inc.		
	4	JP 2010-509369	2010-03-25	Genentech, Inc.	See WO 2008/063932 for English Equivalent	

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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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (June 2006)	
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	3	CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 21-756 MEDICAL REVIEW(S) (December 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>	
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	5	CHARLES, Steve (Guest Lecturer) "VEGF Trap Has Positive DME Data" Tenth Annual Retina Fellows Forum Jan 29 and 30, Chicago, Article Date 03/01/2010	

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.

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Receipt date: 12/10/2018

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
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				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	2	of	3	Attorney Docket Number	REGN-008CIPCON4

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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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	6	DIXON et al., "VEGF Trap-Eye for the treatment of neobascular age-related macular degeneration" Expert Opin. Investig. Drugs (2009) 18 (10): 1-8.	
	7	DO et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema" Br J Opthamol. 93(2):144-1449 (February 2009)	
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	13	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" version available and updated on 17 March 2008.	
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Examiner Signature		Date Considered	

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Receipt date: 12/10/2018

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	3	of	3	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	22	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 20013)	
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	25	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007	
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	27	Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" November 22, 2010	
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	29	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (September 28, 2008) (XP-002770952)	
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	34	WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)" Vol. 20, No. 2, 2006, pages 115-119.	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/29/2019

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4

CONFIRMATION NO. 8618

POA ACCEPTANCE LETTER

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

OC00000106691022

Date Mailed: 03/20/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/14/2019.

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**.

/sibrahim/

Petitioner Fresenius Ex. 1002, 0355

Doc Code: PA..
Document Description: Power of Attorney

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

Application Number	Filing Date
16/159,282	October 12, 2018

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OR

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

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

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OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

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

Regeneron Pharmaceuticals, Inc.

☐ Inventor or Joint Inventor (title not required below)

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

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

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

SIGNATURE of Applicant for Patent

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

Signature	/Frank R. Cottingham/	Date (Optional)	March 13, 2019
Name	Frank R. Cottingham		
Title	Executive Director, Assistant General Counsel, Patents, Regeneron Pharmaceuticals, Inc.		

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

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 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.**

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

Electronic Acknowledgement Receipt

EFS ID:	35422476
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	14-MAR-2019
Filing Date:	12-OCT-2018
Time Stamp:	13:08:19
Application Type:	Utility under 35 USC 111(a)

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	Assignee showing of ownership per 37 CFR 3.73	REGN-008CIPCON4_2019-03-14_373c.pdf	118211 51ac9a1244bbe0f61df4fd6be1f92a35680d86f0	no	3

Warnings:

Information:					
2	Power of Attorney	REGN-008CIPCON4_exec_POA_.pdf	169062 d66ac63fd083dbcb03c835c72261b1d94efa85e2	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	287273	

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/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.

Application No./Patent No.: 16/159,282 Filed/Issue Date: October 12, 2018

Titled: Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

Regeneron Pharmaceuticals, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

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 047899, Frame 0083, or for which a copy thereof is attached.

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.

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.**

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

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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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(c)(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.

/Karl Bozicevic, Reg. No. 28,807/	2019-03-14
Signature	Date
Karl Bozicevic	28,807
Printed or Typed Name	Title or Registration 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.

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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.
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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 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.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4

CONFIRMATION NO. 8618

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

PUBLICATION NOTICE

OC00000105908587

Title:USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Publication No.US-2019-0046609-A1
Publication Date:02/14/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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

Petitioner Fresenius Ex. 1002, 0362

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7396664	2008-07-08	Daly et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	20050163798	2005-07-28	Papadopoulos et al.	
	2	20050260203	2005-11-24	Wiegand et al.	
	3	20060058234	2006-03-16	Daly et al.	
	4	20060172944	2006-08-03	Wiegand et al.	
	5	20070190058	2007-08-16	Shams	
	6	20030171320	2003-09-11	Guyer	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	2	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		
	3	WO 2008/063932	2008-05-29	Genentech, Inc.		
	4	JP 2010-509369	2010-03-25	Genentech, Inc.	See WO 2008/063932 for English Equivalent	

NON PATENT LITERATURE DOCUMENTS

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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (June 2006)	
	2	Information from ClinicalTrials.gov archive View of NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" *ClinicalTrials.gov*. Web. 2010-11-30.	
	3	CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 21-756 MEDICAL REVIEW(S) (December 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>	
	4	CENTER FOR DRUG EVALUATION AND RESEARCH BLA APPLICATION NUMBER: 125156 MEDICAL REVIEW, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000_Lucentis_MedR.pdf>	
	5	CHARLES, Steve (Guest Lecturer) "VEGF Trap Has Positive DME Data" Tenth Annual Retina Fellows Forum Jan 29 and 30, Chicago, Article Date 03/01/2010	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	2	of	3	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	6	DIXON et al., "VEGF Trap-Eye for the treatment of neobascular age-related macular degeneration" Expert Opin. Investig. Drugs (2009) 18 (10): 1-8.	
	7	DO et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema" Br J Opthamol. 93(2):144-1449 (February 2009)	
	8	DO et al., "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema" Opthamology 118(9):1819-1826 (September 2011)	
	9	THE EYETECH STUDY GROUP, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration" American Academy of Ophthamology, 110(5):979-986 (May 2003)	
	10	HEIERet al., " rhuFab V2 (anti-VEGF Antibody) for Treatment of Exudative AMD" Symposium 8:Experimental and Emerging Treatments for Choroidal Neovascularization, 10 pp (2002)	
	11	HEIER et al., "RhuFab V2 in Wet AMD - 6 Month Continued Improvement Following Multiple Intravitreal Injections" Invest Ophthalmol Vis Sci, 44:E-Abstract 972 (2003)	
	12	HEIER et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012)	
	13	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" version available and updated on 17 March 2008.	
	14	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (12-01-2009)	
	15	Information from ClinicalTrials.gov archive on the view of NCT00789477 "DME and VEGF Trap-Eye: Investigation of Clinical Impact" (11-18-2010)	
	16	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (01-07-2011)	
	17	KRZYSTOLIK et al., "Prevention of Experimental Choroidal NEovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment" Arch Ophthamol., 120:338-346 (Mar. 2002)	
	18	MITRA et al., "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions" Expert Review in Ophthalmo, Taylor & Francis, GB (January 1, 2011) 6(6):623-629	
	19	MOUSA AND MOUSA, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration" Biodrugs 2010; 24(3); 183-194.	
	20	NGUYEN et al., "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" Opthamology, J.B. Lippincott Co., Philadelphia, PA, US, 116(11):2141-2148 (November 1, 2009) 116(11):2141-2148 (November 1, 2009)	
	21	NGUYEN et al., "A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration" Ophthalmology (Sept 2006) 113(9):1522e1-1522e14 (epub July 28,2006)	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Lockard, Jon McClelland
Sheet	3	of	3	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
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, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	22	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 20013)	
	23	OLIVERA et al., "VEGF Trap R1R2 suppresses experimental corneal angiogenesis" European Journal of Ophthalmology (January 1, 2010) 20(1):48-54	
	24	PAI et al., "Current concepts in intravitreal drug therapy for diabetic retinopathy" Saudi Journal of Opthamology 24(4):143-149 (June 30, 2010)	
	25	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007	
	26	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.	
	27	Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" November 22, 2010	
	28	Regeneron Press Release "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)" December 20, 2010	
	29	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (September 28, 2008) (XP-002770952)	
	30	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, Volume 32, Number 8, August 2009	
	31	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008.	
	32	STEWART, "THe expanding role of vascular endothelial growth factor inhibitors in opthamology" Mayo Clin Proc. 87(1):77-88 (January 2012)	
	33	THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 28, 2008)	
	34	WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)" Vol. 20, No. 2, 2006, pages 115-119.	

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.

Electronically Filed 12/10/2018

INFORMATION DISCLOSURE STATEMENT		
	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	GEORGE D. YANCOPOULOS
	Application Number	16/159,282
	Filing Date	October 12, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Lockard, Jon McClelland
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

All of the references identified herein were disclosed in parent application serial number 15/471,506, and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** 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; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 10, 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Electronic Acknowledgement Receipt

EFS ID:	34524078
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	10-DEC-2018
Filing Date:	12-OCT-2018
Time Stamp:	13:41:26
Application Type:	Utility under 35 USC 111(a)

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	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON4_2018-12-10_IDS_SB08A.pdf	48342 217fffd17a57b3b3fc09b9e32318e3d151cfce52	no	3

Warnings:

Information:					
This is not an USPTO supplied IDS fillable form					
2	Transmittal Letter	REGN-008CIPCON4_2018-12-10_IDS_trans.pdf	49342 031324fab0f86f8f7ec32c8e85272cca1fb8d06d	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	97684	

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/159,282	10/12/2018	1647	1920	REGN-008CIPCON4	22	2

CONFIRMATION NO. 8618

CORRECTED FILING RECEIPT

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065



Date Mailed: 11/05/2018

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

Inventor(s)

George D. Yancopoulos, Yorktown Heights, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/471,506 03/28/2017 PAT 10130681
which is a CON of 14/972,560 12/17/2015 PAT 9669069
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/23/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/159,282**

Projected Publication Date: 02/14/2019

Non-Publication Request: No

Early Publication Request: No

Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

424

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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).

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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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner Fresenius Ex. 1002, 0373

Electronically filed 10/30/2018		
REQUEST FOR CORRECTED FILING RECEIPT	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	8618
	First Named Inventor	GEORGE D. YANCOPOULOS
	Application Number	16/159,282
	Filing Date	October 12, 2018
Address to:	Group Art Unit	
Commissioner for Patents	Examiner Name	
P.O. Box 1450 Alexandria, VA 22313-1450	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

A filing receipt for the above-identified patent application has been issued by the U.S. Patent and Trademark Office (copy attached) and has been found to contain the following error(s):

(1) Please correct the "Domestic Priority data as claimed by application" to include U.S. Provisional Patent Application No. 61/432,245 as indicated on the originally filed Application Data Sheet.

If for any reason a fee is found to be necessary, the Commissioner is authorized to charge such fee to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: October 30, 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

DOCKETED
By CPATEMP1 at 4:44 am, Oct 25, 2018

RECEIVED
By CPATEMP1 at 4:44 am, Oct 25, 2018

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/159,282	10/12/2018	1629	1920	REGN-008CIPCON4	22	2

CONFIRMATION NO. 8618

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

FILING RECEIPT



Date Mailed: 10/24/2018

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

Inventor(s)

George D. Yancopoulos, Yorktown Heights, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/471,506 03/28/2017
which is a CON of 14/972,560 12/17/2015 PAT 9669069
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011
and claims benefit of 61/432,245 01/13/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/23/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/159,282**

Projected Publication Date: 01/31/2019

Non-Publication Request: No

Early Publication Request: No

Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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).

SelectUSA

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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner Fresenius Ex. 1002, 0378

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	George	D.	YANCOPOULOS	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Yorktown Heights	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

Address 1	c/o Regeneron Pharmaceuticals, Inc.
Address 2	777 Old Saw Mill River Road

City	Tarrytown	State/Province	NY
Postal Code	10591	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	96387		
Email Address	docket@bozpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS		
Attorney Docket Number	REGN-008CIPCON4	Small Entity Status Claimed	☐
Application Type			
Subject Matter			
Total Number of Drawing Sheets (if any)	1	Suggested Figure for Publication (if any)	1

Petitioner Fresenius Ex. 1002, 0379

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	96387		

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	
					Remove
Registration Number					
Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	
					Remove
Registration Number					

Additional Representative Information blocks may be generated within this form by selecting the **Add** button.

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15471506	2017-03-28

Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15471506	Continuation of	14972560	2015-12-17	9669069	2017-06-06

Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14972560	Continuation of	13940370	2013-07-12	9254338	2016-02-09

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13940370	Continuation in part of	PCT/US2012/020855	2012-01-11

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61432245	2011-01-13

Prior Application Status	Expired		Remove
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PCT/US2012/020855	Claims benefit of provisional	61434836	2011-01-21

Petitioner Fresenius Ex. 1002, 0381

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61561957	2011-11-21

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country	Filing Date (YYYY-MM-DD)	Access Code (if applicable)
	US		

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is 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 State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Petitioner Fresenius Ex. 1002, 0383

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee	◯ Legal Representative under 35 U.S.C. 117	◯ Joint Inventor
◉ Person to whom the inventor is obligated to assign.	◯ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:	

If the Applicant is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.		
Mailing Address Information For Applicant:			
Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country[i]	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Petitioner Fresenius Ex. 1002, 0384

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country i	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e. g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Karl Boziceivc/			Date (YYYY-MM-DD)	
First Name	Karl	Last Name	Bozicevic	Registration Number	28807

Additional Signature may be generated within this form by selecting the Add button.

COPY

Electronic Acknowledgement Receipt

EFS ID:	34163456
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic
Filer Authorized By:	
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	30-OCT-2018
Filing Date:	12-OCT-2018
Time Stamp:	17:24:35
Application Type:	Utility under 35 USC 111(a)

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	Request for Corrected Filing Receipt	REGN-008CIPCON4_2018-10-30_Request_CorrectOFR.pdf	913451 d0d6a768e8a4df6279043643be75202750746e03	no	13

Warnings:

Information:	
Total Files Size (in bytes):	913451

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/159,282	10/12/2018	1629	1920	REGN-008CIPCON4	22	2

CONFIRMATION NO. 8618

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

FILING RECEIPT

OC000000103287325

Date Mailed: 10/24/2018

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

Inventor(s)

George D. Yancopoulos, Yorktown Heights, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/471,506 03/28/2017
which is a CON of 14/972,560 12/17/2015 PAT 9669069
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Petitioner Fresenius Ex. 1002, 0389

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/23/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/159,282**

Projected Publication Date: 01/31/2019

Non-Publication Request: No

Early Publication Request: No

Title

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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).

SelectUSA

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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner Fresenius Ex. 1002, 0392

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/159,282

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	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	22 minus 20 =	* 2			OR	x 100 =	200
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1920

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT A	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	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	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 found in the appropriate box in column 1.

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Sequence Listing was accepted.
See attached Validation Report.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Wheat Jr, Scott (ASRC)
Timestamp: [year=2018; month=10; day=17; hr=9; min=16; sec=45; ms=788; ]
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Validated By CRFValidator v 1.0.5

Application No: 16159282 Version No: 1.0

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Output Set:

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Finished: 2018-10-12 17:30:42.469
Elapsed: 0 hr(s) 0 min(s) 0 sec(s) 87 ms
Total Warnings: 2
Total Errors: 1
No. of SeqIDs Defined: 2
Actual SeqID Count: 2

Error code		Error Description
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W	213	Artificial or Unknown found in <213> in SEQ ID (1)
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SEQUENCE LISTING

<110> George D. Yancopoulos

<120> Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

<130> 725A1

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/159,282	Filing Date 10/12/2018	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)		
	10/12/2018	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 22	Minus	** 22	= 0	X $100 =	0
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AMENDMENT	☐ Application Size Fee (37 CFR 1.16(s))						
AMENDMENT	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)		
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
AMENDMENT	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
AMENDMENT	☐ Application Size Fee (37 CFR 1.16(s))						
AMENDMENT	☐ 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
CAROLYN THOMAS

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.

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 16159282 Document Date: 10/12/2018

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

Electronically Filed

PRELIMINARY AMENDMENT Under CFR 1.115 Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-008CIPCON4
	Confirmation No.	To Be Assigned
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	October 12, 2018
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
	Title: *"Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"*	

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph [0001] on page1 of the specification to read as follows:

[0001] This application **is a continuation of U.S. Patent Application Serial No. 15/471,506, filed March 28, 2017 (now allowed) which is a continuation of U.S. Patent Application Serial No. 14/972,560, filed December 17, 2015, now U.S. Patent No. 9,669,069 issued June 6, 2017 which is a continuation of U.S. Patent Application Serial No. 13/940,370 filed July 12, 2013, now U.S. Patent No. 9,254,338 issued February 9, 2016 which** is a continuation-in-part of International Patent Application No. PCT/US2012/020855, filed on January 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on January 13, 2011, 61/434,836, filed on January 21, 2011, and 61/561,957, filed on November 21, 2011, the contents of which are hereby incorporated by reference in their entireties.

Petitioner Fresenius Ex. 1002, 0402

AMENDMENTS TO THE CLAIMS

1. - 20. (**Canceled**)

21. (**New**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient

a single initial dose of a VEGF antagonist, followed by

one or more secondary doses of the VEGF antagonist, followed by

one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

22. (**New**) The method of claim 21, wherein the VEGF antagonist is aflibercept.

23. (**New**) The method of claim 22, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

24. (**New**) The method of claim 23, wherein the intraocular administration is intravitreal administration.

25. (**New**) The method of claim 24, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

26. (**New**) The method of claim 25, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

Petitioner Fresenius Ex. 1002, 0403

27. (**New**) The method of claim 25, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

28. (**New**) The method of claim 27, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

29. (**New**) The method of claim 28 wherein the angiogenic eye disorder is age related macular degeneration.

30. (**New**) The method of claim 28 wherein the angiogenic eye disorder is diabetic retinopathy.

31. (**New**) The method of claim 28, wherein the angiogenic eye disorder is diabetic macular edema.

32. (**New**) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient

a single initial dose of a VEGF antagonist, followed by

one or more secondary doses of the VEGF antagonist, followed by

one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising

an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

33. (**New**) The method of claim 22, wherein the VEGF antagonist is aflibercept.

34. (**New**) The method of claim 23, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

Petitioner Fresenius Ex. 1002, 0404

35. (**New**) The method of claim 24, wherein the intraocular administration is intravitreal administration.

36. (**New**) The method of claim 25, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

37. (**New**) The method of claim 36, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

38. (**New**) The method of claim 36, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

39. (**New**) The method of claim 38, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

40. (**New**) The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.

41. (**New**) The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.

42. (**New**) The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.

Petitioner Fresenius Ex. 1002, 0405

REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 21-42 are pending after entry of the amendments set forth herein.

Claims 1-20 are canceled without prejudice.

Claims 21-42 are added.

Support for new claims 21-42 can be found in originally pending now canceled claims 1-20, and throughout the specification.

The specification has been amended to update the cross-reference to related application section.

No new matter has been added.

PARENT APPLICATION

The parent application has been allowed. Further, as indicated above, correspondence and support for the current claims relative to those of the parent application can be reviewed and confirmed. In the event the Examiner has any questions with respect to claim support or other issues in connection with the application, the Examiner is respectfully requested to contact the undersigned attorney at the indicated telephone number to arrange for an interview to expedite this position of this application.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention that a Notice of Allowance was mailed on July 26, 2018 in co-pending U.S. Patent Application No. 15/471,506, filed March 28, 2017.

Petitioner Fresenius Ex. 1002, 0406

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/055,847, filed August 6, 2018.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 12 October 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Registration No. 28,807

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201 Redwood Shores Parkway, Suite 200
Redwood City, California 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

Petitioner Fresenius Ex. 1002, 0407

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	George	D.	YANCOPOULOS	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Yorktown Heights	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

Address 1	c/o Regeneron Pharmaceuticals, Inc.
Address 2	777 Old Saw Mill River Road

City	Tarrytown	State/Province	NY
Postal Code	10591	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	96387		
Email Address	docket@bozpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS		
Attorney Docket Number	REGN-008CIPCON4	Small Entity Status Claimed	☐
Application Type			
Subject Matter			
Total Number of Drawing Sheets (if any)	1	Suggested Figure for Publication (if any)	1

Petitioner Fresenius Ex. 1002, 0408

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	96387		

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	Remove

Registration Number	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	Remove

Registration Number	

Additional Representative Information blocks may be generated within this form by selecting the **Add** button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15471506	2017-03-28

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15471506	Continuation of	14972560	2015-12-17	9669069	2017-06-06

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14972560	Continuation of	13940370	2013-07-12	9254338	2016-02-09

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13940370	Continuation in part of	PCT/US2012/020855	2012-01-11

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61432245	2011-01-13

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61434836	2011-01-21

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/020855	Claims benefit of provisional	61561957	2011-11-21

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country	Filing Date (YYYY-MM-DD)	Access Code (if applicable)
	US		

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

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B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee	◯ Legal Representative under 35 U.S.C. 117	◯ Joint Inventor
◉ Person to whom the inventor is obligated to assign.	◯ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:	

If the Applicant is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Applicant:

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Country[i]	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Assignee Information including Non-Applicant Assignee Information:

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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country i	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-008CIPCON4
	Application Number	
Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	

Signature:

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See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Karl Boziceivc/			Date (YYYY-MM-DD)	
First Name	Karl	Last Name	Bozicevic	Registration Number	28807

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Filer:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	2	100	200
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1920**

Electronic Acknowledgement Receipt

EFS ID:	33999315
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic
Filer Authorized By:	
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	12-OCT-2018
Filing Date:	
Time Stamp:	17:13:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1920
RAM confirmation Number	101518INTEFSW17141600
Deposit Account	
Authorized User	

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-008CIPCON4_2018-10-12_Appln_as_fld.pdf	153933 6121ec056faa53a9a0bc99105653645a20021d96	yes	24
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	21	
	Claims		22	23	
	Abstract		24	24	
Warnings:					
Information:					
2	Drawings-only black and white line drawings	REGN-008CIPCON4_Figure.pdf	105393 2d582f645d0c5d17d717e589b029a39331991bdb	no	1
Warnings:					
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Information:					
3	Oath or Declaration filed	REGN-008CIPCON4_declaration.pdf	173097 6bda7272374e6af80c8c3d8cf30d012e4657b588	no	2
Warnings:					
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4	Sequence Listing	REGN-008CIPCON4_2018-10-12_seq_list_trans.pdf	27035 586582d4708d13328608154c6c8ca1603f1c2485	no	1
Warnings:					
Information:					

5	Sequence Listing	REGN-008CIPCON4_SeqList.pdf	16691 9765d4347cf728233e41c44216cc7732d4c253dc	no	3
Warnings:					
Information:					
6		REGN-008CIPCON4_2018-10-12_pre_amend_asfld.pdf	56366 948eea3319768c5edb208a791032bc396296b0e9	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	7

Warnings:					
Information:					
7	Sequence Listing (Text File)	REGN-008CIPCON4_SeqList.txt	6076	no	-
Warnings:					
Information:					
8	Application Data Sheet	WebADS.pdf	134613 7bbbb906c993b9f53a8e5f90e680a6fdc0afd6f3	no	8
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	36643 9d649508074350d27e878e9645b1a16b8fb7cd7a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	709847		

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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.

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of International Patent Application No. PCT/US2012/020855, filed on January 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on January 13, 2011, 61/434,836, filed on January 21, 2011, and 61/561,957, filed on November 21, 2011, the contents of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention relates to the field of therapeutic treatments of eye disorders. More specifically, the invention relates to the administration of VEGF antagonists to treat eye disorders caused by or associated with angiogenesis.

BACKGROUND

[0003] Several eye disorders are associated with pathological angiogenesis. For example, the development of age-related macular degeneration (AMD) is associated with a process called choroidal neovascularization (CNV). Leakage from the CNV causes macular edema and collection of fluid beneath the macula resulting in vision loss. Diabetic macular edema (DME) is another eye disorder with an angiogenic component. DME is the most prevalent cause of moderate vision loss in patients with diabetes and is a common complication of diabetic retinopathy, a disease affecting the blood vessels of the retina. Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness. Yet another eye disorder associated with abnormal angiogenesis is central retinal vein occlusion (CRVO). CRVO is caused by obstruction of the central retinal vein that leads to a back-up of blood and fluid in the retina. The retina can also become ischemic, resulting in the growth of new, inappropriate blood vessels that can cause further vision loss and more serious complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. Thus, inhibiting the angiogenic-promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders.

[0004] FDA-approved treatments of angiogenic eye disorders such as AMD and CRVO include the administration of an anti-VEGF antibody called ranibizumab (Lucentis®, Genentech, Inc.) on a monthly basis by intravitreal injection.

[0005] Methods for treating eye disorders using VEGF antagonists are mentioned in, *e.g.*, US 7,303,746; US 7,306,799; US 7,300,563; US 7,303,748; and US 2007/0190058. Nonetheless,

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there remains a need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist to a patient over time. In particular, the methods of the invention comprise sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonists. The present inventors have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks. Thus, according to the methods of the present invention, each secondary dose of VEGF antagonist is administered 2 to 4 weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 weeks after the immediately preceding dose. An example of a dosing regimen of the present invention is shown in Figure 1. One advantage of such a dosing regimen is that, for most of the course of treatment (*i.e.*, the tertiary doses), it allows for less frequent dosing (*e.g.*, once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations throughout the entire course of treatment. (*See*, *e.g.*, prescribing information for Lucentis® [ranibizumab], Genentech, Inc.).

[0007] The methods of the present invention can be used to treat any angiogenic eye disorder, including, *e.g.*, age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, corneal neovascularization, etc.

[0008] The methods of the present invention comprise administering any VEGF antagonist to the patient. In one embodiment, the VEGF antagonist comprises one or more VEGF receptor-based chimeric molecule(s), (also referred to herein as a "VEGF-Trap" or "VEGFT"). An exemplary VEGF antagonist that can be used in the context of the present invention is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as "VEGFR1R2-FcΔC1(a)" or "aflibercept."

[0009] Various administration routes are contemplated for use in the methods of the present invention, including, *e.g.*, topical administration or intraocular administration (*e.g.*, intravitreal administration).

[0010] Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011, for the treatment of patients with neovascular (wet) age-related macular degeneration, with a recommended dose of 2 mg administered by intravitreal injection every 4

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weeks for the first three months, followed by 2 mg administered by intravitreal injection once every 8 weeks.

[0011] Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURE

[0012] Figure 1 shows an exemplary dosing regimen of the present invention. In this regimen, a single "initial dose" of VEGF antagonist ("VEGFT") is administered at the beginning of the treatment regimen (*i.e.* at "week 0"), two "secondary doses" are administered at weeks 4 and 8, respectively, and at least six "tertiary doses" are administered once every 8 weeks thereafter, *i.e.*, at weeks 16, 24, 32, 40, 48, 56, etc.).

DETAILED DESCRIPTION

[0013] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0014] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0015] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

DOSING REGIMENS

[0016] The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering to a patient multiple doses of a VEGF antagonist. As used herein, "sequentially administering" means that each dose of VEGF antagonist is administered to the patient at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of a VEGF

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antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist.

[0017] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment.

[0018] In one exemplary embodiment of the present invention, each secondary dose is administered 2 to 4 (*e.g.*, 2, 2½, 3, 3½, or 4) weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 (*e.g.*, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of VEGF antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0019] In one exemplary embodiment of the present invention, a single initial dose of a VEGF antagonist is administered to a patient on the first day of the treatment regimen (*i.e.*, at week 0), followed by two secondary doses, each administered four weeks after the immediately preceding dose (*i.e.*, at week 4 and at week 8), followed by at least 5 tertiary doses, each administered eight weeks after the immediately preceding dose (*i.e.*, at weeks 16, 24, 32, 40 and 48). The tertiary doses may continue (at intervals of 8 or more weeks) indefinitely during the course of the treatment regimen. This exemplary administration regimen is depicted graphically in Figure 1.

[0020] The methods of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of a VEGF antagonist. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0021] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 4 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered

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to the patient 8 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. For example, the present invention includes methods which comprise administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by at least 5 tertiary doses of the VEGF antagonist, wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered from 8 to 12 (*e.g.*, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12) weeks after the immediately preceding dose. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

VEGF ANTAGONISTS

[0022] The methods of the present invention comprise administering to a patient a VEGF antagonist according to specified dosing regimens. As used herein, the expression "VEGF antagonist" means any molecule that blocks, reduces or interferes with the normal biological activity of VEGF.

[0023] VEGF antagonists include molecules which interfere with the interaction between VEGF and a natural VEGF receptor, *e.g.*, molecules which bind to VEGF or a VEGF receptor and prevent or otherwise hinder the interaction between VEGF and a VEGF receptor. Specific exemplary VEGF antagonists include anti-VEGF antibodies, anti-VEGF receptor antibodies, and VEGF receptor-based chimeric molecules (also referred to herein as "VEGF-Traps").

[0024] VEGF receptor-based chimeric molecules include chimeric polypeptides which comprise two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also referred to as Flt1) and/or VEGFR2 (also referred to as Flk1 or KDR), and may also contain a multimerizing domain (*e.g.*, an Fc domain which facilitates the multimerization [*e.g.*, dimerization] of two or more chimeric polypeptides). An exemplary VEGF receptor-based chimeric molecule is a molecule referred to as VEGFR1R2-FcΔC1(a) which is encoded by the nucleic acid sequence of SEQ ID NO:1. VEGFR1R2-FcΔC1(a) comprises three components: (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acid of SEQ ID NO:2 [*i.e.*, K458] may or may not be included in the VEGF antagonist used in the methods of the invention; *see e.g.*, US Patent 7,396,664). Amino acids 1-26 of SEQ ID NO:2 are the signal sequence.

[0025] The VEGF antagonist used in the Examples set forth herein below is a dimeric molecule comprising two VEGFR1R2-FcΔC1(a) molecules and is referred to herein as "VEGFT." Additional

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VEGF receptor-based chimeric molecules which can be used in the context of the present invention are disclosed in US 7,396,664, 7,303,746 and WO 00/75319.

ANGIOGENIC EYE DISORDERS

[0026] The methods of the present invention can be used to treat any angiogenic eye disorder. The expression "angiogenic eye disorder," as used herein, means any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable using the methods of the present invention include age-related macular degeneration (*e.g.*, wet AMD, exudative AMD, etc.), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO; *e.g.*, macular edema following CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV; *e.g.*, myopic CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, and diabetic retinopathies.

PHARMACEUTICAL FORMULATIONS

[0027] The present invention includes methods in which the VEGF antagonist that is administered to the patient is contained within a pharmaceutical formulation. The pharmaceutical formulation may comprise the VEGF antagonist along with at least one inactive ingredient such as, *e.g.*, a pharmaceutically acceptable carrier. Other agents may be incorporated into the pharmaceutical composition to provide improved transfer, delivery, tolerance, and the like. The term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the antibody is administered. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa., 1975), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in the context of the methods of the present invention, provided that the VEGF antagonist is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Powell et al. PDA (1998) J Pharm Sci

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Technol. 52:238-311 and the citations therein for additional information related to excipients and carriers well known to pharmaceutical chemists.

[0028] Pharmaceutical formulations useful for administration by injection in the context of the present invention may be prepared by dissolving, suspending or emulsifying a VEGF antagonist in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there may be employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule if desired.

MODES OF ADMINISTRATION

[0029] The VEGF antagonist (or pharmaceutical formulation comprising the VEGF antagonist) may be administered to the patient by any known delivery system and/or administration method. In certain embodiments, the VEGF antagonist is administered to the patient by ocular, intraocular, intravitreal or subconjunctival injection. In other embodiments, the VEGF antagonist can be administered to the patient by topical administration, *e.g.*, via eye drops or other liquid, gel, ointment or fluid which contains the VEGF antagonist and can be applied directly to the eye. Other possible routes of administration include, *e.g.*, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral.

AMOUNT OF VEGF ANTAGONIST ADMINISTERED

[0030] Each dose of VEGF antagonist administered to the patient over the course of the treatment regimen may contain the same, or substantially the same, amount of VEGF antagonist. Alternatively, the quantity of VEGF antagonist contained within the individual doses may vary over the course of the treatment regimen. For example, in certain embodiments, a first quantity of VEGF antagonist is administered in the initial dose, a second quantity of VEGF antagonist is administered in the secondary doses, and a third quantity of VEGF antagonist is administered in the tertiary doses. The present invention contemplates dosing schemes in which the quantity of VEGF antagonist contained within the individual doses increases over time (*e.g.*, each subsequent dose contains more VEGF antagonist than the last), decreases over time (*e.g.*, each subsequent dose contains less VEGF antagonist than the last), initially increases then decreases, initially decreases then increases, or remains the same throughout the course of the administration regimen.

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[0031] The amount of VEGF antagonist administered to the patient in each dose is, in most cases, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means a dose of VEGF antagonist that results in a detectable improvement in one or more symptoms or indicia of an angiogenic eye disorder, or a dose of VEGF antagonist that inhibits, prevents, lessens, or delays the progression of an angiogenic eye disorder. In the case of an anti-VEGF antibody or a VEGF receptor-based chimeric molecule such as VEGFR1R2-FcΔC1(a), a therapeutically effective amount can be from about 0.05 mg to about 5 mg, *e.g.*, about 0.05 mg, about 0.1 mg, about 0.15 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.65 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 0.85 mg, about 0.9 mg, about 1.0 mg, about 1.05 mg, about 1.1 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, about 1.75 mg, about 1.8 mg, about 1.85 mg, about 1.9 mg, about 2.0 mg, about 2.05 mg, about 2.1 mg, about 2.15 mg, about 2.2 mg, about 2.25 mg, about 2.3 mg, about 2.35 mg, about 2.4 mg, about 2.45 mg, about 2.5 mg, about 2.55 mg, about 2.6 mg, about 2.65 mg, about 2.7 mg, about 2.75 mg, about 2.8 mg, about 2.85 mg, about 2.9 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, or about 5.0 mg of the antibody or receptor-based chimeric molecule.

[0032] The amount of VEGF antagonist contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (*i.e.*, mg/kg). For example, the VEGF antagonist may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight.

TREATMENT POPULATION AND EFFICACY

[0033] The methods of the present invention are useful for treating angiogenic eye disorders in patients that have been diagnosed with or are at risk of being afflicted with an angiogenic eye disorder. Generally, the methods of the present invention demonstrate efficacy within 104 weeks of the initiation of the treatment regimen (with the initial dose administered at "week 0"), *e.g.*, by the end of week 16, by the end of week 24, by the end of week 32, by the end of week 40, by the end of week 48, by the end of week 56, etc. In the context of methods for treating angiogenic eye disorders such as AMD, CRVO, and DME, "efficacy" means that, from the initiation of treatment, the patient exhibits a loss of 15 or fewer letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. In certain embodiments, "efficacy" means a gain of one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or more) letters on the ETDRS chart from the time of initiation of treatment.

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EXAMPLES

[0034] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0035] The exemplary VEGF antagonist used in all Examples set forth below is a dimeric molecule having two functional VEGF binding units. Each functional binding unit is comprised of Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of a human IgG1 Fc domain (VEGFR1R2-FcΔC1(a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the examples below as "VEGFT". For purposes of the following Examples, "monthly" dosing is equivalent to dosing once every four weeks.

Example 1: Phase I Clinical Trial of Intravitreally Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD

[0036] In this Phase I study, 21 subjects with neovascular AMD received a single intravitreal (IVT) dose of VEGFT. Five groups of three subjects each received either 0.05, 0.15, 0.5, 2 or 4 mg of VEGFT, and a sixth group of six subjects received 1 mg. No serious adverse events related to the study drug, and no identifiable intraocular inflammation was reported. Preliminary results showed that, following injection of VEGFT, a rapid decrease in foveal thickness and macular volume was observed that was maintained through 6 weeks. At Day 43 across all dose groups, mean excess retinal thickness [excess retinal thickness = (retinal thickness – 179μ)] on optical coherence tomography (OCT) was reduced from 119μ to 27μ as assessed by Fast Macular Scan and from 194μ to 60μ as assessed using a single Posterior Pole scan. The mean increase in best corrected visual acuity (BCVA) was 4.75 letters, and BCVA was stable or improved in 95% of subjects. In the 2 highest dose groups (2 and 4 mg), the mean increase in BCVA was 13.5 letters, with 3 of 6 subjects demonstrating improvement of ≥ 3 lines.

Example 2: Phase II Clinical Trial of Repeated Doses of Intravitreally Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD

[0037] This study was a double-masked, randomized study of 3 doses (0.5, 2, and 4 mg) of VEGFT tested at 4-week and/or 12-week dosing intervals. There were 5 treatment arms in this study, as follows: 1) 0.5 mg every 4 weeks, 2) 0.5 mg every 12 weeks, 3) 2 mg every 4 weeks, 4) 2 mg every 12 weeks and 5) 4 mg every 12 weeks. Subjects were dosed at a fixed interval for the

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first 12 weeks, after which they were evaluated every 4 weeks for 9 months, during which additional doses were administered based on pre-specified criteria. All subjects were then followed for one year after their last dose of VEGFT. Preliminary data from a pre-planned interim analysis indicated that VEGFT met its primary endpoint of a statistically significant reduction in retinal thickness after 12 weeks compared with baseline (all groups combined, decrease of 135μ, $p < 0.0001$). Mean change from baseline in visual acuity, a key secondary endpoint of the study, also demonstrated statistically significant improvement (all groups combined, increase of 5.9 letters, $p < 0.0001$). Moreover, patients in the dose groups that received only a single dose, on average, demonstrated a decrease in excess retinal thickness ($p < 0.0001$) and an increase in visual acuity ($p = 0.012$) at 12 weeks. There were no drug-related serious adverse events, and treatment with the VEGF antagonists was generally well-tolerated. The most common adverse events were those typically associated with intravitreal injections.

Example 3: Phase I Clinical Trial of Systemically Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD

[0038] This study was a placebo-controlled, sequential-group, dose-escalating safety, tolerability and bioeffect study of VEGFT by IV infusion in subjects with neovascular AMD. Groups of 8 subjects meeting eligibility criteria for subfoveal choroidal neovascularization (CNV) related to AMD were assigned to receive 4 IV injections of VEGFT or placebo at dose levels of 0.3, 1, or 3 mg/kg over an 8-week period.

[0039] Most adverse events that were attributed to VEGFT were mild to moderate in severity, but 2 of 5 subjects treated with 3 mg/kg experienced dose-limiting toxicity (DLT) (one with Grade 4 hypertension and one with Grade 2 proteinuria); therefore, all subjects in the 3 mg/kg dose group did not enter the study. The mean percent changes in excess retinal thickness were: -12%, -10%, -66%, and -60% for the placebo, 0.3, 1, and 3 mg/kg dose groups at day 15 (ANOVA $p< 0.02$), and -5.6%, +47.1%, and -63.3% for the placebo, 0.3, and 1 mg/kg dose groups at day 71 (ANOVA $p< 0.02$). There was a numerical improvement in BCVA in the subjects treated with VEGFT. As would be expected in such a small study, the results were not statistically significant.

Example 4: Phase III Clinical Trials of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGFT in Subjects with Neovascular Age-Related Macular Degeneration

A. Objectives, Hypotheses and Endpoints

[0040] Two parallel Phase III clinical trials were carried out to investigate the use of VEGFT to treat patients with the neovascular form of age-related macular degeneration (Study 1 and Study 2). The primary objective of these studies was to assess the efficacy of IVT administered VEGFT

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compared to ranibizumab (Lucentis®, Genentech, Inc.), in a non-inferiority paradigm, in preventing moderate vision loss in subjects with all subtypes of neovascular AMD.

[0041] The secondary objectives were (a) to assess the safety and tolerability of repeated IVT administration of VEGFT in subjects with all sub-types of neovascular AMD for periods up to 2 years; and (b) to assess the effect of repeated IVT administration of VEGFT on Vision-Related Quality of Life (QOL) in subjects with all sub-types of neovascular AMD.

[0042] The primary hypothesis of these studies was that the proportion of subjects treated with VEGFT with stable or improved BCVA (<15 letters lost) is similar to the proportion treated with ranibizumab who have stable or improved BCVA, thereby demonstrating non-inferiority.

[0043] The primary endpoint for these studies was the prevention of vision loss of greater than or equal to 15 letters on the ETDRS chart, compared to baseline, at 52 weeks. Secondary endpoints were as follows: (a) change from baseline to Week 52 in letter score on the ETDRS chart; (b) gain from baseline to Week 52 of 15 letters or more on the ETDRS chart; (c) change from baseline to Week 52 in total NEI VFQ-25 score; and (d) change from baseline to Week 52 in CNV area.

B. Study Design

[0044] For each study, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: (1) 2 mg VEGFT administered every 4 weeks (2Q4); (2) 0.5 mg VEGFT administered every 4 weeks (0.5Q4); (3) 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks (with sham injection at the interim 4-week visits when study drug was not administered (2Q8); and (4) 0.5 mg ranibizumab administered every 4 weeks (RQ4). Subjects assigned to (2Q8) received the 2 mg injection every 4 weeks to week 8 and then a sham injection at interim 4-week visits (when study drug is not to be administered) during the first 52 weeks of the studies. (No sham injection were given at Week 52).

[0045] The study duration for each subject was scheduled to be 96 weeks plus the recruitment period. For the first 52 weeks (Year 1), subjects received an IVT or sham injection in the study eye every 4 weeks. (No sham injections were given at Week 52). During the second year of the study, subjects will be evaluated every 4 weeks and will receive IVT injection of study drug at intervals determined by specific dosing criteria, but at least every 12 weeks. (During the second year of the study, sham injections will not be given.) During this period, injections may be given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to the following criteria: (i) increase in central retinal thickness of ≥100 μm compared to the lowest previous value as measured by optical coherence tomography (OCT); or (ii) a loss from the best previous letter score of at least 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; or (iii) new or persistent fluid as indicated by OCT; or (iv) new onset classic neovascularization, or new or persistent leak on fluorescein angiography (FA); or (v) new macular hemorrhage; or (vi) 12 weeks

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have elapsed since the previous injection. According to the present protocol, subjects must receive an injection at least every 12 weeks.

[0046] Subjects were evaluated at 4 weeks intervals for safety and best corrected visual acuity (BCVA) using the 4 meter ETDRS protocol. Quality of Life (QOL) was evaluated using the NEI VFQ-25 questionnaire. OCT and FA examinations were conducted periodically.

[0047] Approximately 1200 subjects were enrolled, with a target enrollment of 300 subjects per treatment arm.

[0048] To be eligible for this study, subjects were required to have subfoveal choroidal neovascularization (CNV) secondary to AMD. "Subfoveal" CNV was defined as the presence of subfoveal neovascularization, documented by FA, or presence of a lesion that is juxtafoveal in location angiographically but affects the fovea. Subject eligibility was confirmed based on angiographic criteria prior to randomization.

[0049] Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse VA was selected as the study eye. If both eyes had equal VA, the eye with the clearest lens and ocular media and least amount of subfoveal scar or geographic atrophy was selected. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology and subject preference were considered in making the selection.

[0050] Inclusion criteria for both studies were as follows: (i) signed Informed consent; (ii) at least 50 years of age; (iii) active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye; (iv) CNV at least 50% of total lesion size; (v) early treatment diabetic retinopathy study (ETDRS) best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye; (vi) willing, committed, and able to return for all clinic visits and complete all study-related procedures; and (vii) able to read, understand and willing to sign the informed consent form (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member).

[0051] Exclusion criteria for both studies were as follows: 1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins. 2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins. 3. Prior treatment with anti-VEGF agents as follows: (a) Prior treatment with anti-VEGF therapy in the study eye was not allowed; (b) Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) was allowed up to 3 months prior to first dose in the study, and such treatments were not allowed during the study. Prior treatment with an approved anti-VEGF therapy in the fellow eye was allowed; (c) Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, was only allowed up to 3 months prior to first dose, and was not allowed during

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the study. 4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as it was unlikely to interfere with the injection. 16. Prior trabeculectomy or other filtration surgery in the study eye. 17. Uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication) in the study eye. 18. Active intraocular inflammation in either eye. 19. Active ocular or periocular infection in either eye. 20. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye. 21. Any history of uveitis in either eye. 22. Active scleritis or episcleritis in either eye. 23. Presence or history of scleromalacia in either eye. 24. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye. 25. Previous therapeutic radiation in the region of the study eye. 26. History of corneal transplant or corneal dystrophy in the study eye. 27. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography. 28. Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 96 week study period. 29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety. 30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. 31. Participation as a subject in any clinical study

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within the 12 weeks prior to Day 1. 32. Any systemic or ocular treatment with an investigational agent in the past 3 months prior to Day 1. 33. The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1. 34. Any history of allergy to povidone iodine. 35. Known serious allergy to the fluorescein sodium for injection in angiography. 36. Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®). 37. Females who were pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera®; Norplant® System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.

[0052] Subjects were not allowed to receive any standard or investigational agents for treatment of their AMD in the study eye other than their assigned study treatment with VEGFT or ranibizumab as specified in the protocol until they completed the Completion/Early Termination visit assessments. This includes medications administered locally (e.g., IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the study and/or fellow eye.

[0053] The study procedures are summarized as follows:

[0054] Best Corrected Visual Acuity: Visual function of the study eye and the fellow eye were assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group) at 4 meters. Visual Acuity examiners were certified to ensure consistent measurement of BCVA. The VA examiners were required to remain masked to treatment assignment.

[0055] Optical Coherence Tomography: Retinal and lesion characteristics were evaluated using OCT on the study eye. At the Screen Visit (Visit 1) images were captured and transmitted for both eyes. All OCT images were captured using the Zeiss Stratus OCT™ with software Version 3 or greater. OCT images were sent to an independent reading center where images were read by masked readers at visits where OCTs were required. All OCTs were electronically archived at the site as part of the source documentation. A subset of OCT images were read. OCT technicians were required to be certified by the reading center to ensure consistency and quality in image acquisition. Adequate efforts were made to ensure that OCT technicians at the site remained masked to treatment assignment.

[0056] Fundus Photography and Fluorescein Angiography (FA): The anatomical state of the retinal vasculature of the study eye was evaluated by funduscopic examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopic examination, fundus photography and FA were captured and transmitted for both eyes. Fundus and angiographic images were sent to an independent reading center where images were read by masked readers. The reading center confirmed subject eligibility based on angiographic criteria prior to randomization. All FAs and

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fundus photographs were archived at the site as part of the source documentation. Photographers were required to be certified by the reading center to ensure consistency and quality in image acquisition. Adequate efforts were made to ensure that all photographers at the site remain masked to treatment assignment.

[0057] Vision-Related Quality of Life: Vision-related QOL was assessed using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) in the interviewer-administered format. NEI VFQ-25 was administered by certified personnel at a contracted call center. At the screening visit, the sites assisted the subject and initiated the first call to the call center to collect all of the subject's contact information and to complete the first NEI VFQ-25 on the phone prior to randomization and IVT injection. For all subsequent visits, the call center called the subject on the phone, prior to IVT injection, to complete the questionnaire.

[0058] Intraocular Pressure: Intraocular pressure (IOP) of the study eye was measured using applanation tonometry or Tonopen. The same method of IOP measurement was used in each subject throughout the study.

[0059]

C. Results Summary (52 Week Data)

[0060] The primary endpoint (prevention of moderate or severe vision loss as defined above) was met for all three VEGFT groups (2Q4, 0.5Q4 and 2Q8) in this study. The results from both studies are summarized in Table 1.

Table 1

	Ranibizumab 0.5 mg monthly (RQ4)	VEGFT 0.5 mg monthly (0.5Q4)	VEGFT 2 mg monthly (2Q4)	VEGFT 2 mg every 8 weeks[a] (2Q8)
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
Study 1	94.4%	95.9%**	95.1%**	95.1%**
Study 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value vs RQ4)***				
Study 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a] Following three initial monthly doses
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
*** Test for superiority
NS = non-significant

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[0061] In Study 1, patients receiving VEGFT 2mg monthly (2Q4) achieved a statistically significant greater mean improvement in visual acuity at week 52 versus baseline (secondary endpoint), compared to ranibizumab 0.5mg monthly (RQ4); patients receiving VEGFT 2mg monthly on average gained 10.9 letters, compared to a mean 8.1 letter gain with ranibizumab 0.5mg dosed every month ($p<0.01$). All other dose groups of VEGFT in Study 1 and all dose groups in Study 2 were not statistically different from ranibizumab in this secondary endpoint.

[0062] A generally favorable safety profile was observed for both VEGFT and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease, and/or the aging process. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events were falls, pneumonia, myocardial infarction, atrial fibrillation, breast cancer, and acute coronary syndrome. There were no notable differences among the study arms.

Example 5: Phase II Clinical Trial of VEGFT in Subjects with Diabetic Macular Edema (DME)

[0063] In this study, 221 patients with clinically significant DME with central macular involvement were randomized, and 219 patients were treated with balanced distribution over five groups. The control group received macular laser therapy at baseline, and patients were eligible for repeat laser treatments, but no more frequently than at 16 week intervals. The remaining four groups received VEGFT by intravitreal injection as follows: Two groups received 0.5 or 2 mg of VEGFT once every four weeks throughout the 12-month dosing period (0.5Q4 and 2Q4, respectively). Two groups received three initial doses of 2 mg VEGFT once every four weeks (*i.e.*, at baseline, and weeks 4 and 8), followed through week 52 by either once every 8 weeks dosing (2Q8) or as needed dosing with very strict repeat dosing criteria (PRN). Mean gains in visual acuity versus baseline were as shown in Table 2:

Table 2

	n	Mean change in visual acuity at week 24 versus baseline (letters)	Mean change in visual acuity at week 52 versus baseline (letters)
Laser	44	2.5	-1.3
VEGFT 0.5 mg monthly (0.5Q4)	44	8.6**	11.0**
VEGFT 2 mg monthly (2Q4)	44	11.4**	13.1**
VEGFT 2 mg every 8	42	8.5**	9.7**

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weeks[a] (2Q8)			
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a] Following three initial monthly doses
** $p < 0.01$ versus laser

[0064] In this study, the visual acuity gains achieved with VEGFT administration at week 24 were maintained or numerically improved up to completion of the study at week 52 in all VEGFT study groups, including 2 mg dosed every other month

[0065] As demonstrated in the foregoing Examples, the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity.

Example 6: A Randomized, Multicenter, Double-Masked Trial in Treatment Naïve Patients with Macular Edema Secondary to CRVO

[0066] In this randomized, double-masked, Phase 3 study, patients received 6 monthly injections of either 2 mg intravitreal VEGFT (114 patients) or sham injections (73 patients). From Week 24 to Week 52, all patients received 2 mg VEGFT as-needed (PRN) according to retreatment criteria. Thus, "sham-treated patients" means patients who received sham injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed from Week 24 through Week 52. "VEGFT-treated patients" means patients who received VEGFT intravitreal injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed from Week 24 through Week 52. The primary endpoint was the proportion of patients who gained ≥15 ETDRS letters from baseline at Week 24. Secondary visual, anatomic, and Quality of Life NEI VFQ-25 outcomes at Weeks 24 and 52 were also evaluated.

[0067] At Week 24, 56.1% of VEGFT-treated patients gained ≥15 ETDRS letters from baseline vs 12.3% of sham-treated patients ($P<0.0001$). Similarly, at Week 52, 55.3% of VEGFT-treated patients gained ≥15 letters vs 30.1% of sham-treated patients ($P<0.01$). At Week 52, VEGFT-treated patients gained a mean of 16.2 letters vs 3.8 letters for sham-treated patients ($P<0.001$). Mean number of injections was 2.7 for VEGFT-treated patients vs 3.9 for sham-treated patients. Mean change in central retinal thickness was -413.0 µm for VEGFT-treated patients vs -381.8 µm for sham-treated patients. The proportion of patients with ocular neovascularization at Week 24 were 0% for VEGFT-treated patients and 6.8% for sham-treated patients, respectively; at Week 52 after receiving VEGFT PRN, proportions were 0% and 6.8% for VEGFT-treated and sham-treated. At Week 24, the mean change from baseline in the VFQ-25 total score was 7.2 vs 0.7 for the

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VEGFT-treated and sham-treated groups; at Week 52, the scores were 7.5 vs 5.1 for the VEGFT-treated and sham-treated groups.

[0068] This Example confirms that dosing monthly with 2 mg intravitreal VEGFT injection resulted in a statistically significant improvement in visual acuity at Week 24 that was maintained through Week 52 with PRN dosing compared with sham PRN treatment. VEGFT was generally well tolerated and had a generally favorable safety profile.

Example 7: Dosing Regimens

[0069] Specific, non-limiting examples of dosing regimens within the scope of the present invention are as follows:

[0070] VEGFT 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly).

[0071] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 8 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0072] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 8 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0073] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 8 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0074] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 12 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0075] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 12 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0076] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 12 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0077] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0078] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on

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visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0079] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 16 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0080] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0081] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0082] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 20 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0083] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 24 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0084] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 24 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0085] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 24 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0086] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 28 weeks, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

[0087] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 28 weeks, followed by 2 mg (0.05 mL) via intravitreal injection on a less frequent basis based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0088] VEGFT 2 mg (0.5 mL) administered by intravitreal injection once every 4 weeks for the first 28 weeks, followed by 2 mg (0.05 mL) via intravitreal injection administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

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[0089] VEGFT 2 mg (0.05 mL) administered by intravitreal injection as a single initial dose, followed by additional doses administered *pro re nata* (PRN) based on visual and/or anatomical outcomes (as assessed by a physician or other qualified medical professional).

[0090] Variations on the above-described dosing regimens would be appreciated by persons of ordinary skill in the art and are also within the scope of the present invention. For example, the amount of VEGFT and/or volume of formulation administered to a patient may be varied based on patient characteristics, severity of disease, and other diagnostic assessments by a physician or other qualified medical professional.

[0091] Any of the foregoing administration regimens may be used for the treatment of, *e.g.*, age-related macular degeneration (*e.g.*, wet AMD, exudative AMD, etc.), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO; *e.g.*, macular edema following CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV; *e.g.*, myopic CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, etc.

SEQUENCES

[0092] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

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[0093] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

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KFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGI
ELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0094] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

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What is claimed is:

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.

2. The method of claim 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

3. The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

4. The method of claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

8. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.

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9. The method of claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

10. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

11. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

12. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

14. The method of claim 13, wherein the intraocular administration is intravitreal administration.

15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

17. The method of claim 16, wherein the intraocular administration is intravitreal administration.

18. The method of claim 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

19. The method of claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

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ABSTRACT

The present invention provides methods for treating angiogenic eye disorders by sequentially administering multiple doses of a VEGF antagonist to a patient. The methods of the present invention include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 8 or more weeks. The methods of the present invention are useful for the treatment of angiogenic eye disorders such as age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

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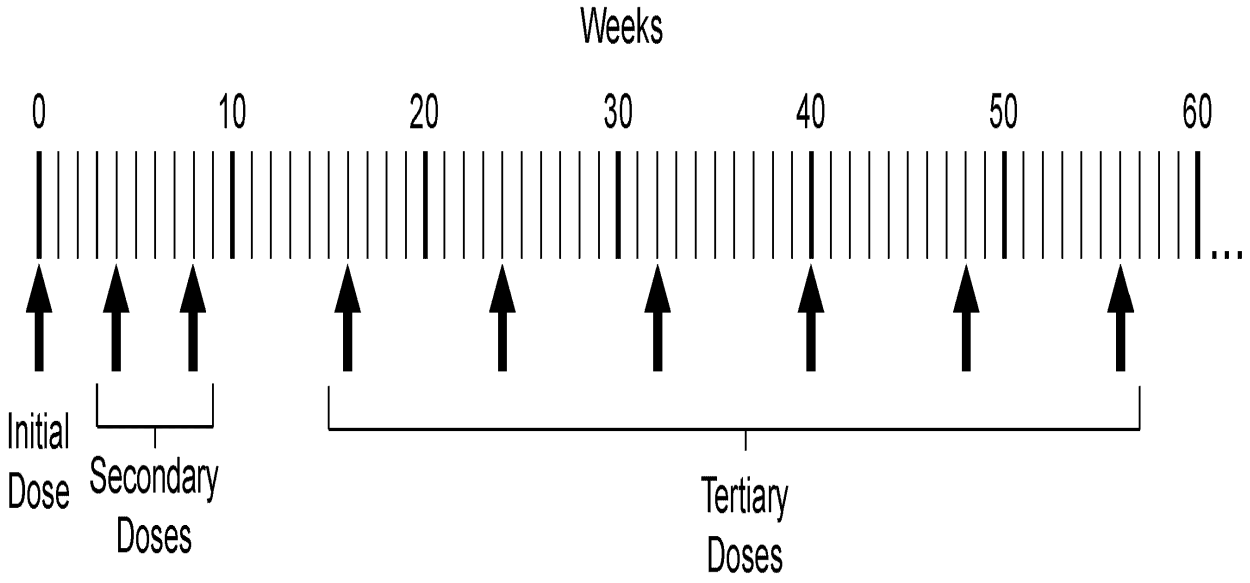

Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT International application number 13/940,370

filed on July 12, 2013.

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

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

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

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LEGAL NAME OF INVENTOR

Inventor: YANCOPOULOS, GEORGE D. Date (Optional): 10/20/13

Signature: X

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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10.

Electronically Filed

NOTIFICATION OF PRIOR SEQUENCE LISTING		
	Attorney Docket	REGN-008CIPCON4
	First Named Inventor	YANCOPOULOS, GEORGE D.
	Application Number	To Be Assigned
	Filing Date	October 12, 2018
Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Confirmation Number	To Be Assigned
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
	Title: "USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS"	

Sir:

The above-identified patent application contains sequences of nucleic acid and polypeptides. A sequence listing was prepared for parent application, **15/471,506,** filed **March 28, 2017**, in paper and computer-readable format. The sequence information in the paper or compact disk copy of the sequence listing (required by 1.821(c)) of this application is identical to the sequence information in the computer-readable format (CRF) of the above-identified other application. No new matter has been added. Therefore, please transfer to this application, in accordance with 37 CFR § 1.821(e), the fully compliant computer readable copy from applicants' other application. A paper (.txt) copy of this sequence listing is enclosed.

Applicants respectfully submit that the present patent application is now in compliance with 37 CFR §§ 1.821 - 1.825. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number REGN-008CIPCON4.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Dated: 12 October 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Registration No. 28,807

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Facsimile: (650) 327-3231

SEQUENCE LISTING

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<120> Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

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Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
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