

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		
	Filing Date		2017-08-31
	First Named Inventor	DIX, Daniel	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	238811-21.89 (4030US11)	

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	1	6267958	B1	2001-07-31	Andya, et al.	
	2	6875432	B2	2005-04-05	Liu, et al	
	3	7060268	B2	2006-06-13	Andya, et al.	
	4	7001892	B1	2006-02-21	Chmielweski, et al.	
	5	5399670	A	1995-03-21	Bhattacharya, et al.	
	6	5851999	A	1998-12-22	Ulrich, et al.	
	7	6011003	A	2000-01-04	Charmock-Jonee, et al.	
	8	6270993	B1	2001-08-07	Shibuya, et al.	

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Attorney Docket Number	238811-21.89 (4030US11)	

9	7087411	B2	2006-08-08	Daly, et al.	
10	7374757	B2	2008-05-20	Papadopoulos, et al.	
11	7052691	B2	2006-05-30	Sleeman, et al.	
12	6100071	A	2000-08-08	Davis-Smyth, et al.	
13	6897294	B2	2005-05-24	Davis-Smyth, et al.	
14	5763401	A	1998-06-09	Rajiv, Nayar	
15	7070959	B1	2006-07-04	Papadopoulos et al.	
16	7087411	B2	2006-08-08	Daly et al.	
17	8084234	B2	2011-12-27	Papadopoulos et al.	
18	8343737	B2	2013-01-01	Papadopoulos et al.	
19	8647842	B2	2014-02-11	Papadopoulos et al.	

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	2	20040197324	A1	2004-10-07	Liu, et al.	
	3	20030092606	A1	2003-05-15	L'Italien, et al.	
	4	20050281831	A1	2005-12-22	Davis-Smyth, et al.	
	5	20030202972	A1	2003-10-30	Andya, et al.	
	6	20050032699	A1	2005-02-10	Holash, et al.	
	7	20050276808	A1	2005-12-05	Cedarbaum, Jesse M.	

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Examiner Name		
Attorney Docket Number	238811-21.89 (4030US11)	

1	WO0220060489	WO	A1	2002-08-08	Regeneron Pharmaceuticals, Inc.		
2	WO2005000895	WO	A2	2005-01-06	Regeneron Pharmaceuticals, Inc.		
3	WO2006047325	WO	A1	2006-05-04	Genentech, Inc.		
4	WO2007149334	WO	A2	2007-12-27	Regeneron Pharmaceuticals, Inc.		
5	WO1993000807	WO	A1	1993-01-21	Cryolife, Inc.		
6	WO2000075319	WO	A1	2000-12-14	Regeneron Pharmaceuticals, Inc.		
7	WO2004106378	WO	A2	2004-12-09	Regeneron Pharmaceuticals, Inc.		
8	WO1999013909	WO	A1	1999-03-25	Toagosei Co., Ltd.		
9	WO2005020972	WO	A1	2005-03-10	Eyetech Pharm, Inc.		
10	WO2005072772	WO	A1	2005-08-11	Suomen Punainen Risti Veripalvelu		
11	WO199962536	WO	A2	1999-12-09	Celtrix Pharmaceuticals, Inc.		

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Attorney Docket Number	238811-21.89 (4030US11)	

	12	WO2004103159	WO	A2	2004-12-02	UNIV Leland Stanford Junior		
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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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	CARPENTER, J.F. (1997) Rational Design of Stable Lyophilized..., Pharm. Res. 14(8): 969-975	
	2	WANG, W. (1999) Instability, stabilization, and formulation of liquid protein..., Int'l J. Pharmaceutics 185(2): 129-188	
	3	WEBB et al. (2002) A new mechanism for decreasing aggregation..., J. Pharm. Sci 93(10): 2609-2623	
	4	DAUGHERTY, et al. (2006) Formulation and delivery issues for monoclonal..., Adv. Drug Delivery Rev. 58:668-706	
	5	FRASER et al. (2004) Single injections of Vascular Trap..., J.Clin. Endocrin. & Metabol. 90(2):1114-1122	
	6	STEWART, M.W. (2012) Clinical and Differential Utility of VEGF Inhibitors..., Clinical Ophthalmology, 2012:6, 1175-1186	
	7	Hanks Solution http://www.lifetechnologies.com/us/en/home/technical-resources/media-formulation.152.html	
	8	MI, et al. (2002) Effects of polyethylene glycol molecular weight and concentration..., PDS J. Pharm. Sci. Technol., 56, 115-123	

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9	HOLASH, Jocelyn et al. (2002) VEGF-Trap: A VEGF blocker with potent antitumor effects, Proceedings of the National Academy of Sciences of the United States of America, Vol. 99 No. 17 August 20, 2002, 11393-11398
10	GLADE-BENDER, J et al. VEGF Blocking Therapy in the Treatment of Cancer, Expert Opinion on Biological Therapy, Ashley London GB Vol. 3, No. 2 April 2003, Pages 263-276
11	KIM, Eugene S. et al. Proceedings of the National Academy of Sciences of the United States of America, Vol. 99, No. 17, August 20, 2002
12	KATAYAMA, et al. (2004) Retrospective statistical analysis of lyophilized...J. Pharm. Sci. 93(10): 2609-2623

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Examiner Name	
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CERTIFICATION STATEMENT

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

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

OR

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

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

Signature	/Joseph E. Zahner/	Date (YYYY-MM-DD)	2017-08-31
Name/Print	Joseph E. Zahner	Registration Number	48,224

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

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Title of Invention:		VEGF ANTAGONIST FORMULATIONS		
First Named Inventor/Applicant Name:		Daniel B. DIX		
Filer:		Joseph Zahner/Andrea Black		
Attorney Docket Number:		238811-21.89 (4030US11)		
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	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
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Extension-of-Time:				
Miscellaneous:				
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EFS ID:	30237744
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	VEGF ANTAGONIST FORMULATIONS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	138357
Filer:	Joseph Zahner/Andrea Black
Filer Authorized By:	Joseph Zahner
Attorney Docket Number:	238811-21.89 (4030US11)
Receipt Date:	31-AUG-2017
Filing Date:	
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Application Type:	Utility under 35 USC 111(a)

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2		4030US11_con_spec.pdf	243799	yes	19
			dc4cf93f66eded4a4a6285e6da669ea624aa77b7		
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	Specification		1	14	
	Claims		15	18	
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New International Application Filed with the USPTO as a Receiving Office

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	238811-21.89 (4030US11)
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS		
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.)
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Inventor Information:

Inventor 1				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniel	B.	DIX	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	LaGrangeville	State/Province	NY	Country of Residence ⁱ US
Mailing Address of Inventor:				
Address 1		c/o Regeneron Pharmaceuticals, Inc.		
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Postal Code	10591	Country ⁱ	US	
Inventor 2				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Kelly		FRYE	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
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Address 2				
City	Mendham	State/Province	NJ	
Postal Code	07945	Country ⁱ	US	
Inventor 3				
Legal Name				
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	238811-21.89 (4030US11)
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS		

Residence Information (Select One)		☒ US Residency	☐ Non US Residency	☐ Active US Military Service
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		US		
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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.				
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Application Information:

Title of the Invention	VEGF ANTAGONIST FORMULATIONS		
Attorney Docket Number	238811-21.89 (4030US11)	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

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

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		Application Number	
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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.

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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 this 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 blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15342989	2016-11-03

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	238811-21.89 (4030US11)
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS		

Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15342989	Continuation of	15064343	2016-03-08	9511140	2016-12-06
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15064343	Continuation of	14550385	2014-11-21	9416167	2016-08-16
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14550385	Continuation of	13909745	2013-06-04	8921316	2014-12-30
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13909745	Continuation of	13428510	2012-03-23	8710004	2014-04-29
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13428510	Continuation of	13343214	2012-01-04	8404638	2013-03-26
Prior Application Status		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13343214	Division of	12835065	2010-07-13	8110546	2012-02-07
Prior Application Status		Abandoned		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
12835065	Continuation of	11387256	2006-03-22		
Prior Application Status		Pending		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
11387256	Claims benefit of provisional	60665125	2005-03-25		

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		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS		

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 ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)

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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
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	238811-21.89 (4030US11)
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS		

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.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	238811-21.89 (4030US11)
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS		

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	
☐ 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
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		Application Number	
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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.				☐
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	238811-21.89 (4030US11)
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS		

Signature:

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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	/Joseph E. Zahner/			Date (YYYY-MM-DD)	
First Name	Joseph	Last Name	Zahner	Registration Number	48224
Additional Signature may be generated within this form by selecting the Add button.					

VEGF ANTAGONIST FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Patent Application No. 15/342,989, filed on 11/3/2016, which is a continuation of U.S. Patent Application No. 15/064,343, filed on 3/8/2016 and granted on 12/6/2016 as U.S. Patent No. 9,511,140, which is a continuation of U.S. Patent Application No. 14/550,385, filed on 11/21/2014 and granted on 8/16/2016 as U.S. Patent No. 9,416,167, which is a continuation of U.S. Patent Application No. 13/909,745, filed on 6/4/2013 and granted on 12/30/2014 as U.S. Patent No. 8,921,316, which is a continuation of U.S. Patent Application No. 13/428,510, filed on 3/23/2012 and granted on 4/29/2014 as U.S. Patent No. 8,710,004, which is a continuation of US Patent Application No. 13/343,214, filed on 1/4/2012 and granted on 3/26/2013 as U.S. Patent No. 8,404,638, which is a division of U.S. Patent Application No. 12/835,065, filed on 7/13/2010 and granted on 2/7/2012 as U.S. Patent No. 8,110,546, which is a continuation of U.S. Patent Application No. 11/387,256, filed on 3/22/2006, which claims the benefit of priority under 35 USC § 119(e) of U.S. Provisional Application No. 60/665,125, filed on 3/25/2005, all of which are herein specifically incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present invention is directed to pharmaceutical formulations comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations. The invention includes pharmaceutical formulations having increased stability.

Statement of Related Art

[0003] Vascular endothelial growth factor (VEGF) expression is nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis. Blockade of VEGF function, by binding to the molecule or its VEGFR-2 receptor, inhibits growth of implanted tumor cells in multiple different xenograft models (see, for example, Gerber *et al.*

(2000) Cancer Res. 60:6253-6258). A soluble VEGF-specific fusion protein antagonist, termed a “VEGF trap” has been described (Kim *et al.* (2002) Proc. Natl. Acad. Sci. USA 99:11399-404; Holash *et al.* (2002) Proc. Natl. Acad. Sci. USA 99:11393-8), which references are specifically incorporated by reference in their entirety.

[0004] Lyophilization (freeze drying under controlled conditions) is commonly used for long term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state (see, for example, U.S. 6,436,897).

BRIEF SUMMARY OF THE INVENTION

[0005] Stable formulations of a VEGF-specific fusion protein antagonist are herein provided. The pharmaceutically acceptable formulations of the invention comprise the VEGF “trap” antagonist with a pharmaceutically acceptable carrier. In specific embodiments, liquid and freeze-dried, or lyophilized formulations are provided.

[0006] In a first aspect, the invention features a stable liquid formulation of a VEGF-specific fusion protein antagonist, comprising a fusion protein comprising a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component, one or more buffers, and one or more thermal stabilizers. In a specific embodiment of the VEGF-specific fusion protein antagonist, the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1 or Flt4. In a more specific embodiment the fusion protein has the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4. In one embodiment, the buffer is a phosphate buffer and/or citrate. More preferably, the buffers are phosphate and citrate. In one embodiment, the thermal stabilizers are NaCl and/or sucrose. More preferably, the thermal stabilizers are both NaCl and sucrose.

[0007] In a specific embodiment, the stable liquid formulation of a VEGF-specific fusion protein antagonist comprises 1-10 mM phosphate buffer, 1-10 mM citrate, 25-150 mM NaCl, 5-30% sucrose, 10-50 mg/ml of the fusion protein, at a pH of about 6-6.5. In a more specific embodiment, the stable liquid formulation comprises 5 mM phosphate buffer, 5 mM citrate buffer, 100 mM NaCl, 20% sucrose, 25 mg/ml of the fusion protein, at a pH of

about 6.0. Additionally, polysorbate may be present, for example 0.05-0.15% polysorbate 20. The stable liquid formulation of the VEGF-specific fusion protein antagonist of the invention exhibits little or no precipitation after storage of a 25 mg/ml VEGF formulation for about 6 months at -80° C and little or no precipitation after storage for 6 months at 5°C.

[0008] In a second aspect, the invention features a high concentration stable liquid formulation of a VEGF antagonist comprising 1-50 mM histidine, 25-150 mM NaCl, 5-30% sucrose, 50-100 mg/ml of the fusion protein, at a pH of about 6-6.5, and either 0.1-0.5% polysorbate or 1-5% PEG. In a more specific embodiment, the high concentration stable liquid formulation comprises 10 mM histidine, 50 mM NaCl, 5-20% sucrose, 50-100 mg/ml of the fusion protein, at a pH of about 6.0-6.5, with either 0.1% polysorbate (*e.g.*, polysorbate 20) or 3% PEG (*e.g.*, PEG 3350). The high concentration stable liquid formulation of the VEGF-specific fusion protein antagonist of the invention exhibits less than about 3% degradation after 15 months of storage at 5°C (75 or 100 mg/ml VEGF trap protein) or less than about 1.5% degradation after 24 months (50 mg/ml).

[0009] In a third aspect, the invention features a pre-lyophilized formulation of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist, comprising a (i) fusion protein comprising a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component, (ii) a buffer, (iii) an organic co-solvent or bulking agent, and (iv) one or more lyoprotectants. In various embodiments, the buffer is histidine, the organic co-solvent or bulking agent is PEG, and the lyoprotectant(s) is at least one of glycine and sucrose. In one embodiment, the pre-lyophilized formulation of the invention does not contain a preservative.

[00010] In one embodiment of the pre-lyophilized formulation of the invention, the formulation comprises 5-50 mM histidine, 0.1-3.0% PEG, 0.25-3.0% glycine, 0.5-6.0% sucrose, and 5-75 mg/ml of the fusion protein, at a pH of about 6.0- 6.5. In any embodiment, the pre-lyophilized formulation may further comprise up to 0.05 mM citrate and/or 0.003-0.005% polysorbate. The polysorbate present may be, for example, polysorbate 20.

[00011] In a more specific embodiment, the pre-lyophilized formulation comprises about 10 mM histidine, about 1.5% PEG 3350, about 0.75% glycine, about 2.5% sucrose, and about 12.5 to 75 mg/ml VEGF-specific fusion protein, at a pH of about 6.25. In specific embodiments, the fusion

protein comprises the protein sequence of SEQ ID NO:4, present as a multimer, *e.g.*, a dimer. In separate embodiments, the reconstituted formulation is 2 times the concentration of the pre-lyophilized formulation, *e.g.*, a 20 mg fusion protein/ml pre-lyophilized formulation is reconstituted to a final formulation of 60 mg fusion protein/ml. Generally, the lyophilized formulation is reconstituted with sterile water suitable for injection. In one embodiment, the reconstitution liquid may be bacteriostatic water.

[00012] In a preferred embodiment, the pre-lyophilized formulation consists essentially of about 10 mM histidine, about 1.5% PEG 3350, about 0.75% glycine, about 2.5% sucrose, and about 50 mg/ml of the fusion protein having the sequence of SEQ ID NO:4 as a dimer, at a pH of about 6.25. Citrate (less than or equal to about 0.02 mM) and/or polysorbate (less than or equal to about 0.0005%) may be present. Optionally, the pre-lyophilized formulation does not contain a preservative, a phosphate buffer, and/or more than trace amounts of NaCl. In one embodiment, the pre-lyophilized formulation consists of about 10 mM histidine, about 1.5% PEG 3350, about 0.75% glycine, about 2.5% sucrose, and about 50 mg/ml of the VEGF trap protein (SEQ ID NO:4), pH 6.3, and upon reconstitution contains 20 mM histidine, 3% PEG, 1.5% glycine, about 5% sucrose, and about 100 mg/ml VEGF trap protein.

[00013] In a fourth aspect, the invention features a method of producing a lyophilized formulation of a VEGF-specific fusion protein antagonist, comprising subjecting the pre-lyophilized formulation of the invention to lyophilization to generate a lyophilized formulation. The lyophilized formulation may be lyophilized by any method known in the art for lyophilizing a liquid.

[00014] In a fifth related aspect, the invention features a method of producing a reconstituted lyophilized formulation of a VEGF-specific fusion protein antagonist, comprising reconstituting the lyophilized formulation of the invention to a reconstituted formulation. In one embodiment, the reconstituted formulation is twice the concentration of the pre-lyophilized formulation, *e.g.*, the method of the invention comprises: (a) producing a pre-lyophilized formulation of a VEGF-specific fusion protein antagonist, (b) subjecting the pre-lyophilized formulation of step (a) to lyophilization; and (c) reconstituting the lyophilized formulation of step (b).

[00015] In specific embodiments of the method of producing a reconstituted lyophilized formulation, a pre-lyophilized solution is present in a vial as a 25 mg VEGF-specific fusion protein

antagonist per ml solution of pre-lyophilized formulation, which is lyophilized and reconstituted to an 50 mg/ml solution. In another embodiment, a 30 mg/ml pre-lyophilized solution is lyophilized and reconstituted to a 60 mg/ml solution. In another embodiment, a 40 mg/ml pre-lyophilized solution is lyophilized and reconstituted to a 80 mg/ml solution. In another embodiment, a 12.5 mg/ml pre-lyophilized solution is lyophilized and reconstituted to a 25 mg/ml solution. In another embodiment, a 50 mg/ml pre-lyophilized solution is lyophilized and reconstituted to a 100 mg/ml solution. In another embodiment, a 75 mg/ml pre-lyophilized solution is lyophilized and reconstituted to a 150 mg/ml solution. Preferably, the reconstituted lyophilized formulation does not contain a preservative.

[00016] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[00017] The present 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 unless indicated, since the scope of the present invention will be limited only by the appended claims.

[00018] 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, references to “a method” include 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.

[00019] Unless stated otherwise, all technical and scientific terms and phrases used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the 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.

General Description

[00020] Safe handling and administration of formulations comprising proteins represent significant challenges to pharmaceutical formulators. Proteins possess unique chemical and

physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation.

[00021] Chemical and physical stability can be promoted by removing water from the protein. Lyophilization (freeze-drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state. The lyophilized protein is normally reconstituted with water optionally containing a bacteriostatic preservative (*e.g.*, benzyl alcohol) prior to administration.

Definitions

[00022] The term “carrier” includes a diluent, adjuvant, excipient, or vehicle with which a composition is administered. Carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like.

[00023] The term “excipient” includes a non-therapeutic agent added to a pharmaceutical composition to provide a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, 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.

[00024] The term “lyophilized” or “freeze-dried” includes a state of a substance that has been subjected to a drying procedure such as lyophilization, where at least 50% of moisture has been removed.

[00025] The phrase “bulking agent” includes a compound that is pharmaceutically acceptable and that adds bulk to a lyo cake. Generally, acceptable bulking agents known to the art include, for example, carbohydrates, including simple sugars such as dextrose, ribose, fructose and the like, alcohol sugars such as mannitol, inositol and sorbitol, disaccharides including trehalose, sucrose and lactose, naturally occurring polymers such as starch, dextrans, chitosan, hyaluronate, proteins (*e.g.*, gelatin and serum albumin), glycogen, and synthetic monomers and polymers. In the

formulations of the invention, PEG 3350 is an organic co-solvent which is used to stabilize the fusion protein when agitated, mixed, or handled, and as a bulking agent to help produce an acceptable bulk.

[00026] The term “lyoprotectant” includes a substance that may be added to a freeze-dried or lyophilized formulation to help maintain protein structure when freeze-dried or lyophilized.

[00027] A “preservative” includes a bacteriostatic, bacteriocidal, fungistatic or fungicidal compound that is generally added to formulations to retard or eliminate growth of bacteria or other contaminating microorganisms in the formulations. Preservatives include, for example, benzyl alcohol, phenol, benzalkonium chloride, m-cresol, thimerosol, chlorobutanol, methylparaben, propylparaben and the like. Other examples of pharmaceutically acceptable preservatives can be found in the USP.

VEGF Antagonists

[00028] An VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO:2 or 4; more preferably, SEQ ID NO:4. In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified posttranslationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308.

[00029] The VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known. The VEGF antagonist is preferably substantially free of protein contaminants at the time it is used to prepare the pharmaceutically acceptable formulation. By “substantially free of protein contaminants” is meant, preferably, that at least 90 % of the weight of protein of the VEGF-specific fusion protein antagonist preparation used for making a formulation is VEGF fusion protein antagonist protein, more preferably at least 95%, most preferably at least 99%. The fusion protein is preferably substantially free of aggregates. “Substantially free of aggregates” means that at least 90% of the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation. The fusion protein of the methods and formulations of the

invention may contain low or trace amounts of compounds as a results of the purification process, for example, low or trace amounts of citrate and/or polysorbate. In one embodiment of the pre-lyophilized formulation of the invention containing about 50 mg of fusion protein/ml, citrate may be present at a concentration of about 0.02 mM and/or polysorbate may be present at a concentration of about 0.0005%. If the pre-lyophilized formulation is reconstituted after lyophilization to half of the original volume (*e.g.*, 100 mg/ml of fusion protein), the resulting concentrations may be 0.04 mM citrate and/or 0.001% polysorbate.

Lyophilization and Lyophilized Formulations

[00030] In one aspect of the invention, a pharmaceutically acceptable formulation comprising a VEGF-specific fusion protein antagonist is provided, wherein the formulation is a freeze-dried or lyophilized formulation. Lyophilized formulations can be reconstituted into solutions, suspensions, emulsions, or any other suitable form for administration or use. Lyophilized formulations are typically first prepared as liquids, then frozen and lyophilized. The total liquid volume before lyophilization can be less, equal to, or more than, the final reconstituted volume of the lyophilized formulation. The lyophilization process is well known to those of ordinary skill in the art, and typically includes sublimation of water from a frozen formulation under controlled conditions.

[00031] Lyophilized formulations can be stored at a wide range of temperatures. Lyophilized formulations may be stored below 25°C, for example, refrigerated at 4°C, or at room temperature (*e.g.*, approximately 25°C). Preferably, lyophilized formulations are stored below about 25°C, more preferably, at about 4-20°C; below about 4°C; below about -20°C; about -40°C; about -70°C, or about -80°C.

[00032] Lyophilized formulations are typically reconstituted for use by addition of an aqueous solution to dissolve the lyophilized formulation. A wide variety of aqueous solutions can be used to reconstitute a lyophilized formulation. Preferably, lyophilized formulations are reconstituted using water. Lyophilized formulations are preferably reconstituted with a solution consisting essentially of water (*e.g.*, USP WFI, or water for injection) or bacteriostatic water (*e.g.*, USP WFI with 0.9% benzyl alcohol). However, solutions comprising buffers and/or excipients and/or one or more pharmaceutically acceptable carries can also be used.

[00033] Freeze-dried or lyophilized formulations are typically prepared from liquids, that is,

from solutions, suspensions, emulsions, and the like. Thus, the liquid that is to undergo freeze-drying or lyophilization preferably comprises all components desired in a final reconstituted liquid formulation. As a result, when reconstituted, the freeze-dried or lyophilized formulation will render a desired liquid formulation upon reconstitution. A preferred liquid formulation used to generate a freeze-dried or lyophilized formulation comprises a VEGF-specific fusion protein antagonist in a pharmaceutically effective amount, a buffer, a stabilizer, and a bulking agent. Freeze-dried or lyophilized formulations preferably comprise histidine, since histidine, in comparison to phosphate, is more effective at stabilizing the fusion protein when the fusion protein is lyophilized. Organic co-solvents, such as PEG 3350, are used to stabilize the fusion protein when agitated, mixed, or handled. A lyoprotectant is preferably used in freeze-dried or lyophilized formulations. Lyoprotectants help to maintain the secondary structure of proteins when freeze-dried or lyophilized. Two preferred example lyoprotectants are glycine and sucrose, which are preferably used together.

Stable Liquid Formulations

[00034] In one aspect, the invention provides a stable pharmaceutically acceptable formulation comprising a VEGF-specific fusion protein antagonist, wherein the formulation is a liquid formulation. Preferably, the liquid formulation comprises a pharmaceutically effective amount of the fusion protein. The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, bulking agents, stabilizers, preservatives, and/or excipients. An example of a pharmaceutically acceptable liquid formulation comprises a VEGF-specific fusion protein antagonist in a pharmaceutically effective amount, a buffer, a co-solvent, and one or more stabilizers.

[00035] A preferred liquid formulation comprises phosphate buffer, an organic co-solvent, and one or more thermal stabilizers to minimize formation of aggregates and low molecular weight products when stored, and about 10 mg/ml to about 50 mg/ml fusion protein, wherein the formulation is from about pH 6.0-6.5. A preferred liquid formulation comprises about 5 mM phosphate buffer, about 5 mM citrate, about 100 mM NaCl, about 25% sucrose, and about 1050 mg/ml fusion protein, wherein the formulation is at a pH of about 6.0; optionally polysorbate may be present (*e.g.*, 0.1% polysorbate 20). Although either NaCl or sucrose can be used as a stabilizer, a combination of NaCl and sucrose has been established to stabilize the fusion protein more effectively than either individual stabilizer alone.

[00036] Stability is determined in a number of ways at specified time points, including

determination of pH, visual inspection of color and appearance, determination of total protein content by methods known in the art, *e.g.*, UV spectroscopy, SDS-PAGE, size-exclusion HPLC, bioassay determination of activity, isoelectric focusing, and isoaspartate quantification. In one example of a bioassay useful for determining VEGF antagonist activity, a BAF/3 VEGFR1/EPOR cell line is used to determine VEGF165 binding by the VEGF-specific fusion protein antagonist of the invention.

[00037] Formulations, whether liquid or freeze-dried and lyophilized, can be stored in an oxygen-deprived environment. Oxygen-deprived environments can be generated by storing the formulations under an inert gas such as, for example, argon, nitrogen, or helium.

EXAMPLES

[00038] 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 to the appended claims.

[00039] 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.

[00040] 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.

Example 1. Stability of a 50 mg/ml Liquid Formulation of VEGF Trap

[00041] A liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25, was stored at 5 °C and

samples tested at 3, 6, 9, 12, 18 and 24 months. Stability was determined by SE-HPLC. The results, shown in Table 1, show that 98.6% and 98.3% of VEGF trap protein remained intact (non-degraded) at 12 and 24 months, respectively. Turbidity was measured at OD₄₀₅ nm; and percent recovered protein by size exclusion HPLC.

Table 1. Stability of 50 mg/ml VEGF Trap Protein When Stored at 5 °C (VGFT-SS065)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	99.0
3	Pass	0.00	6.2	102	98.8
6	Pass	0.01	6.2	103	98.7
9	Pass	0.01	6.3	102	98.2
12	Pass	0.01	6.3	106	98.6
18	Pass	0.00	6.3	103	98.4
24	Pass	0.00	6.2	93	98.3

[00042] A liquid formulation containing 10 mM phosphate, 50 mM NaCl, 3% PEG 3350, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25, was stored at 5 °C and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability results are shown in Table 2.

Table 2. Stability of 50 mg/ml VEGF Trap Protein When Stored at 5 °C (VGFT-SS065)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	99.0
3	Pass	0.00	6.2	100	98.8
6	Pass	0.01	6.3	103	98.5
9	Pass	0.00	6.3	103	98.3
12	Pass	0.01	6.3	110	98.3
18	Pass	0.00	6.3	113	98.0
24	Pass	0.01	6.2	90	97.8

Example 2. Stability of a 75 mg/ml Liquid Formulation of VEGF Trap

[00043] A liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 75 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25, was stored at 5 °C and samples tested at 0, 1, 2.3, 3, 9, 12 and 15 months. Stability results are shown in Table 3.

Table 3 Stability of 75 mg/ml VEGF Trap Protein When Stored at 5 °C (VGFT-SS101)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	97.1
1	Pass	0.00	6.2	96	97.0
2.3	Pass	0.00	6.2	98	96.7
3	Pass	0.00	6.2	97	96.1
9	Pass	-0.01	6.0	101	96.0
12	Pass	0.00	6.3	110	94.5
15	Pass	0.00	6.3	92	95.6

[00044] A liquid formulation containing 10 mM phosphate, 50 mM NaCl, 3% PEG 3350, 20% sucrose, and 75 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25, was stored at 5 °C and samples tested at 0, 1, 2.3, 3, 9, 12 and 15 months. Stability results are shown in Table 4.

Table 4. Stability of 75 mg/ml VEGF Trap Protein When Stored at 5 °C (VGFT-SS101)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	96.8
1	Pass	0.00	6.2	99	96.7
2.3	Pass	0.00	6.2	97	96.3
3	Pass	0.00	6.2	89	95.6
9	Pass	-0.01	6.2	98	95.4
12	Pass	-0.01	6.3	112	94.1
15	Pass	0.00	6.3	98	94.8

Example 3. Stability of a 100 mg/ml Liquid Formulation of VEGF Trap

[00045] A liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 100 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25, was stored at 5 °C and samples tested at 0, 1, 2.3, 3, 9, 12 and 15 months. Stability results are shown in Table 5.

Table 5. Stability of 100 mg/ml VEGF Trap Protein Stored at 5 °C (VGFT-SS101)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	96.7
1	Pass	0.00	6.2	92	96.6
2.3	Pass	0.00	6.2	92	96.2
6	Pass	0.00	6.2	99	95.5
9	Pass	-0.01	6.2	92	95.5
12	Pass	-0.01	6.2	110	93.9
15	Pass	0.00	6.3	108	94.8

[00046] A liquid formulation containing 10 mM phosphate, 50 mM NaCl, 3% PEG 3350, 20% sucrose, and 100 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25, was stored at 5 °C and samples tested at 0, 1, 2.3, 3, 9, 12 and 15 months. Stability results are shown in Table 6.

Table 6. Stability of 100 mg/ml VEGF Trap Protein Stored at 5 °C (VGFT-SS101)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	96.5
1	Pass	0.01	6.2	94	96.2
2.3	Pass	0.01	6.2	93	95.7
6	Pass	0.01	6.2	102	94.6
9	Pass	0.00	6.2	95	94.6
12	Pass	0.00	6.3	96	92.8
15	Pass	0.01	6.3	102	93.9

Example 4. Further Embodiments of Stable VEGF Trap Formulations

[00047] In one embodiment, the invention provides a stable liquid VEGF-binding fusion

protein (VEGF trap) formulations comprising 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% Polysorbate 20, 20% sucrose, 25 mg/ml VEGF trap protein, pH 6.0. This formulation can either be delivered subcutaneously or diluted and delivered by intravenous infusion. Due to the high osmolality of this formulation, it is diluted 3-fold to achieve an iso-osmolar solution for intravenous administration. Stability studies showed less than about 1 % degradation was detected after 3 years of storage at 2-8°C.

[00048] In one embodiment, the invention features a lyophilized formulation which is preferably concentrated two-fold from the pre-lyophilized to the post-lyophilized formulation, *e.g.*, 50 to 100 mg/ml; 75 to 150 mg/ml, or 100 to 200 mg/ml VEGF trap protein. In one specific embodiment, the pre-lyophilized formulation comprises 10 mM histidine, 1.5% PEG 3350, 0.75% glycine, 2.5% sucrose, 50 mg/ml VEGF trap protein, pH 6.3, and is reconstituted to a formulation comprising 20 mM histidine, 3% PEG 3350, 1.5% glycine, 5% sucrose, 100 mg/ml VEGF trap protein, pH 6.3. Stability studied showed no degradation of the VEGF trap was detected after 6 months of storage at 2-8 °C.

[00049] In one embodiment of a liquid formulation, the formulation comprises 10 mM histidine, 50 mM NaCl, 5-20% sucrose, 50-100 mg/ml VEGF trap, and one of 0.1% polysorbate 20 or TY° PEG 3350. One advantage of this liquid formulation is that it provides a higher concentration of VEGF trap without requiring the manufacture of a lyophilized product. Thus, this formulation provides ease for subcutaneous delivery, for example, by allowing provision of a liquid pre-filled syringe at a concentration higher than that delivered by IV infusion. Also, this formulation could advantageously be used to provide lower infusion volumes and shorter infusion times. The amount of degradation determined by SE-HPLC following incubation at 5 °C for up to 15 or 24 months is summarized in Table 7.

Table 7. Stability of Liquid Formulation with 50-100 mg/ml VEGF Trap (VGFT-SS101)

Incubation (months)	VEGF Trap (mg/ml)	% Polysorbate 20	% PEG 3350	% Degradation
24	50	0.1	-	0.7
24	50	-	3	1.3
15	75	0.1	-	1.5
15	75	-	3	2.0

Incubation (months)	VEGF Trap (mg/ml)	% Polysorbate 20	% PEG 3350	% Degradation
15	100	0.1	-	1.9
15	100	-	3	2.6

Example 5. Stability and Activity of Lyophilized and Liquid

[00050] The stability of a reconstituted lyophilized formulation was determined over a 6 month period. The pre-lyophilized formulation contained 10 mM histidine, 1.5% PEG 3350, 2.5% sucrose, 0.75% glycine and 50 mg/ml VEGF trap protein. After lyophilization, the reconstituted formulation contained 20 mM histidine, 3% PEG 3350, 5% sucrose, 1.5% glycine, and 100 mg/ml VEGF trap protein (SEQ ID NO:4). The results are shown in Table 8. Activity was determined in a cell based bioassay which directly measures the ability of the VEGF trap to inhibit the biological effects of human VEGF on a mouse Baf/3 VEGFR1/EpoR cell line. Therefore, this bioassay directly measures the biological activity of the protein. The results are expressed as percent relative potency (test sample IC₅₀/ reference VEGF IC₅₀ standard x 100). The binding affinity of VEGF to the VEGF trap is measured using a sensitive ELISA that specifically measures free VEGF in equilibrated mixtures containing VEGF and various concentrations of the VEGF trap. Results are expressed as percent relative binding (IC₅₀ of test sample/IC₅₀ of reference x 100). Measured pH ranged between 6.3 - 6.5. All solutions were visually clear. The concentration of VEGF trap recovered was determined with a UV spectrophotometer as mg/ml at A280 nm. The percent VEGF trap recovered in the native configuration (main peak purity) was determined with SE-HPLC.

Table 8. Stability of VEGF Trap Lyophilized Formulation Stored at 5 °C (VGT-RS475)

Months	Bioassay	Binding Assay	% Recovered	% Native Configuration
0	120	126	97.9	98.7
1	117	74	97.9	98.6
1 + 24 hr	126	72	99.0	98.5
1 + 4 hr	94	81	101.5	98.2
3	101	98	98.1	98.6
3 + 24 hr	65	94	98.1	98.2

Months	Bioassay	Binding Assay	% Recovered	% Native Configuration
6 + 4 hr			96.9	98.7
6 + 24 hr			98.8	98.6

[00051] A formulation containing about 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein was tested for stability and activity over 36 months when stored at 5 °C. The results are shown in Table 9. All samples were clear and colorless as determined by visual inspection. pH ranged from 6.0-6.1. *Binding assay results for two measurements (1 and 2 months) are expressed directly and not as a percent of the standard.

Table 9. Stability and Activity of Liquid Formulation (VGT-FS405)

Months	% Native Configuration	Bioassay	Binding Assay	Protein Content mg/ml
0	99.7	106	72	25.0
1	99.9	119	4.4 pM*	25.2
2	99.6	102	5.4 pM*	25.1
3	99.6	97	88	25.1
6	99.6	101	106	25.0
9	99.4	89	126	25.4
12	99.5	85	95	25.2
18	99.4	99	81	25.5
24	99.3	75	95	25.6
36	98.8	109	79	25.6

WE CLAIM:

1. A mammalian cell comprising a polynucleotide that encodes a fusion protein, wherein said fusion protein comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component; wherein said fusion protein does not comprise a signal peptide and does not comprise a C-terminal lysine; and wherein said fusion protein binds vascular endothelial growth factor (VEGF).
2. The mammalian cell of claim 1, wherein said mammalian cell is a Chinese hamster ovary (CHO) cell.
3. The mammalian cell of claim 1, wherein said first VEGF receptor is Flt1.
4. The mammalian cell of claim 3, wherein said second VEGF receptor is Flk1 or Flt2.
5. The mammalian cell of claim 4, wherein said fusion protein comprises amino acids 27-457 of SEQ ID NO:2.
6. The mammalian cell of claim 5, wherein said fusion protein is glycosylated at asparagine residues 59, 91, 146, 219, and 308.
7. The mammalian cell of claim 5, wherein said polynucleotide comprises nucleotides 146-1439 of SEQ ID NO:1.
8. The mammalian cell of claim 4, wherein said fusion protein comprises amino acids 27-457 of SEQ ID NO:4.
9. The mammalian cell of claim 8, wherein said fusion protein is glycosylated at asparagine residues 62, 94, 149, 222 and 308.
10. The mammalian cell of claim 8, wherein said polynucleotide comprises nucleotides 78-1371 of SEQ ID NO:3.
11. A method of manufacturing a VEGF antagonist fusion protein that comprises in order from the N-terminus to the C-terminus an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component, and does not comprise a signal peptide or a C-terminal lysine, said method comprising:
 - a. expressing said VEGF antagonist fusion protein in a mammalian cell, wherein said mammalian cell comprises a polynucleotide that encodes said VEGF antagonist fusion protein; and
 - b. purifying said VEGF antagonist fusion protein.

12. The method of claim 11, wherein said first VEGF receptor is Flt1 and said second VEGF receptor is Flk1 or Flt2.
13. The method of claim 11, wherein said mammalian cell is a CHO cell.
14. The method of claim 11, wherein said fusion protein is substantially free of protein contaminants.
15. The method of claim 14, wherein at least 90% of the weight of said fusion protein is not present as an aggregate.
16. The method of claim 11, wherein said VEGF antagonist fusion protein is glycosylated at one or more asparagine residues.
17. The method of claim 12, wherein said VEGF antagonist fusion protein comprises amino acids 27-457 of SEQ ID NO:4.
18. The method of claim 17, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues 62, 94, 149, 222 and 308.
19. The method of claim 12, wherein said VEGF antagonist fusion protein comprises amino acids 27-457 of SEQ ID NO:2.
20. The method of claim 19, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues 59, 91, 146, 219 and 308.s

ABSTRACT

[00052] Formulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist are provided including a pre-lyophilized formulation, a reconstituted lyophilized formulation, and a stable liquid formulation. Preferably, the fusion protein has the sequence of SEQ ID NO:4.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application of: DIX et al.	Confirmation No.: TBD
Application No.: TBD	Art Unit: TBD
Filed: August 31, 2017	Examiner: TBD
For: VEGF ANTAGONIST FORMULATIONS	

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

STATEMENT VERIFYING SEQUENCE LISTING UNDER § 1.821(f)

Applicants submit herewith a paper copy and a computer readable form of the identical sequence listing, which is incorporated in its entirety into the specification by reference. The sequence listing information recorded in computer readable form is identical to the written (PDF) sequence listing, as specified under 37 CFR § 1.821(e) and (f).

Respectfully Submitted,

Kutak Rock LLP
Customer Number: 138357

By: /Joseph E. Zahner, Reg. No. 48,224/

Joseph E. Zahner
Reg. No. 48,224
Telephone No. 816-502-4663
Joseph.Zahner@KutakRock.com

ATTORNEYS FOR APPLICANT

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of Invention	VEGF ANTAGONIST FORMULATIONS
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 <u>13/909,745</u> filed on <u>June 4, 2013</u> The above-identified application was made or authorized to be made by me. I believe that I am the original inventor or an original joint inventor of a claimed invention in the application. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. WARNING: Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.	
LEGAL NAME OF INVENTOR Inventor: <u>Susan KAUTZ</u> Date (Optional): <u>03 Dec 2013</u> Signature: <u><i>Susan Kautz</i></u>	
Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.	

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute 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.

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.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of
Invention

VEGF ANTAGONIST FORMULATIONS

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 13/909,745

filed on June 4, 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 five (5) years, or both.

WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Daniel DIX

Date (Optional): Jan 14, 2014

Signature: *Daniel D. Dix*

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. 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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**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

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Invention**

VEGF ANTAGONIST FORMULATIONS

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This declaration
is directed to:

☐

The attached application, or

☒

United States application or PCT international application number 13/909,745

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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.

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LEGAL NAME OF INVENTOR

Inventor: Kelly FRYE

Date (Optional): 12-16-13

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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SCORE Placeholder Sheet for IFW Content

Application Number: 15692893

Document Date: 08/31/2017

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):

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- External customers may access SCORE content via PAIR using the Supplemental Content tab.

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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: Anjum, Durreshwar

Timestamp: [year=2017; month=9; day=8; hr=10; min=16; sec=45; ms=837;]

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Application No: 15692893 Version No: 1.0

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No. of SeqIDs Defined: 4
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Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile
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Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu
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Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys
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Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val
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Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
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Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
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Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
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Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
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425

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Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 15/692,893	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(j))	20	minus 20 = *			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2	minus 3 = *				x 420 =	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
							0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
			TOTAL			TOTAL	1600
* If the difference in column 1 is less than zero, enter "0" in column 2.							
APPLICATION AS AMENDED - PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =	OR	x =
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =	OR	x =
	Application Size Fee (37 CFR 1.16(s))					OR	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR	
			TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =	OR	x =
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =	OR	x =
	Application Size Fee (37 CFR 1.16(s))					OR	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR	
			TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.							



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
15/692,893	08/31/2017	1629	1600	238811-21.89 (4030US11)	20	2

CONFIRMATION NO. 8858

FILING RECEIPT



0000000093988642

138357
Kutak Rock LLP
2300 Main Street, Suite 800
Kansas City, MO 64108

Date Mailed: 09/12/2017

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)

Daniel B. DIX, LaGrangeville, NY;
Kelly FRYE, Mendham, NJ;
Susan KAUTZ, Albany, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/342,989 11/03/2016
which is a CON of 15/064,343 03/08/2016 PAT 9511140
which is a CON of 14/550,385 11/21/2014 PAT 9416167
which is a CON of 13/909,745 06/04/2013 PAT 8921316
which is a CON of 13/428,510 03/23/2012 PAT 8710004
which is a CON of 13/343,214 01/04/2012 PAT 8404638
which is a DIV of 12/835,065 07/13/2010 PAT 8110546
which is a CON of 11/387,256 03/22/2006 ABN
which claims benefit of 60/665,125 03/25/2005

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: 09/11/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/692,893**

Projected Publication Date: 12/21/2017

Non-Publication Request: No

Early Publication Request: No

Title

VEGF ANTAGONIST FORMULATIONS

Preliminary Class

514

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

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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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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).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date
15/692,893	August 31, 2017

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

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

96387

OR

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

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

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone			Email		

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

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)	September 19, 2017
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.

STATEMENT UNDER 37 CFR 3.73(c)Applicant/Patent Owner: **REGENERON PHARMACEUTICALS, INC.**Application No./Patent No.: **15/692,893**Filed/Issue Date: **August 31, 2017**Titled: **VEGF ANTAGONIST FORMULATIONS****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), or 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 __, Frame __, 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.

[Page 1 of 2]

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.

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.

/Karl Bozicevic, Reg. No. 28,807/
Signature

October 9, 2017
Date

Karl Bozicevic
Printed or Typed Name

28,807
Title or Registration Number

ASSIGNMENT

WHEREAS, We, Daniel Dix, residing at 55 Memory Trail, LaGrangeville, New York 12540, a citizen of the United States of America; Kelly Frye, residing at 29 N. Ridge Road, Pomona, New York 10970, a citizen of the United States of America; Susan Kautz, residing at 3 Hall Place, Albany, New York 12210, a citizen of the United States of America; (HEREINAFTER CALLED "ASSIGNOR") are inventor(s) of the invention(s) disclosed and/or claimed in the following patent application:

VEGF ANTAGONIT FORMULATIONS

WHEREAS, REGENERON PHARMACEUTICALS INC., a corporation organized and existing under the laws of the State of New York, with offices at 777 Old Saw Mill River Road, Tarrytown, New York 10591-6707, U.S.A. (HEREINAFTER called "ASSIGNEE") is desirous of acquiring our entire right, title and interest in, to, and under the said applications;

NOW, THEREFORE, in consideration of the sum of One Dollar (\$1.00) to us in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, We, the said ASSIGNORS, have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over unto the said ASSIGNEE, its successors, legal representatives, and assigns, our entire right, title and interest for all countries in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed in the above-described United States applications, and in and to said United States Applications and all divisions, renewals, continuations, and continuations-in-part thereof, and all Patents of the United States which may be granted thereon and all reissues and extensions thereof; and all applications for industrial property protection, including, without limitation, all applications for patents utility models, and designs which may hereafter be filed for said inventions in any country or countries foreign to the United States, together with the right to file such applications and the right to claim for the same the priority rights derived from said United States applications under the Patent Laws of the United States, the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention, or under any other available international agreement or under the domestic laws of the country in which any such application is filed, as may be applicable; and all forms of industrial property protection, including, without limitation, patents, utility models, inventors' certificates and designs which

Assignment

may be granted for said inventions in any country or countries foreign to the United States and all extensions, renewals and reissues thereof;

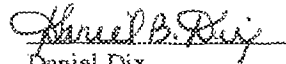
AND WE HEREBY authorize and request the Commissioner of Patents and Trademarks of the United States and any Official of any country or countries foreign to the United States whose duty it is to issue patents or other evidence or forms of industrial property protection on applications as aforesaid, to issue the same to the said ASSIGNEE, their successors, legal representatives and assigns, in accordance with this instrument;

AND WE HEREBY covenant and agree that WE have full right to convey the entire interest HEREINAFTER assigned, and that WE have not executed, and will not execute, any agreement in conflict herewith;

AND WE HEREBY further covenant and agree that WE will communicate to the said ASSIGNEE, its successors, legal representatives and assigns, any facts known to us respecting said inventions, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing, continuation-in-part, reissue and foreign applications, make all rightful oaths, and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper protection for said inventions in all countries.

IN TESTIMONY HEREOF, WE hereunto set our hands and seals the day and year set opposite our signatures.

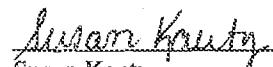
Dated: 04-03-06


Daniel Dix

Dated: _____

Kelly Frye

Dated: 3/16/2006


Susan Kautz

ASSIGNMENT

WHEREAS, We, Daniel Dix, residing at 55 Memory Trail, LaGrangeville, New York 12540, a citizen of the United States of America; Kelly Frye, residing at 29 N. Ridge Road, Pomona, New York 10970, a citizen of the United States of America; Susan Kautz, residing at 3 Hall Place, Albany, New York 12210, a citizen of the United States of America; (HEREINAFTER CALLED "ASSIGNOR") are inventor(s) of the invention(s) disclosed and/or claimed in the following patent application:

VEGF ANTAGONIT FORMULATIONS

WHEREAS, REGENERON PHARMACEUTICALS INC., a corporation organized and existing under the laws of the State of New York, with offices at 777 Old Saw Mill River Road, Tarrytown, New York 10591-6707, U.S.A. (HEREINAFTER called "ASSIGNEE") is desirous of acquiring our entire right, title and interest in, to, and under the said applications;

NOW, THEREFORE, in consideration of the sum of One Dollar (\$1.00) to us in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, We, the said ASSIGNORS, have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over unto the said ASSIGNEE, its successors, legal representatives, and assigns, our entire right, title and interest for all countries in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed in the above-described United States applications, and in and to said United States Applications and all divisions, renewals, continuations, and continuations-in-part thereof, and all Patents of the United States which may be granted thereon and all reissues and extensions thereof; and all applications for industrial property protection, including, without limitation, all applications for patents utility models, and designs which may hereafter be filed for said inventions in any country or countries foreign to the United States, together with the right to file such applications and the right to claim for the same the priority rights derived from said United States applications under the Patent Laws of the United States, the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention, or under any other available international agreement or under the domestic laws of the country in which any such application is filed, as may be applicable; and all forms of industrial property protection, including, without limitation, patents, utility models, inventors' certificates and designs which

Assignment

may be granted for said inventions in any country or countries foreign to the United States and all extensions, renewals and reissues thereof;

AND WE HEREBY authorize and request the Commissioner of Patents and Trademarks of the United States and any Official of any country or countries foreign to the United States whose duty it is to issue patents or other evidence or forms of industrial property protection on applications as aforesaid, to issue the same to the said ASSIGNEE, their successors, legal representatives and assigns, in accordance with this instrument;

AND WE HEREBY covenant and agree that WE have full right to convey the entire interest HEREINAFTER assigned, and that WE have not executed, and will not execute, any agreement in conflict herewith;

AND WE HEREBY further covenant and agree that WE will communicate to the said ASSIGNEE, its successors, legal representatives and assigns, any facts known to us respecting said inventions, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing, continuation-in-part, reissue and foreign applications, make all rightful oaths, and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper protection for said inventions in all countries.

IN TESTIMONY HEREOF, WE hereunto set our hands and seals the day and year set opposite our signatures.

Dated: _____

Daniel Dix

Dated: March 21, 2006

Kelly Frye
Kelly Frye

Dated: _____

Susan Kautz

Electronic Acknowledgement Receipt

EFS ID:	30597821
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	VEGF ANTAGONIST FORMULATIONS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	138357
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	238811-21.89 (4030US11)
Receipt Date:	09-OCT-2017
Filing Date:	31-AUG-2017
Time Stamp:	12:33:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	4030US11_POA.pdf	109684	no	1
			c656b9ebe8e42de5220d7ea19c8a241214526f8c		

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	REGN-023CON8_2017-10-09_373_c_complete.pdf	225654	no	6
			e1991c49a40b17413b9c27eccbe0a2ae3dc6fffa		
Warnings:					
Information:					
Total Files Size (in bytes):				335338	
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/692,893	08/31/2017	Daniel B. DIX	238811-21.89 (4030US11)

CONFIRMATION NO. 8858

POA ACCEPTANCE LETTER

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



Date Mailed: 10/12/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/09/2017.

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.

/ytdemisse/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/692,893
				Filing Date	August 31, 2017
				First Named Inventor	Dix, Daniel
				Art Unit	1647
				Examiner Name	STOICA, ELLY GERALD
Sheet	1	of	1	Attorney Docket Number	REGN-023CON8

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

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1	2002/004478	2002-01-10	Danko et al.	
	2				

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
		Country Code-Number-Kind Code (if known)				
	1	WO 2006/088650	2006-08-24	Regeneron Pharmaceuticals, Inc.		
	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	LOPEZ et al., "Comparative enhancer effects of Span 20 with Tween 20 and Azone of the <i>in vitro</i> percutaneous penetration of compounds with different lipophilicities" International Journal of Pharmaceutics (July 1, 2000) 202(1-2):133-140	
	2		

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 Acknowledgement Receipt

EFS ID:	30874426
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	VEGF ANTAGONIST FORMULATIONS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	238811-21.89 (4030US11)
Receipt Date:	07-NOV-2017
Filing Date:	31-AUG-2017
Time Stamp:	12:01:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-023CON8_2017-11-07_s upp_IDS_trans.pdf	52305 450e10d62810ca2b15bc6b3ab87171638c1 a9933	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-023CON8_2017-11-07_s upp_IDS_SB08A.pdf	24108	no	1
			8e8a6fb33e0fab57469092bb9c357194fc6 0356		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO06088650_Regeneron.pdf	1170705	no	25
			00ac36861bd3320527eb187520adcd3459 d63d8b		
Warnings:					
Information:					
4	Non Patent Literature	Lopez_2000.PDF	568602	no	8
			46dee796ac13bc8713b386bfc3ec0203d94 e48c1		
Warnings:					
Information:					
Total Files Size (in bytes):			1815720		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

Electronically Filed 11/7/2017

INFORMATION DISCLOSURE STATEMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	REGN-023CON8
	First Named Inventor	Dix, Daniel
	Application Number	15/692,893
	Confirmation No.	8858
	Filing Date	August 31, 2017
	Group Art Unit	1647
	Examiner Name	STOICA, ELLY GERALD
	Title:	<i>"VEGF Antagonist Formulations"</i>

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-023CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 7, 2017

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



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8

CONFIRMATION NO. 8858

PUBLICATION NOTICE



OC000000096239454

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

Title:VEGF ANTAGONIST FORMULATIONS

Publication No.US-2017-0360930-A1

Publication Date:12/21/2017

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.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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



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.
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8	8858
96387	7590	09/14/2018		
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065			EXAMINER STOICA, ELLY GERALD	
			ART UNIT	PAPER NUMBER
			1647	
			NOTIFICATION DATE	DELIVERY MODE
			09/14/2018	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

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of the claims

2. Claims 1-20 are pending and are currently examined.

Claim Rejections - 35 USC § 112

3. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 6, 9, 18 and 20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Specifically, the claims address the glycosylation status of constructs claimed by addressing residues by numbers, which, absent a SEQ ID NO: does not mean that the position is actually known.

As such, the metes and bounds of the claims could not be determined.

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

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise,

and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

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

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

6. Claims 1-20 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventors, at the time the application was filed, had possession of the claimed invention.

“[T]he purpose of the written description requirement is to ‘ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.’” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (en banc) (quoting *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004)). To satisfy the written description requirement, the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562-63, 19 USPQ2d 1111 (Fed. Cir. 1991). See also MPEP 2163.04.

For a claim to a genus, a generic statement that defines a genus of substances by partial structure and their functional activity does not provide an adequate written

description of the genus. *Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of the genus must be capable of doing, not of the substance and structure of the members. The Federal Circuit has cautioned that, for claims reciting a genus of antibodies with particular functional properties (e.g., high affinity, neutralization activity, competing with a reference antibody for binding), “[c]laiming antibodies with specific properties, e.g., an antibody that binds to human TNF- α with A2 specificity, can result in a claim that does not meet written description even if the human TNF- α protein is disclosed because antibodies with those properties have not been adequately described.” *Centocor Ortho Biotech Inc. v. Abbott Labs.*, 97 USPQ2d 1870, 1875, 1877-78 (Fed. Cir. 2011).

“[A] sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350 (quoting *Eli Lilly*, 119 F.3d at 1568-69). A “representative number of species” means that those species that are adequately described are representative of the entire genus. *AbbVie Deutschland GMBH v. Janssen Biotech*, 111 USPQ2d 1780, 1790 (Fed. Cir. 2014) (“The ’128 and ’485 patents, however, only describe species of structurally similar antibodies that were derived from Joe-9. Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.”). Thus, when there is

substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus to provide a "representative number" of species.

The "structural features common to the members of the genus" needed for one of skill in the art to 'visualize or recognize' the members of the genus takes into account the state of the art at the time of the invention.

Lastly, even if a selection procedure is disclosed that was, at the time of the invention, sufficient to enable the skilled artisan to identify antibodies with the recited functional properties, the written description provision of 35 U.S.C § 112 is severable from its enablement provision

In *Amgen Inc. v. Sanofi*, 124 USPQ2d 1354 (Fed. Cir. 2017), relying upon *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 94 USPQ2d 1161 (Fed Cir. 2010), it is noted that to show invention, a patentee must convey in its disclosure that is "had possession of the claimed subject matter as of the filing date. Demonstrating possession "requires a precise definition" of the invention. To provide this precise definition" for a claim to a genus, a patentee must disclose "a representative number of species within the scope of the genus of structural features common to the members of the genus so that one of skill in the art can visualize or recognize the member of the genus" (see *Amgen* at page 1358).

Also, it is not enough for the specification to show how to make and use the invention, i.e., to enable it (see *Amgen* at page 1361).

An adequate written description must contain enough information about the actual makeup of the claimed products – "a precise definition, such as structure, formula, chemical name, physical properties of other properties, of species falling within the genus sufficient to distinguish the gene from other materials", which may be present in "functional

terminology when the art has established a correlation between structure and function” (Amgen page 1361).

In the instant case, the specification discloses an VEGF antagonist a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF, comprising a fusion protein comprising a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component. In a specific embodiment of the VEGF-specific fusion protein antagonist, the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1 or Flt4. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO: 2 or 4; more preferably, SEQ ID NO: 4. In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified posttranslationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO: 4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308. ([0006]-[0028]). The claims are also requiring that a signal peptide is lacking and also a C-terminal lysine is lacking, without mentioning any particular sequence number of the fusion protein. From her, the claims expend to encompass a mammalian cell that comprises a polynucleotide that encodes the sequenceless fusion protein and a method of manufacturing the fusion protein by known processes from the mammalian cell claimed.

The present claims attempt to claim every fusion protein that comprises all the immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, a non-descript multimerizing component and with the only restriction that

the fusion protein does not comprise a C-terminally lysine or a signal peptide. It is of note that the Application does not offer any sequence of the fusion protein claimed. Thus the claims fail to disclose a representative number of species falling within the scope of the genus or structural common to the members of the genus so the one of skill in the art can visualize or recognize the member of the genus.

A “representative number of species” means that those species that are adequately described are representative of the entire genus. *AbbVie Deutschland GMBH v. Janssen Biotech*, 111 USPQ2d 1780, 1790 (Fed. Cir. 2014).

Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The “structural features common to the members of the genus” needed for one of skill in the art to ‘visualize or recognize’ the members of the genus takes into account the state of the art at the time of the invention. For example, the Federal Circuit has found that possession of a mouse antibody heavy and light chain variable regions provides a structural “stepping stone” to the corresponding chimeric antibody, but not to human antibodies. *Centocor Ortho Biotech Inc. v. Abbott Labs.*, 97 USPQ2d 1870, 1875 (Fed. Cir. 2011). One of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genera.

7. Claims 1-20 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a mammalian cell comprising a polynucleotide that encodes a fusion protein, wherein said fusion protein comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component; wherein said fusion protein does not comprise a signal peptide and does not comprise a C-terminal lysine; and wherein said fusion protein binds vascular endothelial growth factor (VEGF). The cell is further used to obtain the VEGF antagonist fusion protein.

The specification does not offer an adequate description of the polynucleotide comprised in the mammalian cell (which may be Chinese hamster ovarian cell). There are no structural indication regarding the exact sequence of the fusion protein sought after. The specification does not address the manufacturing aspect at all, since the disclosure is about formulations of the fusion protein as to be used in pharmaceutical industry.

While the art of manufacturing fusion proteins by cultivating cells that comprise the encoding polynucleotides is extremely well developed, but the skilled artisan has to know what the structure of the polynucleotide is. This is not the case in the instant Application and as such the practitioner would be left with some vague indication of which fragments of the fusion protein are present or not, with no indication of what else is present in the fusion and what the structure for these unknown part comes from. Thus, the amount of experimentation would be immense, given the duty to try all possible solutions and also that fact that the results would be unpredictable (since unknown structures would have to be used. Such an amount of experimentation is considered undue and thus claims are not considered enabled.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on M-F 8-5 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

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 phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

ELLY-GERALD STOICA
Primary Examiner
Art Unit 1647

/Elly-Gerald Stoica/
Primary Examiner, Art Unit 1647

<i>Search Notes</i> 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.
	Examiner ELLY GERALD STOICA	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* 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
PALM (inventor and continuity)	09/10/2018	EGS
East Search (US-PGpub; USPAT; USOCR; EPO; JPO; Derwent)	09/10/2018	EGS
STN (Medline; Biosis; CAPlus; EMBASE)	09/10/2018	EGS
Search for SEQ ID NOs: :1-4	09/08/2018	EGS

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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Bibliographic Data

Application No: 15/692,893

Foreign Priority claimed: ☐ Yes ☒ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged:

/Elly-Gerald Stoica/

Examiner's Signature

Initials

Title:

VEGF ANTAGONIST FORMULATIONS

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
08/31/2017	514	1647	REGN-023CON8
RULE			

APPLICANTS

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Kelly FRYE Mendham, NJ, UNITED STATES

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CONTINUING DATA

This application is a CON of 15342989 11/03/2016

15342989 is a CON of 15064343 03/08/2016 PAT 9511140

15064343 is a CON of 14550385 11/21/2014 PAT 9416167

14550385 is a CON of 13909745 06/04/2013 PAT 8921316

13909745 is a CON of 13428510 03/23/2012 PAT 8710004

13428510 is a CON of 13343214 01/04/2012 PAT 8404638

13343214 is a DIV of 12835065 07/13/2010 PAT 8110546

12835065 is a CON of 11387256 03/22/2006

11387256 has PRO of 60665125 03/25/2005

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

09/11/2017

STATE OR COUNTRY

UNITED STATES

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201 REDWOOD SHORES PARKWAY

SUITE 200

REDWOOD CITY, CA 94065

UNITED STATES

FILING FEE RECEIVED

\$1,600

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PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 2 JAN 29 The 2018 version of MEDLINE now available on STN
NEWS 3 FEB 12 Chinese dual filings are now linked within DWPI families
NEWS 4 MAR 29 CCI Now Searchable in CAS REGISTRY(SM)
NEWS 5 SEP 7 Third Emtree(R) Thesaurus Update Now Available in
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FILE 'HOME' ENTERED AT 12:44:08 ON 10 SEP 2018

=> File .Gerry2MBCE
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.34	0.34

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 12:44:37 ON 10 SEP 2018

FILE 'BIOSIS' ENTERED AT 12:44:37 ON 10 SEP 2018
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```
=> S (VEGF (S) (antagonist OR Trap OR chimer? OR Inhibit)) (P) (Flt1 OR Flk1 OR Flt4) AND pd<=20060322
L1      58 (VEGF (S) (ANTAGONIST OR TRAP OR CHIMER? OR INHIBIT)) (P) (FLT1 OR FLK1 OR FLT4) AND PD<=20060322
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=> Dup Rem L1
PROCESSING COMPLETED FOR L1
L2      30 DUP REM L1 (28 DUPLICATES REMOVED)
        ANSWERS '1-11' FROM FILE MEDLINE
        ANSWERS '12-14' FROM FILE BIOSIS
        ANSWERS '15-30' FROM FILE CAPLUS
```

```
=> S ((VEGF (3A) Receptor) (S) (antagonist OR Trap OR chimer? OR Inhibit?)) (P) (Flt1 OR Flk1 OR Flt4) (P) ?nucleotide AND pd<=20060322
L3      11 ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR INHIBIT?)) (P) (FLT1 OR FLK1 OR FLT4) (P) ?NUCLEOTIDE AND PD<=20060322
```

```
=> Dup Rem L3
PROCESSING COMPLETED FOR L3
L4      4 DUP REM L3 (7 DUPLICATES REMOVED)
        ANSWER '1' FROM FILE MEDLINE
        ANSWERS '2-4' FROM FILE CAPLUS
```

```
=> S ((VEGF (3A) Receptor) (S) (antagonist OR Trap OR chimer? OR Inhibit?)) (P) (Flt1 OR Flk1 OR Flt4) (P) multimer AND pd<=20060322
L5      0 ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR INHIBIT?)) (P) (FLT1 OR FLK1 OR FLT4) (P) MULTIMER AND PD<=20060322
```

```
=> S ((VEGF (3A) Receptor) (S) (antagonist OR Trap OR chimer? OR Inhibit?)) (P) (Flt1 OR Flk1 OR Flt4) (P) multimer? AND pd<=20060322L5
DATE SPECIFICATION IS NOT VALID
Date specifications may use ranges and numeric operators. The date itself can be in any of the following general formats:
```

STN Format: YYYYMMDD

Slash Format: MM/DD/YYYY or MM/YYYY

Dot Format: DD.MM.YYYY or MM.YYYY

Text Format:	February 10, 1987	Feb 1989
	Feb. 10, 1987	1990
	Feb. 10, 2000	1998 - 2001
	Feb 10, 1987	July 1997 - May 2002
	10 February 1987	March 5 - 8, 1990
	10 Feb 2007	April - June, 1999

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```
=> S ((VEGF (3A) Receptor) (S) (antagonist OR Trap OR chimer? OR Inhibit?)) (P) (Flt1 OR Flk1 OR Flt4) (P) multimer? AND pd<=20060322
L6      0 ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR INHIBIT?)) (P) (FLT1 OR FLK1 OR FLT4) (P) MULTIMER? AND PD<=20060322
```

```
=> D His
```

(FILE 'HOME' ENTERED AT 12:44:08 ON 10 SEP 2018)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 12:44:37 ON 10 SEP 2018

L1 58 S (VEGF (S) (ANTAGONIST OR TRAP OR CHIMER? OR INHIBIT)) (P) (FL
 L2 30 DUP REM L1 (28 DUPLICATES REMOVED)
 L3 11 S ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR I
 L4 4 DUP REM L3 (7 DUPLICATES REMOVED)
 L5 0 S ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR I
 L6 0 S ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR I

=> D Ibib abs L2 1-30

L2 ANSWER 1 OF 30 MEDLINE ® on STN DUPLICATE 1
 ACCESSION NUMBER: 2006524617 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 16951187
 TITLE: AMG 706, an oral, multikinase inhibitor that selectively
 targets vascular endothelial growth factor,
 platelet-derived growth factor, and kit receptors, potently
 inhibits angiogenesis and induces regression in tumor
 xenografts.
 AUTHOR: Polverino Anthony
 CORPORATE SOURCE: Department of Oncology Research, Amgen, Inc., Thousand
 Oaks, CA 91320-1799, USA. tonyp@amgen.com
 AUTHOR: Coxon Angela; Starnes Charlie; Diaz Zobedia; DeMelfi
 Thomas; Wang Ling; Bready James; Estrada Juan; Cattley
 Russell; Kaufman Stephen; Chen Danlin; Gan Yongmei; Kumar
 Gondi; Meyer James; Neervannan Sesha; Alva Gonzalo;
 Talvenheimo Jane; Montestruque Silvia; Tasker Andrew; Patel
 Vinod; Radinsky Robert; Kendall Richard
 SOURCE: Cancer research, (2006 Sep 01) Vol. 66, No. 17, pp.
 8715-21.
 Journal code: 2984705R. E-ISSN: 1538-7445. L-ISSN:
 0008-5472.
 DIGITAL OBJECT ID: <http://dx.doi.org/10.1158/0008-5472.CAN-05-4665>
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: MEDLINE; Priority Journals
 FILE SEGMENT: Print
 ENTRY MONTH: 200711
 ENTRY DATE: Entered STN: 6 Sep 2006
 Last Updated on STN: 12 Dec 2006
 Entered Medline: 26 Nov 2007
 OS.CITING REF COUNT: 75 There are 75 MEDLINE records that cite this record
 AB The growth of solid tumors is dependent on the continued stimulation of
 endothelial cell proliferation and migration resulting in angiogenesis.
 The angiogenic process is controlled by a variety of factors of which the
 vascular endothelial growth factor (VEGF) pathway and its receptors play a
 pivotal role. Small-molecule inhibitors of VEGF receptors (VEGFR) have
 been shown to inhibit angiogenesis and tumor growth in preclinical
 models and in clinical trials. A novel nicotinamide, AMG 706, was
 identified as a potent, orally bioavailable inhibitor of the
 VEGFR1/Flt1, VEGFR2/kinase domain receptor/Flk-1, VEGFR3/Flt4,
 platelet-derived growth factor receptor, and Kit receptors in preclinical
 models. AMG 706 inhibited human endothelial cell proliferation induced by
 VEGF, but not by basic fibroblast growth factor in vitro, as well as
 vascular permeability induced by VEGF in mice. Oral administration of AMG
 706 potently inhibited VEGF-induced angiogenesis in the rat corneal model
 and induced regression of established A431 xenografts. AMG 706 was well
 tolerated and had no significant effects on body weight or on the general
 health of the animals. Histologic analysis of tumor xenografts from AMG
 706-treated animals revealed an increase in endothelial apoptosis and a
 reduction in blood vessel area that preceded an increase in tumor cell
 apoptosis. In summary, AMG 706 is an orally bioavailable, well-tolerated
 multikinase inhibitor that is presently under clinical investigation for

the treatment of human malignancies.

L2 ANSWER 2 OF 30 MEDLINE ® on STN DUPLICATE 2
ACCESSION NUMBER: 2006461712 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16885067
TITLE: Nerve growth factor (NGF) promotes angiogenesis in the
quail chorioallantoic membrane.
AUTHOR: Lazarovici Philip
CORPORATE SOURCE: School of Biomedical Engineering, Science and Health
Systems, Drexel University, Philadelphia, Pennsylvania,
USA.
AUTHOR: Gazit Aviv; Staniszevska Izabela; Marcinkiewicz Cezary;
Lelkes Peter I
SOURCE: Endothelium : journal of endothelial cell research, (2006
Jan-Feb) Vol. 13, No. 1, pp. 51-9.
Journal code: 9412590. ISSN: 1062-3329. L-ISSN: 1026-793X.
DIGITAL OBJECT ID: <http://dx.doi.org/10.1080/10623320600669053>
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200609
ENTRY DATE: Entered STN: 4 Aug 2006
Last Updated on STN: 16 Sep 2006
Entered Medline: 15 Sep 2006
OS.CITING REF COUNT: 13 There are 13 MEDLINE records that cite this record
AB Angiogenesis, the formation of new blood vessels, is tightly regulated by
growth factors, such as vascular endothelial growth factor (VEGF) and
fibroblast growth factor (FGF). The authors hypothesize that nerve growth
factor (NGF), a well known neurotrophin, may play a direct angiogenic
role. To test this hypothesis, the authors measured the effects of NGF on
the natural vascularization of the quail chorioallantoic membrane (CAM).
The angiogenic effect of NGF was compared to that of human recombinant
VEGF165 (rhVEGF) and basic FGF (rhbFGF). In comparison to
phosphate-buffered saline-treated controls, NGFs from different biological
sources (mouse, viper, and cobra) increased the rate of angiogenesis in a
dose-dependent fashion from 0.5 to 5 microg. For quantitative
morphometry, grayscale images of the blood vessels end points of the CAM
arteries were binarized for visualization and skeletonized for
quantization by fractal analysis. In mouse NGF-treated embryos the
fractal dimension (Df), indicative of arterial vessel length and density,
increased to 1.266 +/- 0.021 compared to 1.131 +/- 0.018 (p < .001) for
control embryos. This effect was similar to that of 0.5 microg rhVEGF
(1.290 +/- 0.021, p < .001) and 1.5 microg rhbFGF (1.264 +/- 0.028, p <
.001). The mouse NGF-induced angiogenic effect was blocked by 1 microM
K252a (1.149 +/- 0.018, p < .001), an antagonist of the NGF/trkA
receptor, but not by 1 microM SU-5416 (1.263 +/- 0.029, p < .001), the
VEGF/Flk1 receptor antagonist, indicating a direct, selective
angiogenic effect of NGF via quail embryo trkA receptor activation. These
results confirm previous observations that NGF has angiogenic activity and
suggest that this neurotrophin may also play an important role in the
cardiovascular system, besides its well-known effects in the nervous
system. The angiogenic properties of NGF may be beneficial in engineering
new blood vessels and for developing novel antiangiogenesis therapies for
cancer.

L2 ANSWER 3 OF 30 MEDLINE ® on STN DUPLICATE 3
ACCESSION NUMBER: 2005198721 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15814646
 TITLE: Anti-flt1 peptide, a vascular endothelial growth factor receptor 1-specific hexapeptide, inhibits tumor growth and metastasis.
 AUTHOR: Bae Dong-Goo
 CORPORATE SOURCE: Department of Life Science, Division of Molecular and Life Sciences, Postech Biotech Center, Pohang University of Science and Technology, Pohang, Korea.
 AUTHOR: Kim Tae-Dong; Li Ge; Yoon Wan-Hee; Chae Chi-Bom
 SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2005 Apr 01) Vol. 11, No. 7, pp. 2651-61.
 Journal code: 9502500. ISSN: 1078-0432. L-ISSN: 1078-0432.
 DIGITAL OBJECT ID: <http://dx.doi.org/10.1158/1078-0432.CCR-04-1564>
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 LANGUAGE: English
 FILE SEGMENT: MEDLINE; Priority Journals
 FILE SEGMENT: Print
 ENTRY MONTH: 200508
 ENTRY DATE: Entered STN: 19 Apr 2005
 Last Updated on STN: 9 Aug 2005
 Entered Medline: 8 Aug 2005

OS.CITING REF COUNT: 19 There are 19 MEDLINE records that cite this record

AB PURPOSE: The purpose of this study was to develop antagonists specific for the vascular endothelial growth factor receptor 1 (VEGFR1) and to investigate the effects of the antagonists on the VEGF-induced endothelial cell functions and tumor progression.

EXPERIMENTAL DESIGN: Hexapeptides that inhibit binding of VEGFR1 and VEGF were identified through screening of synthetic peptide library. A selected peptide, anti-Flt1, was investigated for binding specificity with various receptors and ligand peptides. Effects of the peptide on proliferation, cell migration, and fibrin gel-based angiogenesis of endothelial cells were also investigated. The activity of anti-Flt1, in vivo, was evaluated for inhibition of tumor growth and metastasis in VEGF-secreting cancer cell-implanted mice by s.c. injections of the peptide.

RESULTS: Here, we report on a short peptide that binds to VEGFR1 and prevents binding of VEGF. A hexapeptide, anti-Flt1 (Gly-Asn-Gln-Trp-Phe-Ile or GNQWFI), was identified from peptide libraries. The anti-Flt1 peptide shows specificity toward binding to VEGFR1 and it inhibits binding of VEGF, placental growth factor (PlGF), and VEGF/PlGF heterodimer to VEGFR1. This peptide does not inhibit the proliferation of endothelial cells induced by VEGF and VEGF/PlGF heterodimer but it effectively blocks VEGF-induced migration of endothelial cells and their capacity to form capillary-like structures on fibrin gel-based in vitro angiogenesis system. Furthermore, growth and metastasis of VEGF-secreting tumor cells were also significantly inhibited by s.c. injections of anti-Flt1 peptide in nude mice. Accordingly, VEGF-induced migration and capillary formation are mediated through VEGFR1, and these processes may play an important role in the growth and metastasis of VEGF-secreting tumors.

CONCLUSIONS: We show that a peptide (anti-Flt1) specific for VEGFR1 inhibits growth and metastasis of tumor that secretes VEGF. The effects on endothelial cell functions, in vitro, indicate that the anticancer activity of anti-Flt1 peptide with reduced blood vessel density could also be due to the blocking of VEGFR1-mediated endothelial cell migration and tube formation. Although the effects of anti-Flt1

peptide still remain to be further characterized, the receptor 1-specific peptide antagonist, anti-Flk1, has potential as a therapeutic agent for various angiogenesis-related diseases, especially cancer.

L2 ANSWER 4 OF 30 MEDLINE ® on STN DUPLICATE 4
 ACCESSION NUMBER: 2004625241 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15601548
 TITLE: Construction of a DNA vaccine against extracellular domain 1-3 of Flk1 and its inhibitory effect on growth of liver cancer cell line H22.
 AUTHOR: Lu Fan
 CORPORATE SOURCE: Department of General Surgery, The Second Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi 710004, P.R. China. lvfan78@yahoo.com.cn
 AUTHOR: Qin Zhao-Yin; Li Yi-Ming; Qi Ying-Xin; Liu Yan-Fang; Yang Wen-Bin
 SOURCE: Ai zheng = Aizheng = Chinese journal of cancer, (2004 Dec) Vol. 23, No. 12, pp. 1616-21. Journal code: 9424852.
 PUB. COUNTRY: China
 DOCUMENT TYPE: (ENGLISH ABSTRACT)
 Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 LANGUAGE: Chinese
 FILE SEGMENT: MEDLINE; Priority Journals
 FILE SEGMENT: Print
 ENTRY MONTH: 200510
 ENTRY DATE: Entered STN: 20 Dec 2004
 Last Updated on STN: 26 Oct 2005
 Entered Medline: 25 Oct 2005

AB BACKGROUND & OBJECTIVE: Angiogenesis plays an important role in the

growth, invasion, and metastasis of most solid tumors. Vascular endothelial growth factor (VEGF) and its receptor flk-1 play a key role in tumor angiogenesis. Blocking VEGF-flk1 pathway may inhibit tumor growth. This study was to construct a DNA vaccine against extracellular domain 1-3 of flk1, and test its inhibitory effect on growth of liver cancer cell line H22.

METHODS: Extracellular domain 1-3 of flk1 was cloned by reverse transcriptase-polymerase chain reaction (RT-PCR), and inserted into plasmid pcDNA3.1(+) to construct vaccine pcDNA3.1(+)-flk1-domain 1-3. The vaccine was transfected into COS7 cells, and protein expression of flk1-domain 1-3 was detected by Western blot. Standard 4-h (51)Cr releasing test was used to detect specific cytotoxic T lymphocyte (CTL) activity in vaccine-inoculated mice. To test vaccine's preventive effect, mice were divided into V, P, and S groups, treated with vaccine, pcDNA3.1(+), and saline, respectively. H22 cells were inoculated into mice 10 days later. The tumor size, tumor weight, mice survival time, tumor latent period, and microvessel density were recorded and analyzed.

RESULTS: Extracellular domain 1-3 of flk1 was cloned, and vaccine against it was constructed, both have been proved by DNA sequencing and comparing with data in GenBank. A protein of 44 kDa, which is consisted with flk1-domain 1-3 protein, expressed in COS7 cells inoculated with the DNA vaccine, specific CTL activity in these cells raised. After inoculated with H22 cells, tumor latent time of V group was (5.2+/-0.9) d, of P group was (4.0+/-0.7) d, of S group was (3.8+/-0.6) d; survival time of V group was (24.5+/-3.2) d, of P group was (14.7+/-2.6) d, of S group was (14.3+/-2.0) d; microvessel density of V group was 10.1+/-1.7, of P group was 27.3+/-3.3, of S group was 25.3+/-4.6; tumor weight of V group was (1.4+/-0.1) g, of P group was (1.8+/-0.2) g, of S group was (1.8+/-0.2) g.

In comparison among groups, all data in V group were significantly different from P group and S group ($P < 0.05$), no significant difference existed between P group and S group ($P > 0.05$).

CONCLUSION: The DNA vaccine against flk-1 may stimulate potent specific CTL activity, and inhibit growth of H22 cells by its anti-endothelial cell property.

L2 ANSWER 5 OF 30 MEDLINE ® on STN DUPLICATE 6

ACCESSION NUMBER: 2003049515 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12406876

TITLE: Autocrine-paracrine VEGF loops potentiate the maturation of megakaryocytic precursors through Flt1 receptor.

AUTHOR: Casella Ida

CORPORATE SOURCE: Department of Hematology-Oncology, Istituto Superiore di Sanita, Rome, Italy.

AUTHOR: Feccia Tiziana; Chelucci Cristiana; Samoggia Paola; Castelli Germana; Guerriero Raffaella; Parolini Isabella; Petrucci Eleonora; Pelosi Elvira; Morsilli Ornella; Gabbianelli Marco; Testa Ugo; Peschle Cesare

SOURCE: Blood, (2003 Feb 15) Vol. 101, No. 4, pp. 1316-23.
Electronic Publication Date: 24 Oct 2002
Journal code: 7603509. ISSN: 0006-4971. L-ISSN: 0006-4971.

DIGITAL OBJECT ID: <http://dx.doi.org/10.1182/blood-2002-07-2184>

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals

FILE SEGMENT: Print; Electronic

ENTRY MONTH: 200303

ENTRY DATE: Entered STN: 2 Feb 2003
Last Updated on STN: 14 Mar 2003
Entered Medline: 13 Mar 2003

OS.CITING REF COUNT: 37 There are 37 MEDLINE records that cite this record

AB The expression/function of vascular endothelial growth factor (VEGF) receptors (VEGFR1/Flt1 and VEGFR2/KDR/Flk1) in hematopoiesis is under scrutiny. We have investigated the expression of Flt1 and kinase domain receptor (KDR) on hematopoietic precursors, as evaluated in liquid culture of CD34(+) hematopoietic progenitor cells (HPCs) induced to unilineage differentiation/maturation through the erythroid (E), megakaryocytic (Mk), granulocytic (G), or monocytic (Mo) lineage. KDR, expressed on 0.5% to 1.5% CD34(+) cells, is rapidly downmodulated on induction of differentiation. Similarly, Flt1 is present at very low levels in HPCs and is downmodulated in E and G lineages; however, Flt1 is induced in the precursors of both Mo and Mk series; ie, its level progressively increases during Mo maturation, and it peaks at the initial-intermediate culture stages in the Mk lineage. Functional experiments indicate that Mk and E, but not G and Mo, precursors release significant amounts of VEGF in the culture medium, particularly at low O(2) levels. The functional role of VEGF release on Mk maturation is indicated by 2 series of observations. (1) Molecules preventing the VEGF-Flt1 interaction on the precursor membrane (eg, soluble Flt1 receptors) significantly inhibit Mk polyploidization. (2) Addition of exogenous VEGF or placenta growth factor (PlGF) markedly potentiates Mk maturation. Conversely, VEGF does not modify Mo differentiation/maturation. Altogether, our results suggest that in the hematopoietic microenvironment an autocrine VEGF loop contributes to optimal Mk maturation through Flt1. A paracrine loop involving VEGF release by E precursors may also operate. Similarly, recent studies indicate that an autocrine loop involving VEGF and Flt1/Flk1 receptors mediates hematopoietic stem cell survival and differentiation.

L2 ANSWER 6 OF 30 MEDLINE ® on STN DUPLICATE 8
 ACCESSION NUMBER: 2002485498 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12235106
 TITLE: Synergistic enhancement of bone formation and healing by stem cell-expressed VEGF and bone morphogenetic protein-4.
 AUTHOR: Peng Hairong
 CORPORATE SOURCE: Growth and Development Laboratory, Department of Orthopaedic Surgery, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA.
 AUTHOR: Wright Vonda; Usas Arvydas; Gearhart Brian; Shen Hsain-Chung; Cummins James; Huard Johnny
 SOURCE: The Journal of clinical investigation, (2002 Sep) Vol. 110, No. 6, pp. 751-9.
 Journal code: 7802877. ISSN: 0021-9738. L-ISSN: 0021-9738.
 Report No.: NLM-PMC151123; PMC-PMC151123.
 DIGITAL OBJECT ID: <http://dx.doi.org/10.1172/JCI15153>
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
 LANGUAGE: English
 FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
 FILE SEGMENT: Print
 ENTRY MONTH: 200210
 ENTRY DATE: Entered STN: 26 Sep 2002
 Last Updated on STN: 24 Oct 2002
 Entered Medline: 23 Oct 2002
 GRANT FUNDING ORG.: United States NIDCR NIH HHS
 GRANT FUNDING NUM.: R01 DE013420; 1 R01 DE13420-01
 OS.CITING REF COUNT: 135 There are 135 MEDLINE records that cite this record
 MEDLINE REFERENCE COUNT: 29 There are 29 cited references available in MEDLINE for this document.

AB We investigated the interaction between angiogenic and osteogenic factors in bone formation and bone healing with ex vivo gene therapy using muscle-derived stem cells genetically engineered to express human bone morphogenetic protein-4 (BMP4), VEGF, or VEGF-specific antagonist (soluble Flt1). Our results show that although VEGF alone did not improve bone regeneration, it acted synergistically with BMP4 to increase recruitment of mesenchymal stem cells, to enhance cell survival, and to augment cartilage formation in the early stages of endochondral bone formation. These early effects, coupled with accelerated cartilage resorption, eventually led to a significant enhancement of bone formation and bone healing. The beneficial effect of VEGF on bone healing elicited by BMP4 depends critically on the ratio of VEGF to BMP4, with an improper ratio leading to detrimental effects on bone healing. Finally, we show that soluble Flt1 inhibits bone formation elicited by BMP4. Thus, VEGF plays an important role in bone formation elicited by BMP4, and it can significantly enhance BMP4-elicited bone formation and regeneration through multiple mechanisms. This study has important implications for the formulation of new strategies to improve bone healing through increasing mesenchymal stem cell recruitment and survival, in combination with muscle-derived stem cell-based gene therapy.

L2 ANSWER 7 OF 30 MEDLINE ® on STN DUPLICATE 9
 ACCESSION NUMBER: 2001472286 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11516238
 TITLE: Endothelial cell apoptotic genes associated with the pathogenesis of thrombotic microangiopathies: an application of oligonucleotide genechip technology.
 AUTHOR: Kim J
 CORPORATE SOURCE: Laboratory for AIDS Virus Research, Weill Medical College

of Cornell University, New York, New York, 10021,USA.
 JIK2002@med.cornell.edu
 AUTHOR: Wu H; Hawthorne L; Rafii S; Laurence J
 SOURCE: Microvascular research, (2001 Sep) Vol. 62, No. 2, pp.
 83-93.
 Journal code: 0165035. ISSN: 0026-2862. L-ISSN: 0026-2862.
 DIGITAL OBJECT ID: http://dx.doi.org/10.1006/mvre.2001.2326
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
 LANGUAGE: English
 FILE SEGMENT: MEDLINE; Priority Journals
 FILE SEGMENT: Print
 ENTRY MONTH: 200201
 ENTRY DATE: Entered STN: 23 Aug 2001
 Last Updated on STN: 25 Jan 2002
 Entered Medline: 14 Jan 2002
 GRANT FUNDING ORG.: United States NHLBI NIH HHS
 GRANT FUNDING NUM.: HL55646; HL61849

OS.CITING REF COUNT: 2 There are 2 MEDLINE records that cite this record

AB Idiopathic thrombotic thrombocytopenic purpura (TTP) is a disease characterized by the apoptotic injury of all microvascular endothelial cells (MVEC) except those of pulmonary origin. It notably also spares EC of large vessel origin. It is fatal unless treated with plasma exchange. The EC lineage restriction of the apoptotic lesions in vivo is reproduced in vitro following exposure of primary human MVEC derived from various tissues to TTP plasma. Oligonucleotide genechip technology was used to identify genes that may contribute to the resistance of lung MVEC to apoptosis induced by TTP plasma and to explore the intrinsic genotypic heterogeneity between MVEC of TTP-sensitive (skin) versus resistant (lung) lineage. Exposure of cells to TTP or normal plasma yielded 157 genes that were differentially expressed in primary human lung MVEC. A global change in expression of pro- and anti-apoptotic genes was seen, including increases in caspase 1, Fas, and Bcl-xl, already shown by experimental means to be involved in TTP pathogenesis. Additional differences suggest the importance of pathways related to the death receptor ligand TRAIL, as well as a role for disruption of EC-extracellular matrix interactions in the initiation of apoptosis. Maintenance of specific prosurvival signals at baseline may be a feature of lung MVEC resistance in TTP as suggested by higher expression than skin EC of the TRAIL antagonist, osteoprotegerin, and the vascular endothelial growth factors, VEGF/VPF and VEGF-C, and their receptors, VEGFR-2 (KDR) and VEGFR-3 (Flt4).
 Copyright 2001 Academic Press.

L2 ANSWER 8 OF 30 MEDLINE ® on STN DUPLICATE 10
 ACCESSION NUMBER: 2000247148 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10785369
 TITLE: Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3.
 AUTHOR: Achen M G
 CORPORATE SOURCE: Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia. marc.achen@ludwig.edu.au
 AUTHOR: Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A
 SOURCE: European journal of biochemistry, (2000 May) Vol. 267, No. 9, pp. 2505-15.
 Journal code: 0107600. ISSN: 0014-2956. L-ISSN: 0014-2956.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 22 Jun 2000
Last Updated on STN: 22 Jun 2000
Entered Medline: 15 Jun 2000

OS.CITING REF COUNT: 23 There are 23 MEDLINE records that cite this record

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

L2 ANSWER 9 OF 30 MEDLINE ® on STN DUPLICATE 11
ACCESSION NUMBER: 2000260720 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10803575
TITLE: Expression of vascular endothelial growth factors and their receptors during osteoblast differentiation.
AUTHOR: Deckers M M
CORPORATE SOURCE: Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, The Netherlands.
m.m.l.deckers@lumc.nl
AUTHOR: Karperien M; van der Bent C; Yamashita T; Papapoulos S E; Lowik C W
SOURCE: Endocrinology, (2000 May) Vol. 141, No. 5, pp. 1667-74.
Journal code: 0375040. ISSN: 0013-7227. L-ISSN: 0013-7227.
DIGITAL OBJECT ID: <http://dx.doi.org/10.1210/endo.141.5.7458>
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 6 Jun 2000
Last Updated on STN: 6 Jun 2000
Entered Medline: 23 May 2000

OS.CITING REF COUNT: 104 There are 104 MEDLINE records that cite this record

AB Endochondral bone formation is regulated by systemically and locally acting growth factors. A role for vascular endothelial growth factor (VEGF) in this process has recently been proposed, because inactivation of VEGF inhibits endochondral bone formation via inhibition of angiogenesis. Despite the known effect of VEGF as specific endothelial growth factor, its effects on osteoblast differentiation have not been studied. We, therefore, examined the expression of VEGF-A, -B, -C, and -D and their receptors in a model of osteoblast differentiation using the mouse preosteoblast-like cell line KS483. Early in differentiation, KS483

cells express low levels VEGF-A, -B, and -D messenger RNA, whereas during mineralization, KS483 cells express high levels. In addition, expression of the VEGF receptors, VEGFR1, VEGFR2, and VEGF165R/neuropilin, coincided with expression of their ligands, being maximally expressed during mineralization. VEGF-A production during osteoblast differentiation was stimulated by insulin-like growth factor I that enhances osteoblast differentiation and was inhibited by PTH-related peptide that inhibits osteoblast differentiation. Furthermore, continuous treatment of KS483 cells with recombinant human VEGF-A stimulated nodule formation. Although treatment of KS483 cells with soluble FLT1, an agent that blocks binding of VEGF-A and -B to VEGFR1, did not inhibit nodule formation, this observation does not exclude involvement of VEGFR2 in the regulation of osteoblast differentiation. As it is known that VEGF-A, -C, and -D can act through activation of VEGFR2, other isoforms might compensate for VEGF-A loss. The expression pattern of VEGFs and their receptors shown here suggests that VEGFs play an important role in the regulation of bone remodeling by attracting endothelial cells and osteoclasts and by stimulating osteoblast differentiation.

L2 ANSWER 10 OF 30 MEDLINE ® on STN DUPLICATE 12
 ACCESSION NUMBER: 2000211395 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10747021
 TITLE: Identification of a peptide blocking vascular endothelial growth factor (VEGF)-mediated angiogenesis.
 AUTHOR: Binetruy-Tournaire R
 CORPORATE SOURCE: Universite Paris XIII, UFR Leonard de Vinci, UPRES 2360, 'Ciblage Fonctionnel des Tumeurs Solides', 74 rue Marcel Cachin, 93017 Bobigny Cedex, France. tournair@unice.fr
 AUTHOR: Demangel C; Malavaud B; Vassy R; Rouyre S; Kraemer M; Plouet J; Derbin C; Perret G; Mazie J C
 SOURCE: The EMBO journal, (2000 Apr 03) Vol. 19, No. 7, pp. 1525-33.
 Journal code: 8208664. ISSN: 0261-4189. L-ISSN: 0261-4189.
 Report No.: NLM-PMC310222; PMC-PMC310222.
 DIGITAL OBJECT ID: http://dx.doi.org/10.1093/emboj/19.7.1525
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 LANGUAGE: English
 FILE SEGMENT: MEDLINE; Priority Journals
 FILE SEGMENT: Print
 ENTRY MONTH: 200005
 ENTRY DATE: Entered STN: 25 May 2000
 Last Updated on STN: 25 May 2000
 Entered Medline: 15 May 2000
 OS.CITING REF COUNT: 53 There are 53 MEDLINE records that cite this record
 MEDLINE REFERENCE COUNT: 55 There are 55 cited references available in MEDLINE for this document.
 AB Vascular endothelial growth factor (VEGF) binding to the kinase domain receptor (KDR/FLK1 or VEGFR-2) mediates vascularization and tumor-induced angiogenesis. Since there is evidence that KDR plays an important role in tumor angiogenesis, we sought to identify peptides able to block the VEGF-KDR interaction. A phage epitope library was screened by affinity for membrane-expressed KDR or for an anti-VEGF neutralizing monoclonal antibody. Both strategies led to the isolation of peptides binding KDR specifically, but those isolated by KDR binding tended to display lower reactivities. Of the synthetic peptides corresponding to selected clones tested to determine their inhibitory activity, ATWLPPR completely abolished VEGF binding to cell-displayed KDR. In vitro, this effect led to the inhibition of the VEGF-mediated proliferation of human vascular endothelial cells, in a dose-dependent and endothelial cell type-specific manner. Moreover, in vivo, ATWLPPR totally abolished

VEGF-induced angiogenesis in a rabbit corneal model. Taken together, these data demonstrate that ATWLPPR is an effective antagonist of VEGF binding, and suggest that this peptide may be a potent inhibitor of tumor angiogenesis and metastasis.

L2 ANSWER 11 OF 30 MEDLINE ® on STN DUPLICATE 13
 ACCESSION NUMBER: 1998442247 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 9770111
 TITLE: Monoclonal antibodies targeting the VEGF receptor-2 (Flk1/KDR) as an anti-angiogenic therapeutic strategy.
 AUTHOR: Witte L
 CORPORATE SOURCE: Department of Molecular and Cell Biology, ImClone Systems Incorporated, New York, USA. larryw@imclone.com
 AUTHOR: Hicklin D J; Zhu Z; Pytowski B; Kotanides H; Rockwell P; Bohlen P
 SOURCE: Cancer metastasis reviews, (1998 Jun) Vol. 17, No. 2, pp. 155-61. Ref: 21
 Journal code: 8605731. ISSN: 0167-7659. L-ISSN: 0167-7659.
 PUB. COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: MEDLINE; Priority Journals
 FILE SEGMENT: Print
 ENTRY MONTH: 199811
 ENTRY DATE: Entered STN: 6 Jan 1999
 Last Updated on STN: 3 Mar 2000
 Entered Medline: 24 Nov 1998

OS.CITING REF COUNT: 83 There are 83 MEDLINE records that cite this record
 REFERENCE COUNT: 21 There are 21 cited references for this document.

AB Biological evidence suggests that interference with the function of the angiogenic growth factor receptor VEGFR2 (Flk1/KDR) is a particularly promising strategy to inhibit tumor-induced angiogenesis. Proof of concept was established by developing a monoclonal rat anti-mouse VEGFR2 antibody (DC101) and showing that it potently blocked the binding of VEGF to its receptor, inhibited VEGF-induced signaling, and strongly blocked tumor growth in mice through an anti-angiogenic mechanism. Since DC101 does not cross-react with the human VEGFR2 KDR, anti-KDR monoclonal antibodies were generated by standard hybridoma technology and by using phage display library. High affinity antibodies ($K_d = 4.9 \times 10^{-10}$ – 1.1×10^{-9} M) were found with both approaches. The anti-KDR antibodies compete on an equimolar basis with VEGF for binding to KDR and inhibit with similar potency the VEGF-induced signaling and mitogenesis in human endothelial cells. Although these antibodies cannot be tested for in vivo efficacy in standard murine tumor models because of lack of species cross-reactivity, the similarity of their in vitro properties with those of DC101 suggests that they may be effective in blocking KDR function in vivo.

L2 ANSWER 12 OF 30 BIOSIS COPYRIGHT (c) 2018 Clarivate Analytics on STN
 ACCESSION NUMBER: 2006:346850 BIOSIS
 DOCUMENT NUMBER: PREV200600345982
 TITLE: PKC activation differentially increases sFlt1 expression in human vascular endothelium.
 AUTHOR(S): Thomas, Christie P. [Reprint Author]; Liu, Kang Z.
 CORPORATE SOURCE: Univ Iowa, Dept Internal Med, Iowa City, IA 52242 USA
 SOURCE: FASEB Journal, (MAR 6 2006) Vol. 20, No. 4, Part 1, pp. A750.
 Meeting Info.: Experimental Biology 2006 Meeting. San Francisco, CA, USA. April 01 -05, 2006. Amer Assoc Anatomists; Amer Physiol Soc; Amer Soc Biochem

& Mol Biol;

Amer Soc Investigat Pathol; Amer Soc Nutr; Amer Soc Pharmacol & Expt Therapeut.
CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Jul 2006
Last Updated on STN: 12 Jul 2006

AB FLT1 gene produces two transcripts from a common transcription start site: full length Flt1 contains 30 spliced exons and encodes a membrane bound VEGF receptor. sFlt1 shares the first 13 exons but utilizes intron 13 poly(A) signal sequences to create a shorter transcript that lacks exon 14 to 30. sFlt1 encodes a circulating soluble variant that serves as a natural antagonist to VEGF. We investigated the effect of protein kinase C (PKC) activation on sFlt1 and Flt1 expression in human umbilical vein endothelial cells (HUVEC). Phorbol myristic acid (PMA) robustly stimulated sFlt1 mRNA expression and this expression preceded the large increase in sFlt1 protein secreted into conditioned culture media. The effect of PMA on sFlt1 mRNA and protein was substantially reduced by GF109203X and by PD98059 indicating that this stimulation was mediated via the activation of PKC and ERK. The effect of PKC activation on steady state sFlt1 and Flt1 mRNA was then measured simultaneously demonstrating that PKC activation differentially increases sFlt1 expression (fold increase in sFlt1 with PMA: 27.2 +/- 5.9 vs increase in Flt1: 2 fold +/- 0.59). Our data indicates that PKC activation differentially regulates sFlt1 expression in HUVEC, perhaps, by selectively increasing the alternate processing of sFlt1.

L2 ANSWER 13 OF 30 BIOSIS COPYRIGHT (c) 2018 Clarivate Analytics on STN

ACCESSION NUMBER: 2005:478230 BIOSIS

DOCUMENT NUMBER: PREV200510270134

TITLE: Hypoxia-independent regulation of hepatic erythropoietin production by vascular endothelial growth factor.

AUTHOR(S): Tam, Betty Y. Y. [Reprint Author]; Hoffman, Jana; Park, Sang-ki; Lee, Jeng-Shin; Sundram, Uma; Wu, Grace; Schrier, Stanley L.; Johnson, Randall; Mulligan, Richard; Kuo, Calvin J.

CORPORATE SOURCE: Stanford Univ, Sch Med, Stanford, CA 94305 USA

SOURCE: Blood, (NOV 16 2004) Vol. 104, No. 11, Part 1, pp. 595A.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005

AB Erythropoietin (Epo) is an essential regulator of red blood cell production. While adult Epo synthesis occurs almost exclusively in kidney, extrarenal Epo synthesis has been described in liver and brain in response to hypoxia or anemia. We have used adenoviruses to express soluble ectodomains of the VEGF receptors (sVEGFRs) Flk1 and Flt1 in the circulation of mice, achieving high-level VEGF sequestration, potent conditional ablation of VEGF function in adult animals, and inhibition of tumor growth and angiogenesis (Kuo et al. PNAS (2001). 98: 4605). Intriguingly, adenoviral expression of soluble Flk1 or Flt1 ectodomains, or a recently described soluble receptor VEGF Trap, is associated with profound stimulation of erythropoiesis and polycythemia, with hematocrit as high as 75% from basal levels of similar to 45%, and elevation of plasma Epo levels. sVEGFR expression results in a profound >100-fold induction of hepatic erythropoietin synthesis while renal Epo

production is completely repressed. This effect is specific for adenoviruses expressing soluble VEGF receptors and not other receptor ectodomains, does not require liver transduction or hypoxia, and is not affected by Ad Cre-induced deletion of the hepatocyte HIF-1 α gene in HIF-1 α (flox/flox) mice. Selective inhibition of hepatocyte-produced VEGF in Ad Cre-treated VEGF(flox/flox) mice is sufficient to re-activate hepatocyte Epo production, likely via hepatocyte <-> endothelium crosstalk. These data suggest VEGF may function physiologically to repress hepatic Epo synthesis, while VEGF blockade leads to de-repression of hepatic Epo production via a novel hypoxia- and HIF-1 α -independent pathway.

L2 ANSWER 14 OF 30 BIOSIS COPYRIGHT (c) 2018 Clarivate Analytics on STN
 ACCESSION NUMBER: 1999:179231 BIOSIS
 DOCUMENT NUMBER: PREV199900179231
 TITLE: VEGF receptor blockade by an anti-Flk1 monoclonal antibody inhibits tumor associated angiogenesis and tumor growth.
 AUTHOR(S): Prewett, M.; Li, Y.; Huber, J.; King, K.; O'Connor, W.; Overholser, J.; Santiago, A.; Witte, L.; Bohlen, P.; Hicklin, D. J.
 CORPORATE SOURCE: ImClone Systems Incorporated, New York, NY 10014, USA
 SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 414. print. Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research. Philadelphia, Pennsylvania, USA. April 10-14, 1999. American Association for Cancer Research. ISSN: 0197-016X.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 5 May 1999
 Last Updated on STN: 5 May 1999

L2 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN DUPLICATE 5
 ACCESSION NUMBER: 2005:1300220 CAPLUS
 DOCUMENT NUMBER: 144:251532
 TITLE: Angiogenesis and antiangiogenic therapy for malignant gliomas
 AUTHOR(S): Takano, Shingo; Kamiyama, Hiroshi; Tsuboi, Koji; Matsumura, Akira
 CORPORATE SOURCE: Department of Neurosurgery, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki, 305-8575, Japan
 SOURCE: Brain Tumor Pathology (2004), 21(2), 69-73
 CODEN: BTPAFM; ISSN: 1433-7398
 DIGITAL OBJECT ID: 10.1007/BF02484513
 PUBLISHER: Springer Tokyo
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Angiogenesis is crucial to the growth of malignant gliomas. Therefore, antiangiogenic therapy represents a new, promising therapeutic modality for malignant gliomas. This study was designed to define the malignant glioma cases most suitable for antiangiogenic therapy in humans and to demonstrate the efficacy of antiangiogenic therapy in animals. Protein expression of the most potent angiogenic factor, vascular endothelial growth factor (VEGF), and its specific natural inhibitor, soluble Flt-1, as well as vessel architecture, including vessel d., area, and diameter, was evaluated in human malignant glioma samples (24 glioblastomas, 13 anaplastic astrocytomas). Among these, VEGF >1000ng/mL, VEGF/soluble Flt-1 ratio >1, vessel d. >30, and vessel area >7% were prognostic factors for malignant gliomas. Based on these results, we performed three different

antiangiogenic expts. targeted to inhibit VEGF expression in a human malignant glioma (U87) mouse model: anti-VEGF neutralized antibody i.p. injection; interferon-beta i.m. injection; and transfection of an endogenous nonspecific angiogenesis inhibitor, thrombospondin-1, into glioma cells caused inhibition of VEGF secretion and/or mRNA expression and resulted in glioma growth inhibition of 70%, 84%, and 50%, resp., compared with control. We conclude that malignant gliomas with high degrees of VEGF expression and vessel areas are good candidates for antiangiogenic therapy, especially that designed to inhibit VEGF expression.

OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
 REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 2003:380393 CAPLUS
 DOCUMENT NUMBER: 139:345469
 TITLE: Inhibitory effect of clotrimazole on angiogenesis associated with bladder epithelium proliferation in rats
 AUTHOR(S): Takei, Shunsaku; Iseda, Tokuhiro; Yokoyama, Masayoshi
 CORPORATE SOURCE: Division of Urology, Saiseikai Matsuyama Hospital, Ehime University of Medicine, Ehime, Japan
 SOURCE: International Journal of Urology (2003), 10(2), 78-85
 CODEN: IJURF3; ISSN: 0919-8172
 DIGITAL OBJECT ID: 10.1046/j.1442-2042.2003.00575.x
 PUBLISHER: Blackwell Publishing Asia Pty Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Up-regulation of epithelial vascular endothelial growth factor (VEGF) expression was recently reported at an early stage of bladder carcinogenesis in rats. Subsequently, clotrimazole (CLT) was reported to exert an inhibitory effect on the in vitro proliferation of vascular endothelial cells stimulated by VEGF. The present study was performed to evaluate the effect of CLT on the initial stage of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN)-induced carcinogenesis of the urinary bladder in rats. Seven-week-old-female Wistar rats were divided into both a control group and the other four groups that were allowed free access to drinking water containing 0.05% BBN. Two groups of rats (10-CLT and 20-CLT) received CLT (100 mg/kg per day) once daily by gavage for 10 and 20 wk, resp. The other two groups of rats (10-BBN and 20-BBN) were maintained on the same BBN-containing drinking water for 10 and 20 wk, resp., without receiving CLT. After removing the urinary bladder of each rat, expression of VEGF and VEGF receptor FLT1, and new capillaries were examined by immunohistochem. staining. VEGF mRNA was detected by the reverse transcription polymerase chain reaction. The ratio of VEGF-pos. cells and the expression of VEGF mRNA were lower in the 20-CLT group than in the 10-BBN group. Newly formed capillaries in the 20-CLT group were significantly decreased compared with those in the 10-BBN group. These quant. data suggested that CLT can inhibit VEGF expression in vivo and hence inhibit angiogenesis in the early stages of bladder carcinoma.

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
 REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2006:238417 CAPLUS
 DOCUMENT NUMBER: 144:286220
 TITLE: Multimeric VEGF antagonistic traps consisting of Ig domains of VEGF receptors (Flt-1 and Flk-1) for treatment of eye disorders

INVENTOR(S) : Daly, Thomas J.; Papadopoulos, Nicholas J.; Karow, Margaret
PATENT ASSIGNEE(S) : Regeneron Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 16,097.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 10

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060058234	A1	20060316	US 2005-204709	20050816 <--
US 7396664	B2	20080708		
CA 2588221	A1	20001214	CA 2000-2588221	20000523 <--
CA 2588221	C	20130709		
WO 2000075319	A1	20001214	WO 2000-US14142	20000523 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1544299	A1	20050622	EP 2005-1328	20000523 <--
EP 1544299	B1	20081217		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, FI, CY				
CN 101433715	A	20090520	CN 2008-10109355	20000523
CN 101433715	B	20130417		
CN 103349781	A	20131016	CN 2013-10118971	20000523
CN 103349781	B	20150401		
US 7070959	B1	20060704	US 2001-9852	20011206
US 20040014667	A1	20040122	US 2003-609775	20030630 <--
US 7087411	B2	20060808		
US 20050043236	A1	20050224	US 2004-880021	20040629 <--
US 7279159	B2	20071009		
US 20050163798	A1	20050728	US 2004-16097	20041217 <--
US 7374757	B2	20080520		
US 20050245447	A1	20051103	US 2004-16503	20041217 <--
US 7374758	B2	20080520		
JP 2011024595	A	20110210	JP 2010-226970	20101006
JP 5273746	B2	20130828		

PRIORITY APPLN. INFO.:

US 1999-60138133	P	19990608
WO 2000-US14142	W	20000523
US 2001-9852	A3	20011206
US 2003-609775	A2	20030630
US 2004-880021	A2	20040629
US 2004-16097	A2	20041217
US 2004-16503	A2	20041217
CA 2000-2376379	A3	20000523
CN 2000-811544	A3	20000523
EP 2000-932721	A3	20000523
JP 2001-502582	A3	20000523

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides recombinant nucleic acid mols. encoding multimeric proteins capable of binding and inhibiting vascular endothelial growth factor (VEGF). VEGF traps (VEGF blockers) are disclosed which are therapeutically useful for treating VEGF-associated conditions and diseases, such as ocular disease, and are specifically designed for local administration to specific organs, tissues, and/or cells. 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). The protein and DNA sequences for VEGF traps are provided.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L2 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2005:1242960 CAPLUS

DOCUMENT NUMBER: 144:11543

TITLE: Enhancement of antagonist activity of aptamers by conjugation to high molecular weight materials

INVENTOR(S): Calias, Pericles; Cook, Gary P.; Shima, David T.; Adamis, Anthony P.; Ng, Yin-Shan; Robinson, Gregory S.; Turner, David I.; Ganley, Mary A.

PATENT ASSIGNEE(S): Eyetech Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 91 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005110489	A2	20051124	WO 2005-US12469	20050413 <--
WO 2005110489	A3	20061228		
W:	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, KM, 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, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2562948	A1	20051124	CA 2005-2562948	20050413 <--
US 20050260153	A1	20051124	US 2005-104812	20050413 <--
US 20050260651	A1	20051124	US 2005-105279	20050413 <--
EP 1737497	A2	20070103	EP 2005-778139	20050413
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU			
BR 2005009911	A	20070918	BR 2005-9911	20050413
JP 2007532662	T	20071115	JP 2007-508487	20050413
MX 2006011965	A	20070417	MX 2006-11965	20061013

PRIORITY APPLN. INFO.:

US 2004-60561601	P	20040413
US 2005-60658819	P	20050304
WO 2005-US12469	W	20050413

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides compns. and methods for making and using sterically enhanced aptamer antagonist conjugates which include a nucleic acid sequence having a specific affinity for a target mol. and a soluble, high mol. weight steric group that augments or facilitates the antagonist activity of the aptamer. inhibition of binding to, or interaction with, the target mol. binding partner by the target mol. when bound to the aptamer conjugate. The present invention also provides methods and formulations for ocular delivery of a biol. active mol. by attaching a charged moiety to the biol. active mol. and delivering the biol. active mol. by iontophoresis. Iontophoresis of a biol. active mol. that is conjugated to a high mol. weight neutral moiety, is enhanced by replacing the high mol. weight

neutral moiety with a charged mol. of comparable size. Thus, the effect on VEGFR-1 (Flt-1) antagonist activity of conjugation of chemical modified, anti-VEGF oligoribonucleotide to various high mol. weight materials, i.e., PEG, dextran, and CMC, was studied. Also examined was the effects of mol. weight and hydrodynamic volume of the high mol. weight material on antagonist activity.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2005:347054 CAPLUS

DOCUMENT NUMBER: 142:409726

TITLE: Monoclonal anti-human VEGF receptor Flt-1 antibodies, humanized and chimeric antibodies and fragments for treating leukemia and Flt-1-associated disease

INVENTOR(S): Iida, Shigeru; Satoh, Mitsuo; Urakubo, Miho; Wakitani, Masako; Uchida, Kazuhisa; Niwa, Rinpei; Shitara, Kenya

PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan

SOURCE: PCT Int. Appl., 168 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005035581	A1	20050421	WO 2004-JP15321	20041008 <--
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, 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			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: JP 2003-350169 A 20031009

AB It is intended to provide a composition comprising an antibody mol. which specifically binds to human VEGF receptor Flt-1 and has an N-glycoside-binding complex sugar chain in the Fc domain, wherein the N-glycoside-binding complex sugar chain is a sugar chain having no fucose attached to N-acetylglucosamine at the reducing end of the sugar chain; a transformant producing this antibody composition; a process for producing the antibody composition; and a drug containing the antibody composition The antibodies include monoclonal antibodies, humanized or chimeric antibodies and fragments. These antibodies are useful for treating human VEGF receptor Flt-1-associated disease such as leukemia.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2004:80833 CAPLUS

DOCUMENT NUMBER: 140:151913

TITLE: Vascular endothelial growth factor mRNA derived siRNA and therapeutic use for inhibition of angiogenesis

INVENTOR(S): Tolentino, Michael J.; Reich, Samuel Jotham

PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA

SOURCE: PCT Int. Appl., 218 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009769	A2	20040129	WO 2003-US22444	20030718 <--
WO 2004009769	A3	20060413		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, 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				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20040018176	A1	20040129	US 2002-294228	20021114 <--
US 7148342	B2	20061212		
CA 2493499	A1	20040129	CA 2003-2493499	20030718 <--
CA 2493499	C	20160412		
AU 2003253995	A1	20040209	AU 2003-253995	20030718 <--
AU 2003253995	B2	20071213		
EP 1578933	A2	20050928	EP 2003-765708	20030718 <--
EP 1578933	B1	20100310		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006505251	T	20060216	JP 2004-523550	20030718 <--
JP 5337337	B2	20131106		
AT 460500	T	20100315	AT 2003-765708	20030718
IL 166274	A	20100531	IL 2003-166274	20030718
EP 2192187	A2	20100602	EP 2010-151221	20030718
EP 2192187	A3	20100825		
EP 2192187	B1	20130417		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PT, RO, SE, SI, SK, TR				
ES 2340843	T3	20100610	ES 2003-765708	20030718
PT 1578933	E	20100617	PT 2003-765708	20030718
NZ 537833	A	20100827	NZ 2003-537833	20030718
KR 2011063597	A	20110610	KR 2011-7012601	20030718
EP 2345718	A2	20110720	EP 2010-185621	20030718
EP 2345718	A3	20111116		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PT, RO, SE, SI, SK, TR				
IL 196798	A	20120229	IL 2003-196798	20030718
KR 1280269	B1	20130715	KR 2005-7001330	20030718
MX 2005001000	A	20050516	MX 2005-1000	20050124 <--
US 20060286073	A1	20061221	US 2006-422932	20060608
US 7345027	B2	20080318		
US 20060292120	A1	20061228	US 2006-422947	20060608
US 20070003523	A1	20070104	US 2006-423006	20060608
US 7750143	B2	20100706		
US 20070037760	A1	20070215	US 2006-422921	20060608
US 20070037761	A1	20070215	US 2006-422982	20060608
US 8546345	B2	20131001		
US 20070037762	A1	20070215	US 2006-423025	20060608
US 8541384	B2	20130924		
US 20080188437	A1	20080807	US 2008-43229	20080306
US 20090104259	A1	20090423	US 2008-328247	20081204

US 20140056969	A1	20140227	US 2013-14042040	20130930
US 8946403	B2	20150203		
US 20150110861	A1	20150423	US 2014-14577156	20141219
US 9150863	B2	20151006		

PRIORITY APPLN. INFO.:

US 2002-60398417	P	20020724
US 2002-294228	A	20021114
EP 2003-765708	A3	20030718
EP 2010-151221	A3	20030718
IL 2003-166274	A3	20030718
KR 2005-7001330	A3	20030718
WO 2003-US22444	W	20030718
US 2006-422921	B1	20060608
US 2006-422932	A1	20060608
US 2006-422982	A1	20060608
US 2013-14042040	A1	20130930

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB RNA interference using small interfering RNAs which are specific for the vascular endothelial growth factor (VEGF) gene and the VEGF receptor genes Flt1 and Flk-1/KDR inhibit expression of these genes. Diseases which involve angiogenesis stimulated by overexpression of VEGF, such as diabetic retinopathy, age related macular degeneration and many types of cancer, can be treated by administering the small interfering RNAs.

OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)

L2 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2003:221712 CAPLUS

DOCUMENT NUMBER: 138:248495

TITLE: Antagonist peptides to VEGFR receptor FLT-1, their angiogenesis inhibitory activity and use in solid tumor treatment

INVENTOR(S): Shou, Chengchao; Lei, Hetian; An, Ping; Wu, Jian; Meng, Lin; Liu, Xiaoying

PATENT ASSIGNEE(S): Beijing Institute for Cancer Research, Peop. Rep. China

SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
WO 2003022874	A1	20030320	WO 2001-CN1393	20010912 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002220457	A1	20030324	AU 2002-220457	20010912 <--
CN 1545521	A	20041110	CN 2001-823615	20010912 <--
CN 1332978	C	20070822		
US 20050154187	A1	20050714	US 2004-489344	20041028 <--
US 7250395	B2	20070731		

PRIORITY APPLN. INFO.:

WO 2001-CN1393	W	20010912
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OTHER SOURCE(S): MARPAT 138:248495

AB The invention provides VEGFR receptor FLT-1 antagonist peptides in the formula of A-W-H-X1-D-X2-X3-X4-W-W-X5-X6-X7-X8-B, in which A is any nature

amino acid, X1-X5 and X7 are independent non- or any-protected amino acids, X6 and X8 are non- or any-protected hydrophobic amino acids, B are 0-3 amino acid(s), W is tryptophan, H histidine, D aspartic acid, X2 is either not present or proline, and X5 is a polar amino acid. Specifically, three peptides (F56, F87 and F90) are synthesized or expressed as fusion proteins with DHFR. They could completely block VEGF binding to KDR and significantly inhibit the VEGF-mediated proliferation of the human vascular endothelial cells. These peptides or their fusion proteins are tested for. Their angiogenesis inhibitory activities are detected in endothelial cells, chick embryo chorioallantoic membrane and tumor of nude mice. These peptides and related nucleic acids can be used in cancer therapy.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2004:709110 CAPLUS

DOCUMENT NUMBER: 142:49219

TITLE: Peptide derived from vascular endothelial growth factor receptor KDR and therapeutic use for treating angiogenesis-associated diseases

INVENTOR(S): Shou, Chengchao; Lei, Hetian; An, Ping; Wu, Jian; Meng, Lin; Liu, Xiaoying

PATENT ASSIGNEE(S): Beijing Institute of Prevention and Treatment of Tumor, Peop. Rep. China

SOURCE: Faming Zhuanli Shenqing, 30 pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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CN 1406948	A	20030402	CN 2001-142203	20010912 <--
CN 1252085	C	20060419		

PRIORITY APPLN. INFO.: CN 2001-142203 20010912

OTHER SOURCE(S): MARPAT 142:49219

AB The invention relates to the preparation of the polypeptide, A-X1-X2-X3-H-H-X4-X5-H-B (where: A = 0-3 of natural amino acid residues; x1 = hydrophobic amino acid residue or its protected derivative; X2 and/or X5 = natural amino acid residue or its protected derivative; X3 and/or X4 = protected polar amino acid residue; B = 0-5 of protected natural amino acid residues; and H = protected histidine residue), and the construction of its fusion protein of another polypeptide (such as VEGF flt1 receptor antagonist, dihydrofolate reductase, cytokine, soluble VEGF receptor KDR or flt1, specific antibody or antigen fragment, or B7) or its oligomerized protein. The invention also relates to the application of the polypeptide, its fusion protein, and their corresponding polynucleotide to prepare the medical preps. for treating angiogenesis diseases (such as solid neoplasm).

L2 ANSWER 23 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2002:485865 CAPLUS

DOCUMENT NUMBER: 137:320041

TITLE: A peptide fusion protein inhibits angiogenesis and tumor growth by blocking VEGF binding to KDR

AUTHOR(S): Lei, Hetian; Shou, Chengchao; Liu, Xiaoyin; He, Luowen; Wu, Jian; Jiang, Beihai; Liu, Meisheng; Yang, Junshan

CORPORATE SOURCE: Beijing Institute for Cancer Research, Peking

University School of Oncology, Beijing, 100034, Peop.
Rep. China

SOURCE: Chinese Science Bulletin (2002), 47(8), 682-687
CODEN: CSBUEF; ISSN: 1001-6538

DIGITAL OBJECT ID: 10.1360/02tb9155

PUBLISHER: Science in China Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Vascular endothelial growth factor (VEGF) binding to its tyrosine kinase receptors (KDR/Flk1, Flt-1) induces angiogenesis. In search of peptides blocking VEGF binding to its receptor KDR/Flk1 to inhibit tumor angiogenesis and growth, we screened a phage display peptide library with KDR as target protein, and some candidate peptides were isolated. In this study, we cloned the DNA fragment coding the peptide K237 from the library, into a vector pQE42 to express fusion protein DHFR-K237 in E. coli M15. The effect of fusion protein DHFR-K237 on endothelial cell proliferation and angiogenesis was investigated. In vitro, DHFR-K237 could completely block VEGF binding to KDR and significantly inhibit the VEGF-mediated proliferation of the human vascular endothelial cells. In vivo, DHFR-K237 inhibited angiogenesis in chick embryo chorioallantoic membrane and tumor growth in nude mice. These results suggest that K237 is an effective antagonist of VEGF binding to KDR, and could be a potential agent for cancer biotherapy.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2002:386296 CAPLUS

DOCUMENT NUMBER: 137:104148

TITLE: Design of a variant of vascular endothelial growth factor-A (VEGF-A) antagonizing KDR/Flk-1 and Flt-1

AUTHOR(S): Leenders, William; Lubsen, Nicolette; Van Altena, Margarethe; Clauss, Matthias; Deckers, Martine; Lowik, Clemens; Breier, Georg; Ruiter, Dirk; De Waal, Robert

CORPORATE SOURCE: Department of Pathology, University Medical Center Nijmegen, Nijmegen, 6500 HB, Germany

SOURCE: Laboratory Investigation (2002), 82(4), 473-481
CODEN: LAINAW; ISSN: 0023-6837

DIGITAL OBJECT ID: 10.1038/labinvest.3780440

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Because of its central role in pathol. angiogenesis, vascular endothelial growth factor (VEGF) has become a major target for anti-angiogenic therapies. We report here the construction of a heterodimeric antagonistic VEGF variant (HD-VEGF). In this antagonist, binding domains for the VEGF-receptors KDR/Flk-1 and Flt-1 are present at one pole of the dimer, whereas the other pole carries domain swap mutations, which prevent binding to either receptor. As HD-VEGF can only bind to monomeric receptors, it does not lead to signal transduction. Moreover, it antagonizes VEGF and possibly other members of the VEGF family, which are KDR/Flk-1 and Flt-1 ligands. We show here that HD-VEGF is a potent inhibitor of VEGF-mediated proliferation and tissue factor induction in endothelial cell cultures, requiring only a 20-fold and a 4-fold excess, resp., to block the activity of wtVEGF completely. A 4-fold excess of HD-VEGF over wtVEGF was also sufficient to abrogate vascular permeability as determined in the Miles assay in vivo. Furthermore, HD-VEGF inhibited fetal bone angiogenesis in an ex vivo assay. Thus, HD-VEGF blocks KDR- and Flt-1-mediated VEGF activities that are crucial in the angiogenic process and is therefore a promising, multipotent compound in the treatment of angiogenesis-related diseases.

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS
RECORD (16 CITINGS)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 25 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN
ACCESSION NUMBER: 2002:250203 CAPLUS
DOCUMENT NUMBER: 136:380558
TITLE: Fusion expression of peptides binding to VEGFR-1 and
identification of their biological activities
AUTHOR(S): Lei, He-tian; Wu, Jian; Yang, Jun-shan; Shou,
Cheng-chao
CORPORATE SOURCE: Beijing Institute for Cancer Research, Peking
University School of Oncology, Beijing, 100034, Peop.
Rep. China
SOURCE: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao
(2002), 18(1), 19-22
CODEN: ZSHXF2; ISSN: 1007-7626
PUBLISHER: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao
Bianweihui
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Vascular endothelial growth factor (VEGF) binding to its tyrosine kinase
receptors (KDR/FLK1, Flt-1) induces angiogenesis. In previous work, two
pos. clones binding to VEGF receptor Flt-1 were selected from phage
display peptide library. To identify the special binding activity, two
oligonucleotide fragments synthesized according to the pos. phage-12
peptide sequences were cloned into DHFR fusion protein expression vector
pQE42 for their expression in E. coli M15. Soluble DHFR-F56/F90 were
obtained after denaturation and refolding. ELISA demonstrated that
DHFR-F56/F90 were able to bind to sFlt-1 and vascular endothelial cells.
Moreover, DHFR-F56 completely abolished VEGF binding to sFlt-1. Taken
together, these data demonstrate that F56 may be an effective antagonist
of VEGF receptor sFlt-1, and a potent inhibitor of tumor angiogenesis too.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)

L2 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN
ACCESSION NUMBER: 2000:881308 CAPLUS
DOCUMENT NUMBER: 134:51389
TITLE: Flt1 fusion proteins with improved pharmacokinetic
properties for use as vascular endothelial growth
factor antagonists
INVENTOR(S): Papadopoulos, Nicholas J.; Davis, Samuel; Yancopoulos,
George D.
PATENT ASSIGNEE(S): Regeneron Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075319	A1	20001214	WO 2000-US14142	20000523 <--
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,			

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2376379	A1	20001214	CA 2000-2376379	20000523 <--
CA 2376379	C	20070807		
CA 2588221	A1	20001214	CA 2000-2588221	20000523 <--
CA 2588221	C	20130709		
AU 2000050404	A	20001228	AU 2000-50404	20000523 <--
AU 779303	B2	20050113		
EP 1183353	A1	20020306	EP 2000-932721	20000523 <--
EP 1183353	B1	20050413		
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BR 2000011407	A	20020402	BR 2000-11407	20000523 <--
HU 2002001515	A2	20020828	HU 2002-1515	20000523 <--
HU 2002001515	A3	20041228		
HU 229156	B1	20130930		
JP 2003501089	T	20030114	JP 2001-502582	20000523 <--
JP 4723140	B2	20110713		
NZ 515913	A	20040130	NZ 2000-515913	20000523 <--
AT 293164	T	20050415	AT 2000-932721	20000523 <--
EP 1544299	A1	20050622	EP 2005-1328	20000523 <--
EP 1544299	B1	20081217		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, FI, CY				
PT 1183353	E	20050630	PT 2000-932721	20000523 <--
ES 2237429	T3	20050801	ES 2000-932721	20000523 <--
RU 2265661	C2	20051210	RU 2002-100071	20000523 <--
IL 146890	A	20080708	IL 2000-146890	20000523
AT 417928	T	20090115	AT 2005-1328	20000523
PT 1544299	E	20090318	PT 2005-1328	20000523
ES 2319305	T3	20090506	ES 2005-1328	20000523
CN 101433715	A	20090520	CN 2008-10109355	20000523
CN 101433715	B	20130417		
CN 100523187	C	20090805	CN 2000-811544	20000523
SK 287332	B6	20100707	SK 2001-1752	20000523
PL 208247	B1	20110429	PL 2000-352246	20000523
CZ 302689	B6	20110907	CZ 2001-4387	20000523
CZ 303656	B6	20130130	CZ 2010-386	20000523
IL 190234	A	20130829	IL 2000-190234	20000523
CN 103349781	A	20131016	CN 2013-10118971	20000523
CN 103349781	B	20150401		
HU 230159	B1	20150928	HU 2013-86	20000523
US 20030017977	A1	20030123	US 2001-773877	20010131 <--
US 6833349	B2	20041221		
ZA 2001010068	A	20021206	ZA 2001-10068	20011206 <--
US 7070959	B1	20060704	US 2001-9852	20011206
MX 2001012630	A	20020722	MX 2001-12630	20011207 <--
HR 2001000908	A2	20050430	HR 2001-908	20011207 <--
HR 2001000908	B1	20060531		
NO 2001006036	A	20020208	NO 2001-6036	20011210 <--
NO 330775	B1	20110711		
HK 1043388	A1	20050610	HK 2002-105009	20020704 <--
US 20040014667	A1	20040122	US 2003-609775	20030630 <--
US 7087411	B2	20060808		
US 20040266686	A1	20041230	US 2004-825739	20040416 <--
US 20050175610	A1	20050811	US 2004-988243	20041112 <--
US 7303746	B2	20071204		
US 20050163798	A1	20050728	US 2004-16097	20041217 <--
US 7374757	B2	20080520		
US 20050245447	A1	20051103	US 2004-16503	20041217 <--
US 7374758	B2	20080520		
US 20050260203	A1	20051124	US 2005-89803	20050325 <--
US 7306799	B2	20071211		

AU 2005201365	A1	20050428	AU 2005-201365	20050331 <--
AU 2005201365	B2	20070809		
US 20060058234	A1	20060316	US 2005-204709	20050816 <--
US 7396664	B2	20080708		
US 20060030529	A1	20060209	US 2005-218234	20050901 <--
US 7303747	B2	20071204		
US 20080220004	A1	20080911	US 2007-998709	20071130
US 7521049	B2	20090421		
US 20080194799	A1	20080814	US 2008-102648	20080414
US 7524499	B2	20090428		
US 20080194460	A1	20080814	US 2008-102681	20080414
US 7704500	B2	20100427		
US 20090081217	A1	20090326	US 2008-102666	20080414
US 8029791	B2	20111004		
US 20090155899	A1	20090618	US 2008-334927	20081215
US 7964377	B2	20110621		
HK 1132653	A1	20130913	HK 2009-110323	20091105
US 20100221782	A1	20100902	US 2010-715128	20100301
US 8084234	B2	20111227		
NO 2010000656	A	20020208	NO 2010-656	20100506 <--
NO 332559	B1	20121029		
US 20110028698	A1	20110203	US 2010-885185	20100917
JP 2011024595	A	20110210	JP 2010-226970	20101006
JP 5273746	B2	20130828		
US 20120064621	A1	20120315	US 2011-13106910	20110513
US 8343737	B2	20130101		
US 20130149744	A1	20130613	US 2012-13439889	20120405
US 8647842	B2	20140211		
US 20130084635	A1	20130404	US 2012-13683216	20121121
HK 1185798	A1	20151127	HK 2013-113191	20131126
US 20140194597	A1	20140710	US 2013-14109999	20131218
US 9139644	B2	20150922		
US 20160130320	A1	20160512	US 2015-14822929	20150811
US 9708386	B2	20170718		
US 20180051066	A1	20180222	US 2017-15624845	20170616
PRIORITY APPLN. INFO.:			US 1999-60138133	P 19990608
			AU 2000-50404	A3 20000523
			CA 2000-2376379	A3 20000523
			CN 2000-811544	A3 20000523
			EP 2000-932721	A3 20000523
			IL 2000-146890	A3 20000523
			JP 2001-502582	A3 20000523
			WO 2000-US14142	W 20000523
			US 2001-773877	A3 20010131
			US 2001-9852	A2 20011206
			US 2003-609775	A2 20030630
			US 2004-880221	A2 20040628
			US 2004-880021	A2 20040629
			US 2004-988243	A2 20041112
			US 2004-16097	A2 20041217
			US 2004-16503	A2 20041217
			US 2005-89803	A2 20050325
			US 2005-218234	A3 20050901
			US 2008-102648	A1 20080414
			US 2008-102681	A1 20080414
			US 2008-334927	A1 20081215
			US 2010-715128	A1 20100301
			US 2010-885185	B1 20100917
			US 2011-13106910	A1 20110513
			US 2012-13439889	A1 20120405
			US 2013-14109999	A1 20131218
			US 2015-14822929	A1 20150811

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Modified chimeric polypeptides with improved pharmacokinetics are disclosed. Specifically, modified chimeric Flt1 receptor polypeptides that can be used as antagonists of vascular endothelial growth factor (VEGF) that have been modified in such a way as to improve their pharmacokinetic profile are disclosed. The fusion proteins may also use combinations of domains of VEGF receptors to modify self-association or other properties of the receptor. Also disclosed are methods of making and using the modified polypeptides including but not limited to using the modified polypeptides to decrease or inhibit plasma leakage and/or vascular permeability in a mammal. A fusion protein of Flt1 and IgG Fc regions was manufactured by expression of the cloned gene in CHO-K1 cells. Modification of the surface charge of the fusion protein by acetylation, PEGylation and heparin binding did not affect the ability of the protein to bind VEGF but did limit non-specific binding to other proteins. In mice, increasing levels of acetylation of the protein did not affect the time of maximum of serum levels of the fusion protein, but did affect the maximum concns. with concentration rising as the pI dropped. Deletion of a basic

region in the receptor also lowered the degree of non-specific binding by the receptor.

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)
 REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 27 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2001:158191 CAPLUS
 DOCUMENT NUMBER: 134:173434
 TITLE: sFlt-1, a potential antagonist for exogenous VEGF.
 Comments
 AUTHOR(S): Belgore, Funmi M.; Blann, Andrew D.; Lip, Gregory Y. H.
 CORPORATE SOURCE: Haemostasis, Thrombosis, and Vascular Biol. Unit, Univ. Dep. Med. City Hosp., Birmingham, B18 7QH, UK
 SOURCE: Circulation (2000), 102(15), E108
 CODEN: CIRCAZ; ISSN: 0009-7322
 DIGITAL OBJECT ID: 10.1161/01.CIR.102.15.e108
 PUBLISHER: Lippincott Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A polemic. In a study of 60 patients, VEGF levels in patients with coronary artery disease were significantly higher than those of controls whereas levels of the soluble VEGF receptor Flt-1 (sFlt-1) were lower in patients compared to controls. Levels of sFlt-1 in both patients and controls were 33-fold and 306-fold greater than those of VEGF, resp. Although early studies indicate that the therapeutic use of VEGF could improve collateral circulation, the high levels of sFlt-1 may act as a potential antagonist for VEGF. Thus, exogenously administered VEGF would have to completely neutralize the soluble receptor (sFlt-1) before adequate levels would reach target organs.

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
 REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 28 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 1999:53399 CAPLUS
 DOCUMENT NUMBER: 130:123831
 TITLE: Nucleic acids encoding variable or hypervariable regions of monoclonal antibody binding to vascular

INVENTOR(S) : endothelial cell growth factor receptor
 Rockwell, Patricia; Goldstein, Neil I.
 PATENT ASSIGNEE(S) : Imclone Systems Incorporated, USA
 SOURCE: U.S., 33 pp., Cont.-in-part of U.S. Ser. No. 476,533,
 abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5861499	A	19990119	US 1996-706804	19960903 <--
US 5840301	A	19981124	US 1994-326552	19941020 <--
US 6448077	B1	20020910	US 1997-967113	19971110 <--
US 5955311	A	19990921	US 1998-47807	19980325 <--
US 20020009750	A1	20020124	US 1999-401163	19990922 <--
US 6365157	B2	20020402		
US 20030103973	A1	20030605	US 2001-798689	20010302 <--
US 6811779	B2	20041102		
US 20020192213	A1	20021219	US 2002-90711	20020304 <--
US 20030108545	A1	20030612	US 2002-91300	20020304 <--
CN 101474404	A	20090708	CN 2008-10130173	20020304
CN 102133403	A	20110727	CN 2010-10584014	20020304
US 20050004066	A1	20050106	US 2004-900306	20040728 <--

PRIORITY APPLN. INFO.:

US 1994-196041	B2	19940210
US 1994-326552	A1	19941020
US 1995-476533	B2	19950607
US 1996-706804	A2	19960903
US 1997-779450	B1	19970107
US 1997-967113	A1	19971110
US 1999-401163	A2	19990922
US 2001-798689	A2	20010302
CN 2002-809226	A3	20020304
US 2002-90711	B1	20020304

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Nucleic acid mols. comprising a nucleic acid sequence that encodes an amino acid sequence wherein the amino acid sequence consists of the variable region or of the hypervariable region of a monoclonal antibody that specifically binds to an extracellular domain of a VEGF receptor and neutralizes activation of the receptor are disclosed. Rat and mouse anti-FLK1 monoclonal antibodies were prepared and shown to inhibit FLK1 phosphorylation in VEGF receptor-expressing cells. Athymic nude mice injected with glioblastoma cells developed tumors; those receiving injections of the anti-FLK1 monoclonal antibodies also developed tumors, but the tumors were smaller. Addnl. expts. indicated that the antibody inhibited angiogenesis and thereby limited tumor invasion of surrounding tissue.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 29 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 1999:219072 CAPLUS

DOCUMENT NUMBER: 131:28273

TITLE: Alternative splicing of vascular endothelial growth factor (VEGF)-R1 (FLT-1) pre-mRNA is important for the regulation of VEGF activity

AUTHOR(S) : He, Yulong; Smith, Stephen K.; Day, Kate A.; Clark, Dawn E.; Licence, Diana R.; Charnock-Jones, D. Stephen

CORPORATE SOURCE: Reproductive Molecular Research Group Department of

SOURCE: Obstetrics and Gynaecology, The Rosie Hospital,
University of Cambridge, Cambridge, CB2 2SW, UK
Molecular Endocrinology (1999), 13(4), 537-545
CODEN: MOENEN; ISSN: 0888-8809
DIGITAL OBJECT ID: 10.1210/mend.13.4.0265
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Angiogenesis is essential for normal mammalian development and is controlled by the local balance of pro- and antiangiogenic factors. Here we describe a novel mouse cDNA sequence encoding sFLT-1 that is a potent antagonist to vascular endothelial growth factor (VEGF) and show for the first time its in vivo production. In situ hybridization and Northern blot anal. with probes specific for sFLT-1 or FLT-1 showed that the relative abundance of their mRNAs changed markedly in spongiotrophoblast cells in the placenta as gestation progressed. On day 11 of pregnancy, sFLT-1 mRNA was undetectable but FLT-1 readily apparent, and by day 17 sFLT-1 mRNA was abundant but FLT-1 barely detectable. sFLT-1 was identified in conditioned medium of cultured placenta from day 17 pregnant mice and likely to be present in the circulation, as there is a substantial increase of VEGF-binding activity in the serum from day 13 of pregnancy, which coincides with the abundant sFLT-1 expression in placenta. Expression of sFLT-1 was also observed in adult lung, kidney, liver, and uterus. These data suggest a novel mechanism of regulation of angiogenesis by alternative splicing of FLT-1 pre-mRNA. Treatment of pregnant mice with exogenous VEGF from day 9 to 17 of pregnancy, which alters the ratio of VEGF to sFLT-1, resulted in an increase in the number of resorption sites and fibrin deposition in the placenta of ongoing pregnancies. These findings have important implications for understanding placental function and may be relevant in a range of disease states.

OS.CITING REF COUNT: 140 THERE ARE 140 CAPLUS RECORDS THAT CITE THIS RECORD (140 CITINGS)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 30 OF 30 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 1997:776257 CAPLUS
DOCUMENT NUMBER: 128:47303
ORIGINAL REFERENCE NO.: 128:9290h,9291a
TITLE: Chimeric forms of vascular endothelial growth factor receptor proteins as novel inhibitors of vascular endothelial growth factor activity
INVENTOR(S): Davis-Smyth, Terri Lynn; Chen, Helen Hsifei; Presta, Leonard; Ferrara, Napoleone
PATENT ASSIGNEE(S): Genentech, Inc., USA; Davis-Smyth, Terri Lynn; Chen, Helen Hsifei; Presta, Leonard; Ferrara, Napoleone
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9744453	A1	19971127	WO 1997-US7694	19970506 <--
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU			
RW:	GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,			

ML, MR, NE, SN, TD, TG				
US 6100071	A	20000808	US 1996-643839	19960507 <--
CA 2253738	A1	19971127	CA 1997-2253738	19970506 <--
CA 2804657	A1	19971127	CA 1997-2804657	19970506 <--
AU 9730604	A	19971209	AU 1997-30604	19970506 <--
AU 717112	B2	20000316		
EP 907733	A1	19990414	EP 1997-925475	19970506 <--
EP 907733	B1	20060524		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000502357	T	20000229	JP 1997-542429	19970506 <--
JP 3457330	B2	20031014		
EP 1666499	A2	20060607	EP 2005-23819	19970506
EP 1666499	A3	20060621		
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AT 327327	T	20060615	AT 1997-925475	19970506
EP 1710254	A2	20061011	EP 2006-2727	19970506
EP 1710254	A3	20070411		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
ES 2267143	T3	20070301	ES 1997-925475	19970506
EP 2336322	A1	20110622	EP 2010-185121	19970506
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5952199	A	19990914	US 1997-874678	19970613 <--
US 6383486	B1	20020507	US 1999-348886	19990701 <--
US 20030092604	A1	20030515	US 2002-105901	20020320 <--
US 6897294	B2	20050524		
US 20050281831	A1	20051222	US 2005-43693	20050126 <--
US 20070128695	A1	20070607	US 2006-537623	20060930
US 20090010933	A1	20090108	US 2008-104825	20080417
US 7771721	B2	20100810		
US 20090234103	A1	20090917	US 2008-104894	20080417
US 20110213130	A1	20110901	US 2011-13096742	20110428
US 8268313	B2	20120918		
US 20110301337	A1	20111208	US 2011-13096723	20110428
US 8273353	B2	20120925		
US 20110300577	A1	20111208	US 2011-13096734	20110428
US 8268591	B2	20120918		
US 20110301338	A1	20111208	US 2011-13096753	20110428
US 20110300578	A1	20111208	US 2011-13096771	20110428
US 20110301339	A1	20111208	US 2011-13096781	20110428
US 20130178418	A1	20130711	US 2012-13584241	20120813
US 9273113	B2	20160301		
PRIORITY APPLN. INFO.:				
			US 1996-643839	A 19960507
			CA 1997-2253738	A3 19970506
			EP 1997-925475	A3 19970506
			EP 2006-2727	A3 19970506
			WO 1997-US7694	W 19970506
			US 1999-348886	A1 19990701
			US 2002-105901	A1 20020320
			US 2005-43693	A1 20050126
			US 2006-537623	A1 20060930
			US 2008-104894	A3 20080417
			US 2011-13096723	A1 20110428

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention is directed to novel chimeric VEGF receptor proteins comprising amino acid sequences derived from the vascular endothelial growth factor (VEGF) receptors flt-1 and KDR, including the murine homolog to the human KDR receptor FLK-1, wherein said chimeric VEGF receptor proteins bind to VEGF and antagonize the endothelial

cell proliferative and angiogenic activity thereof. The present invention is also directed to nucleic acids and expression vectors encoding these chimeric VEGF receptor proteins, host cells harboring such expression vectors, pharmaceutically acceptable compns. comprising such proteins, methods of preparing such proteins and to methods utilizing such proteins for the treatment of conditions associated with undesired vascularization. Thus, the amino acid sequences of the extracellular ligand-binding region of flt-1, KDR, and FLT4 receptors were aligned and the boundaries of each of the seven Ig-like domains were determined. An flt-1/IgG (immunoadhesin) construct is then constructed and utilized as a template to systematically delete each of the 7 individual Ig-like domains of the flt-1 extracellular ligand-binding region by employing the loop-out mutagenesis technique, while also creating unique restriction sites at the boundaries to be used for inserting other Ig-like domains obtained from other VEGF receptor ligand-binding regions. The Ig-like domain 2 of the flt-1 extracellular ligand-binding region is shown to be required for specific binding to the VEGF ligand but is insufficient by itself to allow binding; the ability to bind VEGF was completely restored when Ig-like domains 1, 2, and 3 were all 3 present in combination. Replacing the flt-1 Ig-like domain 2 with the Ig-like domain 2 of the KDR receptor functions to establish the ability to specifically bind to the VEGF ligand, whereas the presence of FLT4 Ig-like domain 2 did not establish binding ability. Each of the other swap chimeras constructed behaved similar to the wild-type flt-1 receptor. The flt-1(2)/FLT4 and the flt-1(1,2,3)/FLT4 chimeric receptors are able to bind and specifically respond to VEGF.

OS.CITING REF COUNT: 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS
RECORD (36 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D ibib abs L4 1-4

L4 ANSWER 1 OF 4 MEDLINE ® on STN DUPLICATE 2
ACCESSION NUMBER: 2001472286 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11516238
TITLE: Endothelial cell apoptotic genes associated with the
pathogenesis of thrombotic microangiopathies: an
application of oligonucleotide genechip technology.
AUTHOR: Kim J
CORPORATE SOURCE: Laboratory for AIDS Virus Research, Weill Medical College
of Cornell University, New York, New York, 10021,USA.
JIK2002@med.cornell.edu
AUTHOR: Wu H; Hawthorne L; Rafii S; Laurence J
SOURCE: Microvascular research, (2001 Sep) Vol. 62, No. 2, pp.
83-93.
Journal code: 0165035. ISSN: 0026-2862. L-ISSN: 0026-2862.
DIGITAL OBJECT ID: <http://dx.doi.org/10.1006/mvre.2001.2326>
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 23 Aug 2001
Last Updated on STN: 25 Jan 2002
Entered Medline: 14 Jan 2002
GRANT FUNDING ORG.: United States NHLBI NIH HHS
GRANT FUNDING NUM.: HL55646; HL61849
OS.CITING REF COUNT: 2 There are 2 MEDLINE records that cite this record
AB Idiopathic thrombotic thrombocytopenic purpura (TTP) is a disease

characterized by the apoptotic injury of all microvascular endothelial cells (MVEC) except those of pulmonary origin. It notably also spares EC of large vessel origin. It is fatal unless treated with plasma exchange. The EC lineage restriction of the apoptotic lesions in vivo is reproduced in vitro following exposure of primary human MVEC derived from various tissues to TTP plasma. Oligonucleotide genechip technology was used to identify genes that may contribute to the resistance of lung MVEC to apoptosis induced by TTP plasma and to explore the intrinsic genotypic heterogeneity between MVEC of TTP-sensitive (skin) versus resistant (lung) lineage. Exposure of cells to TTP or normal plasma yielded 157 genes that were differentially expressed in primary human lung MVEC. A global change in expression of pro- and anti-apoptotic genes was seen, including increases in caspase 1, Fas, and Bcl-xl, already shown by experimental means to be involved in TTP pathogenesis. Additional differences suggest the importance of pathways related to the death receptor ligand TRAIL, as well as a role for disruption of EC-extracellular matrix interactions in the initiation of apoptosis. Maintenance of specific prosurvival signals at baseline may be a feature of lung MVEC resistance in TTP as suggested by higher expression than skin EC of the TRAIL antagonist, osteoprotegerin, and the vascular endothelial growth factors, VEGF/VPF and VEGF-C, and their receptors, VEGFR-2 (KDR) and VEGFR-3 (Flt4).
Copyright 2001 Academic Press.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2018 ACS on STN DUPLICATE 1
 ACCESSION NUMBER: 2004:355661 CAPLUS
 DOCUMENT NUMBER: 140:332450
 TITLE: Enzymatic nucleic acid-mediated treatment of ocular diseases or conditions related to levels of vascular endothelial growth factor receptor
 INVENTOR(S): Pavco, Pamela; McSwiggen, James; Stinchcomb, Dan; Escobedo, Jaime
 PATENT ASSIGNEE(S): Ribozyne Pharmaceuticals, Inc., USA; Sirna Therapeutics, Inc.; Chiron Corp.
 SOURCE: U.S. Pat. Appl. Publ., 357 pp., Cont.-in-part of U.S. Ser. No. 870,161.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 295
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040077565	A1	20040422	US 2002-138674	20020503 <--
US 7034009	B2	20060425		
US 6346398	B1	20020212	US 1996-584040	19960111 <--
EP 1408111	A2	20040414	EP 2004-536	19961025 <--
EP 1408111	A3	20040908		
EP 1408111	B1	20100609		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 9851819	A	19980611	AU 1998-51819	19980112 <--
AU 729657	B2	20010208		
AU 9939188	A	19990916	AU 1999-39188	19990713 <--
US 6566127	B1	20030520	US 1999-371772	19990810 <--
AU 2000056616	A	20001214	AU 2000-56616	20000911 <--
AU 769175	B2	20040115		
US 20040077565	A1	20040422	US 2002-138674	20020503 <--
US 7034009	B2	20060425		
US 20050227937	A1	20051013	US 2004-951303	20040927 <--
AU 2006203062	A1	20060810	AU 2006-203062	20060713
AU 2006203062	B2	20090312		
AU 2006203725	A1	20060914	AU 2006-203725	20060825

AU 2006203725	B2	20100527		
AU 2006228026	A1	20061102	AU 2006-228026	20061011
PRIORITY APPLN. INFO.:			US 2001-870161	A2 20010529
			US 2000-708690	A2 20001107
			US 1999-371772	A2 19990810
			US 1996-584040	A2 19960111
			US 1995-60005974	P 19951026
			US 2002-138674	20020503
			AU 1995-26422	A3 19950518
			US 1996-623891	A 19960325
			AU 1996-76662	A3 19961025
			EP 1996-939515	A3 19961025
			US 2000-685664	A1 20001010
			AU 2003-216323	A3 20030220
			AU 2003-219817	A3 20030220
			AU 2003-221258	A3 20030220

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention relates to nucleic acid mols. such as ribozymes, DNazymes, and antisense oligonucleotides which modulate the synthesis, expression, and/or stability of an mRNA encoding one or more receptors of vascular endothelial growth factor, such as flt-1 and KDR. The invention especially relates to a compd having the structure 5'-usasc2sa2sauucUGAUuGagggcgaaagccGaaAagacaaB-3', wherein each a is 2'-O-methyladenosine, each g is a 2'-O-methylguanosine, each c is a 2'-O-methylcytidine, each u is a 2'-O-methyluridine, each A is adenosine, each G is guanosine, each s individually represents a phosphorothioate internucleotide linkage, U is 2'-deoxy-2'-C-allyl uridine and B is an inverted deoxyabasic moiety. Nucleic acid mols. and methods for the inhibition of angiogenesis and treatment of cancer and ocular diseases are provided, optionally in conjunction with other therapeutic agents. [This abstract record is one of 5 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2004:709110 CAPLUS
DOCUMENT NUMBER: 142:49219
TITLE: Peptide derived from vascular endothelial growth factor receptor KDR and therapeutic use for treating angiogenesis-associated diseases
INVENTOR(S): Shou, Chengchao; Lei, Hetian; An, Ping; Wu, Jian; Meng, Lin; Liu, Xiaoying
PATENT ASSIGNEE(S): Beijing Institute of Prevention and Treatment of Tumor, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 30 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
CN 1406948	A	20030402	CN 2001-142203	20010912 <--
CN 1252085	C	20060419		
PRIORITY APPLN. INFO.:			CN 2001-142203	20010912
OTHER SOURCE(S):		MARPAT 142:49219		

AB The invention relates to the preparation of the polypeptide, A-X1-X2-X3-H-H-X4-X5-H-B (where: A = 0-3 of natural amino acid residues; x1 = hydrophobic amino acid residue or its protected derivative; X2 and/or X5 = natural amino acid residue or its protected derivative; X3 and/or X4 = protected polar amino acid residue; B = 0-5 of protected natural amino acid residues; and H = protected histidine residue), and the construction

of its fusion protein of another polypeptide (such as VEGF flt1 receptor antagonist, dihydrofolate reductase, cytokine, soluble VEGF receptor KDR or flt1, specific antibody or antigen fragment, or B7) or its oligomerized protein. The invention also relates to the application of the polypeptide, its fusion protein, and their corresponding polynucleotide to prepare the medical preps. for treating angiogenesis diseases (such as solid neoplasm).

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2018 ACS on STN

ACCESSION NUMBER: 2002:250203 CAPLUS
DOCUMENT NUMBER: 136:380558
TITLE: Fusion expression of peptides binding to VEGFR-1 and identification of their biological activities
AUTHOR(S): Lei, He-tian; Wu, Jian; Yang, Jun-shan; Shou, Cheng-chao
CORPORATE SOURCE: Beijing Institute for Cancer Research, Peking University School of Oncology, Beijing, 100034, Peop. Rep. China
SOURCE: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao (2002), 18(1), 19-22
CODEN: ZSHXF2; ISSN: 1007-7626
PUBLISHER: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao
Bianweihui
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Vascular endothelial growth factor (VEGF) binding to its tyrosine kinase receptors (KDR/Flk1, Flt-1) induces angiogenesis. In previous work, two pos. clones binding to VEGF receptor Flt-1 were selected from phage display peptide library. To identify the special binding activity, two oligonucleotide fragments synthesized according to the pos. phage-12 peptide sequences were cloned into DHFR fusion protein expression vector pQE42 for their expression in E. coli M15. Soluble DHFR-F56/F90 were obtained after denaturation and refolding. ELISA demonstrated that DHFR-F56/F90 were able to bind to sFlt-1 and vascular endothelial cells. Moreover, DHFR-F56 completely abolished VEGF binding to sFlt-1. Taken together, these data demonstrate that F56 may be an effective antagonist of VEGF receptor sFlt-1, and a potent inhibitor of tumor angiogenesis too.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

=> D His

(FILE 'HOME' ENTERED AT 12:44:08 ON 10 SEP 2018)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 12:44:37 ON 10 SEP 2018

L1 58 S (VEGF (S) (ANTAGONIST OR TRAP OR CHIMER? OR INHIBIT)) (P) (FL
L2 30 DUP REM L1 (28 DUPLICATES REMOVED)
L3 11 S ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR I
L4 4 DUP REM L3 (7 DUPLICATES REMOVED)
L5 0 S ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR I
L6 0 S ((VEGF (3A) RECEPTOR) (S) (ANTAGONIST OR TRAP OR CHIMER? OR I

=> Log Off H

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:51:00 ON 10 SEP 2018

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	25	("20030092606" "20030113316" "20030202972" "20040197324" "20050032699" "20050276808" "20050281831" "5399670" "5763401" "5851999" "6011003" "6100071" "6267958" "6270993" "6875432" "6897294" "7001892" "7052691" "7060268" "7070959" "7087411" "7374757" "8084234" "8343737" "8647842").PN.	US-PGPUB; USPAT	ADJ	ON	2018/09/10 18:10
L3	1	("20020004478").PN.	US-PGPUB; USPAT	ADJ	ON	2018/09/10 18:12
S1	0	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) WITH (VEGF WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:48
S2	0	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) WITH VEGF	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:49
S3	209	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND (VEGF WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:49
S4	135	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND ((VEGF receptor) WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:50
S5	100	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:35
S6	13	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME (\$nucleotide) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:36
S7	14	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME multimer\$ AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:37
S8	0	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME	US-PGPUB;	ADJ	ON	2018/09/10 12:40

		(Flt1 OR Flk1 OR Flt4) SAME (Glycosyl WITH Asparagine) AND @ad< = "20060322"	USPAT; EPO; JPO; DERWENT			
S9	4	(6100071 6383486).pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 15:09

EAST Search History (I nterference)

< This search history is empty>

9/ 10/ 2018 6:28:36 PM
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 15/692,893		Filing Date 08/31/2017		☐ 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)					
AMENDMENT	12/13/2018	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 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 \$ =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=		X \$ =			
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE				
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.										

SLIE
DEIDRE C. KING-WOODWARD

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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DEC 13 2018

REQUEST FOR TELEPHONE INTERVIEW Address to: Mail Stop AMENDMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-023CON8
	Confirmation No.	8858
	First Named Inventor	Daniel Dix
	Application Number	15/692,893
	Filing Date	August 31, 2017
	Group Art Unit	1647
	Examiner Name	Elly Gerald Stoica
Title: "VEGF Antagonist Formulations"		

Sir:

Applicants through their undersigned attorney request a telephone interview with the Examiner to discuss the proposed new claims shown on pages 2 and 3 of this document.

The claims are for purposes of discussion only and are believed to be responsive to the rejections raised within the Office Action dated September 14, 2018.

Amendments to the Claims begins on page 2 of this document.

Remarks/Arguments begin on page 4 of this document.

Atty Dkt. No.: REGN-023CON8
USSN: 15/692,893

AMENDMENTS TO THE CLAIMS

1. – 20. (Proposed Cancellation)
21. (New) A mammalian cell, comprising:
a polynucleotide encoding a fusion protein comprising amino acids 27-457 of SEQ ID NO:4;
wherein said fusion protein binds vascular endothelial growth factor (VEGF).
22. (New) The mammalian cell of claim 21, wherein said mammalian cell is a Chinese hamster ovary (CHO) cell.
23. (New) The mammalian cell of claim 21, wherein said VEGF antagonist fusion protein is post-translationally glycosylated at one or more asparagine residues.
24. (New) The mammalian cell of claim 23, wherein said fusion protein is post-translationally glycosylated at asparagine residues 59, 91, 146, 219, and 308.
25. (New) A method of manufacturing a VEGF antagonist fusion protein that comprises in order from the N-terminus to the C-terminus an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component, and does not comprise a signal peptide or a C-terminal lysine, said method comprising:
- a. expressing said VEGF antagonist fusion protein in a mammalian cell according to claim 21; and
 - b. purifying said VEGF antagonist fusion protein.
26. (New) The method of claim 25, wherein said mammalian cell is a CHO cell.
27. (New) The method of claim 25, wherein said fusion protein is purified until substantially free of protein contaminants.
28. (New) The method of claim 25, wherein at least 90% of the weight of said fusion protein is not present as an aggregate.

Atty Dkt. No.: REGN-023CON8
USSN: 15/692,893

29 (New) The method of claim 25, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at one or more asparagine residues..

30. (New) The method of claim 29, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at asparagine residues 59, 91, 146, 219 and 308.

Atty Dkt. No.: REGN-023CON8
USSN: 15/692,893

REMARKS

Formal Matters

Claims 21-30 are proposed for entry into this application.

Applicants propose cancelling claims 1-20.

The new claims 21-30 are believed to be supported within the previously pending, now cancelled claims 1-20 and elsewhere within the specification.

No new matter is added.

Atty Dkt. No.: REGN-023CON8
USSN: 15/692,893

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-023CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 13, 2018

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

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Telephone: (650) 327-3400
Facsimile: (650) 327-3231
Direct Dial (650) 833-7735

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 15/692,893		Filing Date 08/31/2017		☐ 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 \$80 =						
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =	*	x \$420 =						
☐ 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	01/15/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	* 22	Minus	** 20	= 2	x \$100 =		200		
	Independent (37 CFR 1.16(h))	* 3	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		200		
		(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.

AMENDMENT UNDER 37 C.F.R. §1.111 Address to: Mail Stop AMENDMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-023CON8
	Confirmation No.	8858
	First Named Inventor	Daniel Dix
	Application Number	15/692,893
	Filing Date	August 31, 2017
	Group Art Unit	1647
	Examiner Name	Elly Gerald Stoica
Title: <i>“VEGF Antagonist Formulations”</i>		

Sir:

This amendment is responsive to the Office Action dated September 14, 2018, for which a three-month period for response was given making this response timely filed on or before December 14, 2018. A petition and fee for a one-month extension of time is attached, making the response timely filed on or before January 14, 2019. However, the USPTO was officially closed on January 14, 2019 making this response timely filed on or before January 15, 2019.

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

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

1.-20. **(Cancelled)**

21. **(New)** A Chinese hamster ovary (CHO) cell, comprising:
a polynucleotide encoding a fusion protein comprising amino acids 27-457 of SEQ ID NO:2;
wherein said fusion protein binds vascular endothelial growth factor (VEGF).

22. **(New)** The Chinese hamster ovary (CHO) cell of claim 21, wherein said first VEGF receptor is Flt1.

23. **(New)** The Chinese hamster ovary (CHO) cell of claim 21, wherein said second VEGF receptor is Flk1 or Flt2.

24. **(New)** The Chinese hamster ovary (CHO) cell of claim 21, wherein said fusion protein is post-translationally glycosylated at asparagine residues 59, 91, 146, 219, and 308.

25. **(New)** The Chinese hamster ovary (CHO) cell of claim 21, wherein said polynucleotide comprises nucleotides 147-1439 of SEQ ID NO:1.

26. **(New)** The Chinese hamster ovary (CHO) cell of claim 21, wherein said fusion protein comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component; wherein said fusion protein does not comprise a signal peptide and does not comprise a C-terminal lysine.

27. **(New)** A Chinese hamster ovary (CHO) cell, comprising:
a polynucleotide encoding a fusion protein comprising amino acids 27-457 of SEQ ID NO: 4;
wherein said fusion protein binds vascular endothelial growth factor (VEGF).

28. **(New)** The Chinese hamster ovary (CHO) cell of claim 27, wherein said fusion protein is post-translationally glycosylated at asparagine residues 59, 91, 146, 219, and 308.

29. (New) The Chinese hamster ovary (CHO) cell of claim 27, wherein said polynucleotide comprises nucleotides 79-1371 of SEQ ID NO: 3.

30. (New) The Chinese hamster ovary (CHO) cell of claim 27, wherein said fusion protein comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component; wherein said fusion protein does not comprise a signal peptide and does not comprise a C-terminal lysine.

31. (New) A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a Chinese hamster ovary (CHO) cell, wherein said mammalian cell comprises polynucleotides 147-1439 of SEQ ID NO: 1 that encodes said VEGF antagonist fusion protein; and
- b. purifying said VEGF antagonist fusion protein.

32. (New) The method of claim 31, wherein said first VEGF receptor is Flt1 and said second VEGF receptor is Flk1 or Flt2.

33. (New) The method of claim 31, wherein said fusion protein is purified until substantially free of protein contaminants.

34. (New) The method of claim 31, wherein at least 90% of the weight of said fusion protein is not present as an aggregate.

35. (New) The method of claim 31, wherein said VEGF antagonist fusion protein comprises amino acids 27-457 of SEQ ID NO:2.

36. (New) The method of claim 31, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at asparagine residues 59, 91, 146, 219 and 308.

37. **(New)** The method of claim 31, wherein the fusion protein comprises in order from the N-terminus to the C-terminus an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component, and does not comprise a signal peptide or a C-terminal lysine.

38. **(New)** A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a mammalian cell, wherein said mammalian cell comprises polynucleotides 79-1371 of SEQ ID NO: 3 that encodes said VEGF antagonist fusion protein; and
- b. purifying said VEGF antagonist fusion protein.

39. **(New)** The method of claim 38, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at one or more asparagine residues.

40. **(New)** The method of claim 38, wherein said VEGF antagonist fusion protein comprises amino acids 27-457 of SEQ ID NO:4.

41. **(New)** The method of claim 38, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at asparagine residues 62, 94, 149, 222 and 308.

42. **(New)** The method of claim 38, wherein the fusion protein comprises in order from the N-terminus to the C-terminus an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor, and a multimerizing component, and does not comprise a signal peptide or a C-terminal lysine.

REMARKS

Formal Matters

Claims 21-42 are now pending in this application.

Claims 1-20 have been called without prejudice.

New claims 21-42 have been added to more particularly point out and distinctly claim the invention.

The new claims 21-42 are supported within the previously pending, now cancelled claims 1-19. However, the independent claims have all been written in order to recite specific sequences. For example, new independent claims 21 and 27 recite the amino acid sequence of SEQ ID NO. 2 and 4 respectively. Independent claims 31 and 38 recite the polynucleotide sequences of SEQ ID NO. 1 and 3 respectively.

Further, all of the claims are now limited to Chinese Hamster Ovary (CHO) cells as recited within previously pending now cancelled claim 2.

No new matter has been added.

Rejections

Claims 6, 9, 12 and 18 were rejected under 35 U.S.C. §112 (b) as referring to a glycosylation position without specifically referring to SEQ ID NOs.

Claims 1-20 were rejected under 35 U.S.C. §112 first paragraph as failing to comply with the written description requirement. The basis of the rejection is traversed. However, the rejection appears to be based on arguments that the claims 1-20 did not specifically recite amino acid sequences or nucleotide sequences by the SEQ ID NO.

The rejections are traversed as applied and as they might be applied to the presently pending claims. However, as indicated above, all of the claims now pending include a reference to a specific sequence as specifically recited within the original application.

The mammalian cell lines and specifically the CHO cell lines as claimed are supported in the original specification in paragraph [0028] along with the specific sequences referred to there and the sequence listing filed with the application.

In view of the newly submitted claims, the rejections are believed to have been overcome or rendered moot.

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-023CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 15, 2019

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

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Electronic Patent Application Fee Transmittal				
Application Number:		15692893		
Filing Date:		31-Aug-2017		
Title of Invention:		VEGF ANTAGONIST FORMULATIONS		
First Named Inventor/Applicant Name:		Daniel B. DIX		
Filer:		Karl Bozicevic/Savanna Fuentes		
Attorney Docket Number:		REGN-023CON8		
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:				
CLAIMS IN EXCESS OF 20	1202	2	100	200
INDEPENDENT CLAIMS IN EXCESS OF 3	1201	1	460	460
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with \$0 paid	1251	1	200	200
Miscellaneous:				
Total in USD (\$)				860

Electronic Acknowledgement Receipt

EFS ID:	34857045
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	VEGF ANTAGONIST FORMULATIONS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-023CON8
Receipt Date:	15-JAN-2019
Filing Date:	31-AUG-2017
Time Stamp:	14:21:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$860
RAM confirmation Number	011619INTEFSW14233800
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-023CON8_2019-01-15_amend.pdf	43567	yes	6
			eb9924b4befabce0f488f5954975e67814ce08d1		
	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	6	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	34321	no	2
			98082442f364384ecd140c637b75d9fdcd5f374b		
Warnings:					
Information:					
Total Files Size (in bytes):			77888		

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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8	8858
96387	7590	03/12/2019	EXAMINER	
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065			STOICA, ELLY GERALD	
			ART UNIT	PAPER NUMBER
			1647	
			NOTIFICATION DATE	DELIVERY MODE
			03/12/2019	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

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Response to Amendment

2. In the amendment filed on the amendment filed 01/15/2019 Applicant cancelled all previous claims and added the new claims 21-42, which are pending and are now examined.

Claim Rejections - 35 USC § 112

3. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 28 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Specifically, the claim recited asparagine residues 59, 91, 146, 219, and 308 of SEQ ID NO: 4. There are no asparagines at the positions cited.

As such, the metes and bounds of the claims could not be determined.

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

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

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

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

6. Claims 24, 28, 36, and 41 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a Chinese hamster ovary (CHO) cell, comprising: a polynucleotide encoding a fusion protein comprising amino acids 27-457 of SEQ ID NO:

2 or 4; wherein the fusion protein binds vascular endothelial growth factor (VEGF) and is post-translationally glycosylated at asparagine residues as well as a method of manufacturing it by expressing the nucleotide in CHO cells.

The art has been, for a long time, aware of the usage of CHO cells for obtaining glycosylated therapeutic proteins (see for instance Amand et al., Controllability analysis of protein glycosylation in CHO cells, PLOS One, 9, e87943, 2014; Borys et al. Culture pH affects expression rates and glycosylation of recombinant mouse placental lactogen proteins by Chinese hamster ovary (CHO) cells, Biotechnology, 11, 720-724, 1993).

Chinese hamster ovary (CHO) cells are widely used for production of many commercial and clinical biopharmaceuticals due to their capacity to produce glycoforms that are, with exceptions, accepted by the human immune system. The N-linked glycosylation pathway in mammalian cells involves a highly complex and interconnected reaction network catalyzed by glycosidases and glycosyltransferases contained within different compartments of the ER and Golgi apparatus, depicted in the schematic of Fig. 1. The biosynthesis of mammalian N-glycans initiates at the cytoplasmic face of the ER membrane with the transfer of GlcNAc-P from UDP-GlcNAc to the dolichol phosphate (Dol-P) lipid carrier to generate dolichol pyrophosphate N-acetylglucosamine (Dol-P-P-GlcNAc). Then 14 sugars are sequentially added to Dol-P-P-GlcNAc to form an oligosaccharide precursor (Glc3Man9GlcNAc2). Next, oligosaccharyl transferase (OST) selects Asn-X-Ser/Thr sequons in a nascent polypeptide and proceeds with an en bloc transfer of Glc3Man9GlcNAc2 to the side chain amide of asparagine and releasing Dol-P-P in the process [11]. The glucose residues on the precursor are sequentially trimmed by ER α -glucosidase I and II to form monoglucosylated glycan, which is a key

intermediate in the ER lectin chaperones calnexin/calreticulin-associated glycoprotein folding control cycle. Once correctly folded, the precursor is trimmed by ER α -mannosidase I to yield Man8GlcNAc2-protein before exiting ER. After translocation into the cis-Golgi, the Man8GlcNAc2 glycoform is further trimmed by Golgi α -mannosidases I to give Man5GlcNAc2, a key intermediate along the pathway to form hybrid and complex N-glycans and sometimes found as a final glycan product. Biosynthesis of hybrid and complex N-glycans begins in the medial-Golgi by the action of an N-acetylglucosaminyl transferase (GnT-1 or Mgat1), which adds a GlcNAc to Man5GlcNAc2. Then the majority of N-glycans are trimmed by Golgi α -mannosidase II removing two mannoses from GlcNAcMan5GlcNAc2 to yield GlcNAcMan3GlcNAc2. Hybrid N-glycans result when a structure such as GlcNAcMan3 GlcNAc2 either undergoes no further extension or trimming to remove exposed mannose residues resulting in structures with one or two terminal Man residue. In addition, sometimes another GlcNAc can be added to the innermost Man group by the enzyme β 1,4-N-acetylglucosaminyltransferase III (GnT-III or Mgat3) in the medial Golgi, resulting in bisecting GlcNAc structures that can also alter the capacity for other downstream enzymes to act on the glycan structure. Next, the enzyme β -1,2-N-acetylglucosaminyltransferase II (GnT-II or Mgat2) adds a GlcNAc to the GlcNAcMan3GlcNAc2 structure to generate the glycan product GlcNAc2Man3GlcNAc2, which is the precursor for all multiantennary complex N-glycans. Tri and tetra-antennary branches can be achieved by adding GlcNAc at α (1,3)-mannose site by N-acetylglucosaminyl transferase IV (GnT-IV or Mgat4) and at α (1,6)-mannose site by N-acetylglucosaminyl transferase V (GnT-V or Mgat 5). Additional modifications of complex and hybrid N-glycans can occur in the trans-Golgi and include the addition of core α (1,6)-

fucose to the GlcNAc adjacent to Asn at the N-glycan sites by α -(1,6)-fucosyl transferase and the branch elongation by the addition of a β -linked galactose residue to GlcNAc by galactosyltransferase to produce Gal β 1-4GlcNAc, or poly-acetyl-lactosamine (poly-LacNAc) sequences. Finally, these terminal Gal residues can serve as acceptors for several sialyl transferases, leading to even more complex structures. The glycosylation of biotherapeutics has been identified as a critical quality attribute because each biotherapeutic requires defining glycosylation characteristics to maintain consistent quality parameters such as solubility, thermal stability, protease resistance, aggregation, serum half-life, immunogenicity, and efficacy. Thus, in order to tailor the glycosylation structures produced by CHO cells, a number of researchers have undertaken metabolic glycoengineering strategies to alter the final glycan profiles and distribution in CHO. Strategies like genetically engineering altering Sialylation pathways, overexpressing of N-acetylglucosaminyl transferase genes, inhibiting sialidase activity have been developed for distinct proteins. Another issue with N-glycans of therapeutic proteins is the generation of heterogeneous glycoforms, which present challenges in protein purification, product consistency, and lot-to-lot reproducibility, resulting in variable therapeutic efficacy. This diversity can sometimes adversely affect drug potency and pharmacokinetics. However, N-glycans can also be crucial for protein folding, so these difficulties cannot necessarily be overcome by removing N-glycosylation sites. Heterogeneity is attributed to the lack of 100% efficiency for each step in mammalian N-glycan biosynthesis due to variability in enzyme levels, substrate concentration, intracellular location, and the competition of different enzymes for the same substrates (Wang et al., Glycoengineering of CHO cells to improve product quality. Paula Meleady (ed.), Heterologous Protein Production in CHO

Cells: Methods and Protocols, Methods in Molecular Biology, vol. 1603, DOI 10.1007/978-1-4939-6972-2_2, © Springer Science+Business Media LLC 2017).

As may be seen, the process of obtaining glycosylated therapeutic proteins from heterologous expression in CHO cell is extremely complex and unpredictable for obtaining exactly glycosylated products. The specification does not offer even a paragraph about obtaining the claimed products in CHO and not even a single method step is detailed. Given the complexity of the process and the unpredictability in the art, it is considered that a vast amount of experimentation would be necessary for obtaining the exactly glycosylated product and this amount of experimentation is undue.

Conclusion

7. Claims 21-23, 25-27, 29-35, 37-40 and 42 are allowed. Claims 24, 28, 36, and 41 are not allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory

action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on M-F 8-5 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

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 phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

ELLY-GERALD STOICA
Primary Examiner
Art Unit 1647

/Elly-Gerald Stoica/
Primary Examiner, Art Unit 1647

<i>Applicant-Initiated Interview Summary</i>	Application No. 15/692,893	Applicant(s) DIX et al.	
	Examiner ELLY GERALD STOICA	Art Unit 1647	AIA (FITF) Status No

All participants (applicant, applicants representative, PTO personnel):

(1) ELLY GERALD STOICA. (3) ____.

(2) KARL BOZICEVIC. (4) ____.

Date of Interview: 15 December 2018.

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: 1-20.

Identification of prior art discussed: ____.

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...)

Applicant was informed that without SEQ ID NOs: the specification and the claims could not fulfill the requirements of the Written Description requirement. Applicant thanked Examiner for the clarification and declared that the response to the Office action would address the rejection.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the 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

/Elly-Gerald Stoica/ Primary Examiner, Art Unit 1647	
---	--

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

<i>Notice of References Cited</i>	Application/Control No. 15/692,893		Applicant(s)/Patent Under Reexamination DIX et al.	
	Examiner ELLY GERALD STOICA		Art Unit 1647	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Amand et al., Controllability analysis of protein glycosylation in CHO cells, PLOS One, 9, e87943, 2014. (Year: 2014)
	V	Borys et al. Culture pH affects expression rates and glycosylation of recombinant mouse placental lactogen proteins by Chinese hamster ovary (CHO) cells, Biotechnology, 11, 720-724, 1993. (Year: 1993)
	W	Wang et al., Glycoengineering of CHO cellsto improve product quality. Paula Meleady (ed.), Heterologous Protein Production in CHOCells: Methods and Protocols, Methods in Molecular Biology, vol. 1603, DOI 10.1007/978-1-4939-6972-2_2, © Springer Science+Business Media LLC 2017. (Year: 2017)
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

<i>Search Notes</i> 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.
	Examiner ELLY GERALD STOICA	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* 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
PALM (inventor and continuity)	09/10/2018	EGS
East Search (US-PGpub; USPAT; USOCR; EPO; JPO; Derwent)	09/10/2018	EGS
STN (Medline; Biosis; CAPlus; EMBASE)	09/10/2018	EGS
Search for SEQ ID NOS:1-4	09/08/2018	EGS
Update PALM (inventor and continuity)	03/06/2019	EGS
Update East Search (US-PGpub; USPAT; USOCR; EPO; JPO; Derwent)	03/04/2019	EGS

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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<i>Index of Claims</i> 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.
	Examiner ELLY GERALD STOICA	Art Unit 1647

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	09/10/2018	03/06/2019							
	1	✓	-							
	2	✓	-							
	3	✓	-							
	4	✓	-							
	5	✓	-							
	6	✓	-							
	7	✓	-							
	8	✓	-							
	9	✓	-							
	10	✓	-							
	11	✓	-							
	12	✓	-							
	13	✓	-							
	14	✓	-							
	15	✓	-							
	16	✓	-							
	17	✓	-							
	18	✓	-							
	19	✓	-							
	20	✓	-							
	21		=							
	22		=							
	23		=							
	24		✓							
	25		=							
	26		=							
	27		=							
	28		✓							
	29		=							
	30		=							
	31		=							
	32		=							
	33		=							
	34		=							
	35		=							
	36		✓							
	37		=							
	38		=							
	39		=							
	40		=							
	41		✓							
	42		=							

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S3	209	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND (VEGF WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:49
S4	135	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND ((VEGF receptor) WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:50
S5	100	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:35
S6	13	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME (\$nucleotide) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:36
S7	14	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME multimer\$ AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:37
S8	0	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME (Glycosyl WITH Asparagine) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:40
S9	4	(6100071 6383486).pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 15:09
S10	25	("20030092606" "20030113316" "20030202972" "20040197324" "20050032699" "20050276808" "20050281831" "5399670" "5763401" "5851999" "6011003" "6100071" "6267958" "6270993" "6875432" "6897294" "7001892" "7052691" "7060268" "7070959" "7087411" "7374757" "8084234" "8343737" "8647842").PN.	US-PGPUB; USPAT	ADJ	ON	2018/09/10 18:10
S11	1	("20020004478").PN.	US-PGPUB; USPAT	ADJ	ON	2018/09/10 18:12
S12	0	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR	US-PGPUB;	ADJ	ON	2018/12/13 15:05

		Regeneron.AS.) AND ((VEGF receptor) WITH Fusion) WITH Glycosyl\$	USPAT; EPO; JPO; DERWENT			
S13	112	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND ((VEGF receptor) WITH Fusion) AND Glycosyl\$	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/12/13 15:05
S14	2	"9045545".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/12/13 15:24
S15	2	"9149427".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/12/13 15:26
S16	9	"9605043".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:18
S17	0	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME multimer\$ SAME ((chinese hamster ovary) OR CHO) AND @ad<="20060322"	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:24
S18	2	(VEGF ADJ4 Receptor) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO) AND @ad<="20060322"	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:27
S19	1	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO) AND @ad<="20060322"	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:29
S20	23	(VEGF ADJ4 Receptor) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO)	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 15:47
S23	2	"6833349".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 18:24
S30	213	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND (VEGF WITH Fusion)	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/06 12:39
S31	108	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND (VEGF WITH Fusion) AND (CHO cell)	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/06 12:41

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S21	0	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimer\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME multimer\$ SAME ((chinese hamster ovary) OR CHO)	USPAT	ADJ	ON	2019/03/04 15:47
S22	5	(VEGF ADJ4 Receptor) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO)	USPAT	ADJ	ON	2019/03/04 15:48

3/ 6/ 2019 7:43:42 PM
C:\ Users\ estoica\ Documents\ EAST\ Workspaces\ 15692893.wsp

AMENDMENT UNDER 37 C.F.R. §1.116 Address to: Mail Stop AMENDMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-023CON8
	Confirmation No.	8858
	First Named Inventor	Daniel Dix
	Application Number	15/692,893
	Filing Date	August 31, 2017
	Group Art Unit	1647
	Examiner Name	Elly Gerald Stoica
Title: “ <i>VEGF Antagonist Formulations</i> ”		

Sir:

This amendment is responsive to the Final Office Action dated March 12, 2019, for which a three-month period for response was given making this response timely filed on or before June 12, 2019.

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

Remarks/Arguments begin on page 5 of this paper.

Electronic Acknowledgement Receipt

EFS ID:	36140779
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	VEGF ANTAGONIST FORMULATIONS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-023CON8
Receipt Date:	29-MAY-2019
Filing Date:	31-AUG-2017
Time Stamp:	14:36:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-023CON8_2019-05-29_a mend_AF.pdf	82505 b89d460f2ede104d9dd96d389b5f96ec4e058d40	yes	6

Multipart Description/PDF files in .zip description			
Document Description	Start	End	
Applicant Arguments/Remarks Made in an Amendment	4	6	
Claims	2	3	
Response After Final Action	1	1	
Warnings:			
Information:			
Total Files Size (in bytes):		82505	
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.			

REMARKS

Formal Matters

Claims 31, 33, 38 and 39 are now pending in this application.

Claims 1-30, 32, 34-37 and 40-42 have been cancelled without prejudice.

Claims 31 and 38 are amended.

No new matter has been added.

Allowed Claims

The applicants appreciate the Examiner's allowance of claims 21-23, 25-27, 29-35, 37-40 and 42.

Rejection under 35 U.S.C. §1.112(b)

Claim 28 was rejected under 35 U.S.C. §112 (b) as being indefinite for failing to particularly point out and distinctly claim the invention.

Claim 28 has been cancelled from the application rendering the rejection moot.

Rejection under 35 U.S.C. §1.112(a)

Claims 24, 28, 36 and 41 were rejected under 35 U.S.C. §112 (1) for failing to comply with the enablement requirement.

Claims 24, 28, 36 and 41 have been cancelled from the application rendering the rejection moot.

Claim Amendments

Applicants recognize that claims cannot be amended as a matter of right after a Final Office Action. However, the present amendment would not require more than a cursory review by Examiner and, thus, should be entered.

Claim 31 is amended to incorporate the elements of previously pending, allowed, now cancelled claim 21, 34 and 35; and claim 15 as filed. All of the claims 21, 31, 34 and 35 were previously indicated as allowable.

Claim 38 has been amended to incorporate the elements of previously pending, allowed, now cancelled claims 27 and 40; and claim 15 as filed. Claims 27, 38 and 40 were previously indicated as allowable.

In that the claim amendments do not add new matter, were previously examined in dependent

claims, and will not require further searching or consideration by the Examiner, entry of these amendments and allowance of the claims is respectfully requested.

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-023CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 29, 2019

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

AMENDMENTS TO THE CLAIMS

1.-30. (Cancelled)

31. (Currently Amended) A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a Chinese hamster ovary (CHO) cell comprising a polynucleotide encoding the VEGF antagonist fusion protein which comprises amino acids 27-457 of SEQ ID NO: 2 wherein said fusion protein binds vascular endothelial growth factor (VEGF), ~~wherein said mammalian cell comprises polynucleotides 147-1439 of SEQ ID NO: 1 that encodes said VEGF antagonist fusion protein;~~ and
- b. purifying said VEGF antagonist fusion protein;
wherein at least 90% of the weight of the purified fusion protein is not present as an aggregate.

32. (Cancelled)

33. (Previously Presented) The method of claim 31, wherein said fusion protein is purified until substantially free of protein contaminants.

34-37. (Cancelled)

38. (Currently Amended) A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a ~~mammalian~~ Chinese hamster ovary (CHO) cell comprising a polynucleotide encoding the VEGF antagonist fusion protein which comprises amino acids 27-457 of SEQ ID NO: 4 wherein said fusion protein binds vascular endothelial growth factor (VEGF), ~~wherein said mammalian cell comprises polynucleotides 79-1371 of SEQ ID NO: 3 that encodes said VEGF antagonist fusion protein;~~ and

b. purifying said VEGF antagonist fusion protein;
wherein at least 90% of the weight of the purified fusion protein is not present as an aggregate.

39. **(Previously Presented)** The method of claim 38, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at one or more asparagine residues.

40. – 42. **(Cancelled)**

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 15/692,893		Filing Date 08/31/2017		☐ 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 \$80 =						
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =	*	x \$420 =						
☐ 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	05/29/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	* 4	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.						LIE				
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/MOLIKI I MAY/				
*** 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 06/13/2019
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER

STOICA, ELLY GERALD

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 06/13/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8	8858

TITLE OF INVENTION: VEGF ANTAGONIST FORMULATIONS

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	09/13/2019

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.

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)

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.

96387 7590 06/13/2019
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

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.
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8	8858

TITLE OF INVENTION: VEGF ANTAGONIST FORMULATIONS

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	09/13/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
STOICA, ELLY GERALD	1647	514-008100

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,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document 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. _____



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.
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8	8858
96387	7590	06/13/2019	EXAMINER	
Regeneron - Bozicevic, Field & Francis			STOICA, ELLY GERALD	
201 REDWOOD SHORES PARKWAY			ART UNIT	
SUITE 200			PAPER NUMBER	
REDWOOD CITY, CA 94065			1647	

DATE MAILED: 06/13/2019

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

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

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

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

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

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

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 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) 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. 15/692,893	Applicant(s) DIX et al.	
	Examiner ELLY GERALD STOICA	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 05/29/2019.
☐ 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 31,33 and 38-39. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

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

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

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

/Elly-Gerald Stoica/ Primary Examiner, Art Unit 1647	
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EXAMINER'S AMENDMENT

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.
2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

The application has been amended as follows:

In the title, please replace the current title: "VEGF antagonist formulations" with the following title:

-- Method of manufacturing VEGF antagonist fusion proteins --.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on M-F 8-5 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

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 phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

ELLY-GERALD STOICA
Primary Examiner
Art Unit 1647

/Elly-Gerald Stoica/
Primary Examiner, Art Unit 1647

<i>Search Notes</i> 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.
	Examiner ELLY GERALD STOICA	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* 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
PALM (inventor and continuity)	09/10/2018	EGS
East Search (US-PGpub; USPAT; USOCR; EPO; JPO; Derwent)	09/10/2018	EGS
STN (Medline; Biosis; CAPlus; EMBASE)	09/10/2018	EGS
Search for SEQ ID NOs:1-4	09/08/2018	EGS
Update PALM (inventor and continuity)	03/06/2019	EGS
Update East Search (US-PGpub; USPAT; USOCR; EPO; JPO; Derwent)	03/04/2019	EGS
Update PALM (inventor and continuity)	06/07/2019	EGS
Update East Search (US-PGpub; USPAT; USOCR; EPO; JPO; Derwent)	06/07/2019	EGS

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<i>Search Notes</i> 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.
	Examiner ELLY GERALD STOICA	Art Unit 1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
None	See search notes	06/07/2019	EGS
None	Sequence search for SEQ ID NOs:	06/07/2019	EGS

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Issue Classification 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.	
	Examiner ELLY GERALD STOICA	Art Unit 1647	

CPC						
Symbol					Type	Version
A61K	/	39	/	39591	F	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	9	/	08	I	2013-01-01
A61K	/	9	/	19	I	2013-01-01
A61K	/	31	/	4172	I	2013-01-01
A61K	/	31	/	7012	I	2013-01-01
A61K	/	47	/	02	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	38	/	179	I	2013-01-01
A61K	/	38	/	16	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
A61K	/	47	/	183	I	2013-01-01
A61K	/	47	/	22	I	2013-01-01
C07K	/	14	/	71	I	2013-01-01
C07K	/	16	/	22	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2318	/	20	A	2013-01-01

CPC Combination Sets					
Symbol				Type	Set

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 4	
/Elly-Gerald Stoica/ Primary Examiner, Art Unit 1647 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1, 3	O.G. Print Figure None

Issue Classification 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.	
	Examiner ELLY GERALD STOICA	Art Unit 1647	

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K39/395	/	39	/	395
A61K9/00	/	9	/	00
A61K38/17	/	38	/	17
A61K38/16	/	38	/	16
C07K14/71	/	14	/	71
C07K16/22	/	16	/	22
CPCONLY	/	NLY	/	

NON-CLAIMED				
A61K9/08	/	9	/	08
A61K9/19	/	9	/	19
A61K31/4172	/	31	/	4172
A61K31/7012	/	31	/	7012
A61K47/02	/	47	/	02
A61K47/26	/	47	/	26
A61K47/10	/	47	/	10
A61K47/18	/	47	/	18
A61K47/22	/	47	/	22
A61K47/12	/	47	/	12

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	8.1

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

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	4	
/Elly-Gerald Stoica/ Primary Examiner, Art Unit 1647	07 June 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1, 3	None

Issue Classification 	Application/Control No. 15/692,893	Applicant(s)/Patent Under Reexamination DIX et al.
	Examiner ELLY GERALD STOICA	Art Unit 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
	1		10		19		28		37						
	2		11		20		29	3	38						
	3		12		21		30	4	39						
	4		13		22	1	31		40						
	5		14		23		32		41						
	6		15		24	2	33		42						
	7		16		25		34								
	8		17		26		35								
	9		18		27		36								

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 4	
/Elly-Gerald Stoica/ Primary Examiner, Art Unit 1647 (Primary Examiner) _____ (Date) _____		O.G. Print Claim(s) 1, 3	O.G. Print Figure None

REMARKS

Formal Matters

Claims 31, 33, 38 and 39 are now pending in this application.

Claims 1-30, 32, 34-37 and 40-42 have been cancelled without prejudice.

Claims 31 and 38 are amended.

No new matter has been added.

Allowed Claims

The applicants appreciate the Examiner's allowance of claims 21-23, 25-27, 29-35, 37-40 and 42.

Rejection under 35 U.S.C. §1.112(b)

Claim 28 was rejected under 35 U.S.C. §112 (b) as being indefinite for failing to particularly point out and distinctly claim the invention.

Claim 28 has been cancelled from the application rendering the rejection moot.

Rejection under 35 U.S.C. §1.112(a)

Claims 24, 28, 36 and 41 were rejected under 35 U.S.C. §112 (1) for failing to comply with the enablement requirement.

Claims 24, 28, 36 and 41 have been cancelled from the application rendering the rejection moot.

Claim Amendments

Applicants recognize that claims cannot be amended as a matter of right after a Final Office Action. However, the present amendment would not require more than a cursory review by Examiner and, thus, should be entered.

Claim 31 is amended to incorporate the elements of previously pending, allowed, now cancelled claim 21, 34 and 35; and claim 15 as filed. All of the claims 21, 31, 34 and 35 were previously indicated as allowable.

Claim 38 has been amended to incorporate the elements of previously pending, allowed, now cancelled claims 27 and 40; and claim 15 as filed. Claims 27, 38 and 40 were previously indicated as allowable.

In that the claim amendments do not add new matter, were previously examined in dependent

claims, and will not require further searching or consideration by the Examiner, entry of these amendments and allowance of the claims is respectfully requested.

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-023CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 29, 2019

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

AMENDMENTS TO THE CLAIMS

1.-30. (Cancelled)

31. (Currently Amended) A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a Chinese hamster ovary (CHO) cell comprising a polynucleotide encoding the VEGF antagonist fusion protein which comprises amino acids 27-457 of SEQ ID NO: 2 wherein said fusion protein binds vascular endothelial growth factor (VEGF), ~~wherein said mammalian cell comprises polynucleotides 147-1439 of SEQ ID NO: 1 that encodes said VEGF antagonist fusion protein;~~ and
- b. purifying said VEGF antagonist fusion protein;
wherein at least 90% of the weight of the purified fusion protein is not present as an aggregate.

32. (Cancelled)

33. (Previously Presented) The method of claim 31, wherein said fusion protein is purified until substantially free of protein contaminants.

34-37. (Cancelled)

38. (Currently Amended) A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a ~~mammalian~~ Chinese hamster ovary (CHO) cell comprising a polynucleotide encoding the VEGF antagonist fusion protein which comprises amino acids 27-457 of SEQ ID NO: 4 wherein said fusion protein binds vascular endothelial growth factor (VEGF), ~~wherein said mammalian cell comprises polynucleotides 79-1371 of SEQ ID NO: 3 that encodes said VEGF antagonist fusion protein; and~~

b. purifying said VEGF antagonist fusion protein;
wherein at least 90% of the weight of the purified fusion protein is not present as an aggregate.

39. **(Previously Presented)** The method of claim 38, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at one or more asparagine residues.

40. – 42. **(Cancelled)**

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	140	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND ((VEGF receptor) WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/06/07 16:39
L3	55	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) WITH ((chinese hamster ovary) OR CHO) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/06/07 16:40
S3	209	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND (VEGF WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:49
S4	135	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND ((VEGF receptor) WITH Fusion)	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/09 10:50
S5	100	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:35
S6	13	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME (\$nucleotide) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:36
S7	14	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME multimer\$ AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:37
S8	0	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME (Glycosyl WITH Asparagine) AND @ad<="20060322"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 12:40
S9	4	(6100071 6383486).pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/09/10 15:09
S10	25	("20030092606" "20030113316" "20030202972" "20040197324" "20050032699" "20050276808" "20050281831" "5399670" "5763401" "5851999" "6011003" "6100071"	US-PGPUB; USPAT	ADJ	ON	2018/09/10 18:10

		"6267958" "6270993" "6875432" "6897294" "7001892" "7052691" "7060268" "7070959" "7087411" "7374757" "8084234" "8343737" "8647842").PN.				
S11	1	("20020004478").PN.	US- PGPUB; USPAT	ADJ	ON	2018/09/10 18:12
S12	0	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND ((VEGF receptor) WITH Fusion) WITH Glycosyl\$	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/12/13 15:05
S13	112	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND ((VEGF receptor) WITH Fusion) AND Glycosyl\$	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/12/13 15:05
S14	2	"9045545".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/12/13 15:24
S15	2	"9149427".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2018/12/13 15:26
S16	9	"9605043".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:18
S17	0	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME multimer\$ SAME ((chinese hamster ovary) OR CHO)AND @ad<="20060322"	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:24
S18	2	(VEGF ADJ4 Receptor) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO) AND @ad<="20060322"	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:27
S19	1	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO) AND @ad<="20060322"	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 13:29
S20	23	(VEGF ADJ4 Receptor) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO)	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 15:47
S23	2	"6833349".pn.	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/04 18:24
S30	213	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR	US- PGPUB;	ADJ	ON	2019/03/06 12:39

		Regeneron.AS.) AND (VEGF WITH Fusion)	USPAT; EPO; JPO; DERWENT			
S31	108	((Dix NEAR Daniel).IN. OR (Frye NEAR Kelly).IN. OR (Kautz NEAR Susan).IN. OR Regeneron.AS.) AND (VEGF WITH Fusion) AND (CHO cell)	US- PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2019/03/06 12:41

EAST Search History (I nterference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	35	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) WITH ((chinese hamster ovary) OR CHO)	USPAT	ADJ	ON	2019/06/07 16:40
S21	0	((VEGF ADJ4 Receptor) WITH (antagonist OR Trap OR chimera\$ OR Inhibit\$)) SAME (Flt1 OR Flk1 OR Flt4) SAME multimer\$ SAME ((chinese hamster ovary) OR CHO)	USPAT	ADJ	ON	2019/03/04 15:47
S22	5	(VEGF ADJ4 Receptor) SAME (Flt1 OR Flk1 OR Flt4) SAME ((chinese hamster ovary) OR CHO)	USPAT	ADJ	ON	2019/03/04 15:48

6/ 7/ 2019 4:41:37 PM
C:\Users\estoica\Documents\EAST\Workspaces\15692893.wsp

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

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
15692893	31-Aug-2017	Daniel DIX	REGN-023CON8	8858

TITLE OF INVENTION :

VEGF ANTAGONIST FORMULATIONS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1647	008100	ELLY GERALD STOICA
Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
\$1000	\$0	\$1000	13-Sep-2019	\$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.



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

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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. Karl Bozicevic
2. Bozicevic, Field & Francis LLP
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	07-25-2019
Name	Karl Bozicevic	Registration Number	28807

Electronic Patent Application Fee Transmittal				
Application Number:		15692893		
Filing Date:		31-Aug-2017		
Title of Invention:		VEGF ANTAGONIST FORMULATIONS		
First Named Inventor/Applicant Name:		Daniel B. DIX		
Filer:		Karl Bozicevic/Savanna Fuentes		
Attorney Docket Number:		REGN-023CON8		
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:	36690447
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	VEGF ANTAGONIST FORMULATIONS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-023CON8
Receipt Date:	25-JUL-2019
Filing Date:	31-AUG-2017
Time Stamp:	16:24:01
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	072619INTEFSW16235900
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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	Issue Fee Payment (PTO-85B)	Web85b.pdf	46398	no	2
			c33897941c451d1345bfc1f10bed984a151e16d5		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31999	no	2
			4f8819d837a6dc9115f025070be161a351368686		
Warnings:					
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Total Files Size (in bytes):			78397		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

INFORMATION DISCLOSURE STATEMENT BY APPLICANT			Application Number	15/692,893	
			Filing Date	August 31, 2017	
			First Named Inventor	Dix, Daniel	
			Art Unit	1647	
			Examiner Name	STOICA, ELLY GERALD	
Sheet	1	of	1	Attorney Docket Number	REGN-023CON8

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

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1	2002/004478	2002-01-10	Danko et al.	
	2				

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
		Country Code-Number-Kind Code (if known)				
	1	WO 2006/088650	2006-08-24	Regeneron Pharmaceuticals, Inc.		
	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	LOPEZ et al., "Comparative enhancer effects of Span 20 with Tween 20 and Azone of the <i>in vitro</i> percutaneous penetration of compounds with different lipophilicities" International Journal of Pharmaceutics (July 1, 2000) 202(1-2):133-140	
	2		

Examiner Signature	/Elly-Gerald Stoica/	Date Considered	09/10/2018
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*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 (Not for submission under 37 CFR 1.99)

Application Number	15/692,893 - GAU: 1647
Filing Date	2017-08-31
First Named Inventor	DIX, Daniel
Art Unit	
Examiner Name	/Elly-Gerald Stoica/
Attorney Docket Number	238811-21.89 (4030US11)

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6267958	B1	2001-07-31	Andya, et al.	
	2	6875432	B2	2005-04-05	Liu, et al	
	3	7060268	B2	2006-06-13	Andya, et al.	
	4	7001892	B1	2006-02-21	Chmielweski, et al.	
	5	5399670	A	1995-03-21	Bhattacharya, et al.	
	6	5851999	A	1998-12-22	Ulrich, et al.	
	7	6011003	A	2000-01-04	Charmock-Jonee, et al.	
	8	6270993	B1	2001-08-07	Shibuya, et al.	

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

Application Number		15/692,893 - GAU: 1647
Filing Date		2017-08-31
First Named Inventor	DIX, Daniel	
Art Unit		
Examiner Name	/Elly-Gerald Stoica/	
Attorney Docket Number		238811-21.89 (4030US11)

9	7087411	B2	2006-08-08	Daly, et al.	
10	7374757	B2	2008-05-20	Papadopoulos, et al.	
11	7052691	B2	2006-05-30	Sleeman, et al.	
12	6100071	A	2000-08-08	Davis-Smyth, et al.	
13	6897294	B2	2005-05-24	Davis-Smyth, et al.	
14	5763401	A	1998-06-09	Rajiv, Nayar	
15	7070959	B1	2006-07-04	Papadopoulos et al.	
16	7087411	B2	2006-08-08	Daly et al.	
17	8084234	B2	2011-12-27	Papadopoulos et al.	
18	8343737	B2	2013-01-01	Papadopoulos et al.	
19	8647842	B2	2014-02-11	Papadopoulos et al.	

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

Application Number	15/692,893 -- GAU: 1647
Filing Date	2017-08-31
First Named Inventor	DIX, Daniel
Art Unit	
Examiner Name	/Elly-Gerald Stoica/
Attorney Docket Number	238811-21.89 (4030US11)

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	1	20030113316	A1	2003-06-19	Kaisheva, et al.	
	2	20040197324	A1	2004-10-07	Liu, et al.	
	3	20030092606	A1	2003-05-15	L'Italien, et al.	
	4	20050281831	A1	2005-12-22	Davis-Smyth, et al.	
	5	20030202972	A1	2003-10-30	Andya, et al.	
	6	20050032699	A1	2005-02-10	Holash, et al.	
	7	20050276808	A1	2005-12-05	Cedarbaum, Jesse M.	

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

Application Number		15/692,893 - GAU: 1647
Filing Date		2017-08-31
First Named Inventor	DIX, Daniel	
Art Unit		
Examiner Name	/Elly-Gerald Stoica/	
Attorney Docket Number		238811-21.89 (4030US11)

1	WO0220060489	WO	A1	2002-08-08	Regeneron Pharmaceuticals, Inc.		
2	WO2005000895	WO	A2	2005-01-06	Regeneron Pharmaceuticals, Inc.		
3	WO2006047325	WO	A1	2006-05-04	Genentech, Inc.		
4	WO2007149334	WO	A2	2007-12-27	Regeneron Pharmaceuticals, Inc.		
5	WO1993000807	WO	A1	1993-01-21	Cryolife, Inc.		
6	WO2000075319	WO	A1	2000-12-14	Regeneron Pharmaceuticals, Inc.		
7	WO2004106378	WO	A2	2004-12-09	Regeneron Pharmaceuticals, Inc.		
8	WO1999013909	WO	A1	1999-03-25	Toagosei Co., Ltd.		
9	WO2005020972	WO	A1	2005-03-10	Eyeteck Pharm, Inc.		
10	WO2005072772	WO	A1	2005-08-11	Suomen Punainen Risti Veripalvelu		
11	WO199962536	WO	A2	1999-12-09	Celtrix Pharmaceuticals, Inc.		

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

Application Number	15/692,893 - GAU: 1647
Filing Date	2017-08-31
First Named Inventor	DIX, Daniel
Art Unit	
Examiner Name	/Elly-Gerald Stoica/
Attorney Docket Number	238811-21.89 (4030US11)

12	WO2004103159	WO	A2	2004-12-02	UNIV Leland Stanford Junior		
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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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	CARPENTER, J.F. (1997) Rational Design of Stable Lyophilized..., Pharm. Res. 14(8): 969-975	
	2	WANG, W. (1999) Instability, stabilization, and formulation of liquid protein..., Int'l J. Pharmaceutics 185(2): 129-188	
	3	WEBB et al. (2002) A new mechanism for decreasing aggregation..., J. Pharm. Sci 93(10): 2609-2623	
	4	DAUGHERTY, et al. (2006) Formulation and delivery issues for monoclonal..., Adv. Drug Delivery Rev. 58:668-706	
	5	FRASER et al. (2004) Single injections of Vascular Trap..., J.Clin. Endocrin. & Metabol. 90(2):1114-1122	
	6	STEWART, M.W. (2012) Clinical and Differential Utility of VEGF Inhibitors..., Clinical Ophthalmology, 2012:6, 1175-1186	
	7	Hanks Solution http://www.lifetechnologies.com/us/en/home/technical-resources/media-formulation.152.html	
	8	MI, et al. (2002) Effects of polyethylene glycol molecular weight and concentration..., PDS J. Pharm. Sci. Technol., 56, 115-123	

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

Application Number	15/692,893 - GAU: 1647
Filing Date	2017-08-31
First Named Inventor	DIX, Daniel
Art Unit	
Examiner Name	/Elly-Gerald Stoica/
Attorney Docket Number	238811-21.89 (4030US11)

9	HOLASH, Jocelyn et al. (2002) VEGF-Trap: A VEGF blocker with potent antitumor effects, Proceedings of the National Academy of Sciences of the United States of America, Vol. 99 No. 17 August 20, 2002, 11393-11398
10	GLADE-BENDER, J et al. VEGF Blocking Therapy in the Treatment of Cancer, Expert Opinion on Biological Therapy, Ashley London GB Vol. 3, No. 2 April 2003, Pages 263-276
11	KIM, Eugene S. et al. Proceedings of the National Academy of Sciences of the United States of America, Vol. 99, No. 17, August 20, 2002
12	KATAYAMA, et al. (2004) Retrospective statistical analysis of lyophilized...J. Pharm. Sci. 93(10): 2609-2623

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

EXAMINER SIGNATURE

Examiner Signature	/Elly-Gerald Stoica/	Date Considered	09/10/2018
--------------------	----------------------	-----------------	------------

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

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

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

Application Number		
Filing Date		2017-08-31
First Named Inventor	DIX, Daniel	
Art Unit		
Examiner Name		
Attorney Docket Number	238811-21.89 (4030US11)	

CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Joseph E. Zahner/	Date (YYYY-MM-DD)	2017-08-31
Name/Print	Joseph E. Zahner	Registration Number	48,224

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

Privacy Act Statement

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

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

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



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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
15/692,893	08/31/2017	1647	2260	REGN-023CON8	20	2

CONFIRMATION NO. 8858

CORRECTED FILING RECEIPT

96387

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



0000000109956295

Date Mailed: 07/29/2019

Receipt is acknowledged of this non-provisional utility 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 FIRST INVENTOR, 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 corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction 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 provided that the request is grantable.

Inventor(s)

Daniel B. DIX, LaGrangeville, NY;
Kelly FRYE, Mendham, NJ;
Susan KAUTZ, Albany, NY;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY;

Power of Attorney: The patent practitioners associated with Customer Number 96387

Domestic Priority data as claimed by applicant

This application is a CON of 15/342,989 11/03/2016 ABN
which is a CON of 15/064,343 03/08/2016 PAT 9511140
which is a CON of 14/550,385 11/21/2014 PAT 9416167
which is a CON of 13/909,745 06/04/2013 PAT 8921316
which is a CON of 13/428,510 03/23/2012 PAT 8710004
which is a CON of 13/343,214 01/04/2012 PAT 8404638
which is a DIV of 12/835,065 07/13/2010 PAT 8110546
which is a CON of 11/387,256 03/22/2006 ABN
which claims benefit of 60/665,125 03/25/2005

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: 09/11/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/692,893**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS

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>.

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LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/692,893	09/10/2019	10406226	REGN-023CON8	8858

96387 7590 08/21/2019
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):

Daniel B. DIX, LaGrangeville, NY;
REGENERON PHARMACEUTICALS, INC., Tarrytown, NY;
Kelly FRYE, Mendham, NJ;
Susan KAUTZ, Albany, 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.

REEXAMINATION OR SUPPLEMENTAL EXAMINATION – PATENT OWNER POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS FOR REEXAMINATION OR SUPPLEMENTAL EXAMINATION AND PATENT	Control Number(s)	90/014,449
	Filing Date(s)	2020-02-11
	First Named Inventor	Daniel B. DIX
	Title	METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROT
	Patent Number	10,406,226
	Examiner Name	Padmashri PONNALURI
	Attorney Docket No(s)	1050138.00033

I. Power of Attorney. This form may be used to change the Power of Attorney in a reexamination or supplemental examination proceeding (or multiple proceedings where merged). This form may also be used to change the Power of Attorney in the patent file; in such a case, a copy of this form will be placed in both the patent file and the reexamination or supplemental examination proceeding.

A. Revocation of Previous Power of Attorney. I hereby revoke all previous patent owner powers of attorney, if any, given:

☒ in the above-identified reexamination or supplemental examination proceeding control number(s) (more than one may be changed only if the proceedings are merged).

☒ in the file of the above-identified patent.

(check BOTH boxes if change in BOTH the patent file and the reexamination or supplemental examination proceeding is requested).

B. Designation of Power of Attorney.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) to prosecute the proceeding(s)/patent identified above and selected in section I(A), and to transact all business in the United States Patent and Trademark Office connected therewith:

170744

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the proceeding(s) identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Authorization for the Power of Attorney is provided by the signature on page 2 of this form.

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 1.14. This collection is estimated to take 15 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.

II. Change of Correspondence Address

Please recognize or change the correspondence address for the above-identified reexamination or supplemental examination proceeding control number(s) (more than one may be changed **only** if they are merged proceedings) **and for the file of the above-identified patent** to be:

☒ The address associated with the above-identified Customer Number.

OR

☐ The address associated with the Customer Number identified in the box at right:

--

OR

☐ Firm or Individual Name				
Address				
City		State		Zip
Country				
Telephone		Email		

NOTE: THE CORRESPONDENCE ADDRESS FOR THE REEXAMINATION OR SUPPLEMENTAL EXAMINATION PROCEEDING CONTROL NUMBER(S) MUST BE THE SAME AS THAT FOR THE PATENT. SEE 37 CFR 1.33.

III. Authorization for Power of Attorney and (if selected) Change of Correspondence Address

I am the:

☐ Inventor, having ownership of the patent being reexamined.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) submitted herewith or filed on _____.

Signature of Inventor or Patent Owner	/ Frank R. Cottingham /	Date	08-May-2020
Name	Frank R. Cottingham, Ph.D., J.D.	Telephone	914.847.1116
Title and Company	Exec. Director & Asst. Gen. Counsel, Patents; Regeneron Pharmaceuticals, Inc.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☒ A total of 2 forms are submitted. If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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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.

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.: US 90/014,449 Filed/Issue Date: 2020-02-11Titled: Method of manufacturing VEGF antagonist fusion proteinsRegeneron 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 043812, Frame 0974, 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.
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- The document was recorded in the United States Patent and Trademark Office at
- Reel _____, Frame _____, or for which a copy thereof is attached.

[Page 1 of 2]

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.

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.

/ Frank R. Cottingham /

Signature

Frank R. Cottingham, Ph.D., J.D.

Printed or Typed Name

08-May-2020

Date

Exec. Director & Asst. Gen. Counsel, Patents

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.

Electronic Acknowledgement Receipt

EFS ID:	39408012
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	96387
Filer:	David R. Marsh/Angela Cox
Filer Authorized By:	David R. Marsh
Attorney Docket Number:	REGN-023CON8
Receipt Date:	11-MAY-2020
Filing Date:	31-AUG-2017
Time Stamp:	17:35:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	POA.pdf	501103	no	3
			437eac9c29962128b8e63e92bdb3609277c f85b7		

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	373c.pdf	181902	no	3
			b8731d3a0f951686752357c1dfc631ec3d45ed95		
Warnings:					
Information:					
Total Files Size (in bytes):				683005	
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8

CONFIRMATION NO. 8858

POWER OF ATTORNEY NOTICE



OC000000116939298

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

Date Mailed: 05/13/2020

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/11/2020.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

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.

/rbell/



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/692,893	08/31/2017	Daniel B. DIX	REGN-023CON8

CONFIRMATION NO. 8858

POA ACCEPTANCE LETTER

170744
A&P - Regeneron
601 Massachusetts Ave., NW
Washington, DC 20001



Date Mailed: 05/13/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/11/2020.

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.

/rbell/

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 10,406,226
DATED : September 10, 2019
INVENTOR(S) : Daniel B. DIX *et al.*

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

Col. 20, line 45, change "1" to --3--

MAILING ADDRESS OF SENDER: Arnold & Porter Kaye Scholer LLP
Attn: IP Docketing
601 Massachusetts Avenue, N.W.
Washington, DC 20001

PATENT NO. 10,406,226

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

Electronic Acknowledgement Receipt

EFS ID:	41466512
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	170744
Filer:	Xianfeng Xu
Filer Authorized By:	
Attorney Docket Number:	REGN-023CON8
Receipt Date:	22-DEC-2020
Filing Date:	31-AUG-2017
Time Stamp:	18:08:36
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	COC1.pdf	114526	no	1
			67a5ab8000084bdb13db06b2d7fd91d322900c5c		

Warnings:

Information:					
2		Request1.pdf	336878	yes	8
			d8af58b82bc92d5079357c1369599a0f137879c3		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Request for Certificate of Correction		1	2	
	Miscellaneous Incoming Letter		3	8	
Warnings:					
Information:					
Total Files Size (in bytes):			451404		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

REGENERON PHARMACEUTICALS, INC.

Appln. No.:	15/692,893	Art Unit:	1647
Filed:	August 31, 2017	Examiner:	Elly Gerald Stoica
Patent No.:	10,406,226	Conf. No.	8858
Issued:	September 10, 2019	Atty. Docket:	1050138.00033
For:	METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS		

**Request for Certificate of Correction of Office Mistake
Under 37 C.F.R. §1.322**

Mail Stop Certificate of Correction
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.322, Patentee hereby requests that a Certificate of Correction for an Office mistake be issued in US Patent No. 10,406,226 (“226 Patent”), to correct the dependency of claim 4 as follows¹:

4. The method of claim ~~[[1]]~~3, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at one or more asparagine residues.

The Office introduced a printing error by making issued claim 4 depend on issued claim 1. The issued claims 1 to 4 correspond to claims 31, 33, 38, and 39, respectively, as they were

¹ Patentee notes that claim 4 contains a further typographical error in that “posttranslationally” is misspelled as “post transitionally.” However, since this error was introduced by the Patentee, and is not an Office mistake, Patentee is seeking correction of this error via a concurrent Request for Certificate of Correction of Patentee Mistake Under 37 C.F.R. § 1.323.

submitted in the Amendment under 37 CFR § 1.116 dated May 29, 2019 (“May 29th Amendment”, a courtesy copy attached herewith). Claims 31, 33, 38, and 39 were subsequently allowed through the Notice of Allowance and Fee(s) Due dated June 13, 2019. Claim 39 depended on claim 38 in the May 29th Amendment. Claim 38 was renumbered and issued as claim 3. As such, issued claim 4 should depend on issued claim 3, not issued claim 1 as mistakenly printed in the 226 Patent. Patentee respectfully requests correction of this Office mistake.

Patentee does not believe any fees are due in conjunction with this filing. Further, if any additional fees are required in the present, patented application, including any fees for extensions of time, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter Kaye Scholer LLP Deposit Account No. 50-2387 referencing matter number 1050138.00033.

The Commissioner is invited to contact the patentee’s undersigned representative at (202) 942-6195 to address any unresolved issues remaining in this patent.

Respectfully submitted,

/Xianfeng Xu/

David R. Marsh, Ph.D. (Reg. Atty. No. 41,408)
Xianfeng Xu, Ph.D. (Reg. Atty. No. 68,376)

Date: December 22, 2020

Arnold & Porter Kaye Scholer LLP
Attn: IP Docketing
601 Massachusetts Ave, NW
Washington, D.C. 20001
(202) 942-5000 telephone
(202) 942-5999 facsimile

AMENDMENT UNDER 37 C.F.R. §1.116 Address to: Mail Stop AMENDMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-023CON8
	Confirmation No.	8858
	First Named Inventor	Daniel Dix
	Application Number	15/692,893
	Filing Date	August 31, 2017
	Group Art Unit	1647
	Examiner Name	Elly Gerald Stoica
Title: “ <i>VEGF Antagonist Formulations</i> ”		

Sir:

This amendment is responsive to the Final Office Action dated March 12, 2019, for which a three-month period for response was given making this response timely filed on or before June 12, 2019.

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

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

1.-30. (Cancelled)

31. (Currently Amended) A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a Chinese hamster ovary (CHO) cell comprising a polynucleotide encoding the VEGF antagonist fusion protein which comprises amino acids 27-457 of SEQ ID NO: 2 wherein said fusion protein binds vascular endothelial growth factor (VEGF), ~~wherein said mammalian cell comprises polynucleotides 147-1439 of SEQ ID NO: 1 that encodes said VEGF antagonist fusion protein;~~ and
- b. purifying said VEGF antagonist fusion protein;
wherein at least 90% of the weight of the purified fusion protein is not present as an aggregate.

32. (Cancelled)

33. (Previously Presented) The method of claim 31, wherein said fusion protein is purified until substantially free of protein contaminants.

34-37. (Cancelled)

38. (Currently Amended) A method of manufacturing a VEGF antagonist fusion protein, said method comprising:

- a. expressing said VEGF antagonist fusion protein in a ~~mammalian~~ Chinese hamster ovary (CHO) cell comprising a polynucleotide encoding the VEGF antagonist fusion protein which comprises amino acids 27-457 of SEQ ID NO: 4 wherein said fusion protein binds vascular endothelial growth factor (VEGF), ~~wherein said mammalian cell comprises polynucleotides 79-1371 of SEQ ID NO: 3 that encodes said VEGF antagonist fusion protein; and~~

b. purifying said VEGF antagonist fusion protein;
wherein at least 90% of the weight of the purified fusion protein is not present as an aggregate.

39. **(Previously Presented)** The method of claim 38, wherein said VEGF antagonist fusion protein is post transitionally glycosylated at one or more asparagine residues.

40. – 42. **(Cancelled)**

REMARKS

Formal Matters

Claims 31, 33, 38 and 39 are now pending in this application.

Claims 1-30, 32, 34-37 and 40-42 have been cancelled without prejudice.

Claims 31 and 38 are amended.

No new matter has been added.

Allowed Claims

The applicants appreciate the Examiner's allowance of claims 21-23, 25-27, 29-35, 37-40 and 42.

Rejection under 35 U.S.C. §1.112(b)

Claim 28 was rejected under 35 U.S.C. §112 (b) as being indefinite for failing to particularly point out and distinctly claim the invention.

Claim 28 has been cancelled from the application rendering the rejection moot.

Rejection under 35 U.S.C. §1.112(a)

Claims 24, 28, 36 and 41 were rejected under 35 U.S.C. §112 (1) for failing to comply with the enablement requirement.

Claims 24, 28, 36 and 41 have been cancelled from the application rendering the rejection moot.

Claim Amendments

Applicants recognize that claims cannot be amended as a matter of right after a Final Office Action. However, the present amendment would not require more than a cursory review by Examiner and, thus, should be entered.

Claim 31 is amended to incorporate the elements of previously pending, allowed, now cancelled claim 21, 34 and 35; and claim 15 as filed. All of the claims 21, 31, 34 and 35 were previously indicated as allowable.

Claim 38 has been amended to incorporate the elements of previously pending, allowed, now cancelled claims 27 and 40; and claim 15 as filed. Claims 27, 38 and 40 were previously indicated as allowable.

In that the claim amendments do not add new matter, were previously examined in dependent

claims, and will not require further searching or consideration by the Examiner, entry of these amendments and allowance of the claims is respectfully requested.

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-023CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 29, 2019

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

REGENERON PHARMACEUTICALS, INC.

Appln. No.:	15/692,893	Art Unit:	1647
Filed:	August 31, 2017	Examiner:	Elly Gerald Stoica
Patent No.:	10,406,226	Conf. No.	8858
Issued:	September 10, 2019	Atty. Docket:	REGN-023CON8
For:	METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS		

**Request for Certificate of Correction of Patentee Mistake
Under 37 C.F.R. § 1.323**

Mail Stop Certificate of Correction
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.323, Patentee hereby requests that a Certificate of Correction of Patentee Mistake be issued in US Patent No. 10,406,226 (“226 Patent”), to correct patentee’s typographical error in claim 4 as follows¹:

4. The method of claim 3, wherein said VEGF antagonist fusion protein is ~~post~~
~~transitionally~~ posttranslationally glycosylated at one or more asparagine residues.

Patentee further submits a fee payment of \$160.00 as set forth in 37 C.F.R. § 1.20(a).

¹ Patentee notes that claim 4 also contains an Office printing error. The Office mistakenly printed the issued claim 4 as dependent on issued claim 1. In a concurrently filed Request for Certificate of Correction of Office Mistake Under 37 C.F.R. § 1.322 (“1.322 CoC Request”), Applicant requests correction of this Office mistake. Claim 4 is shown here to reflect the proper dependency as corrected by the 1.322 CoC Request.

Patentee misspelled “posttranslationally glycosylated” as “post transitionally glycosylated” in claim 4. This error originated from the Amendment under 37 CFR § 1.116 dated May 29, 2019 (“May 29th Amendment”). *See* Claim 39.

This error is “a mistake of a clerical or typographical nature,” and “of minor character.” 35 U.S.C. § 255. Both the 226 Patent and the specification as filed support this correction. The 226 Patent explicitly provides that “[i]n specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified *posttranslationally*. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308.” Column 5, lines 37-42 (emphasis added); *see also*, specification as filed, at paragraph [00028]. In contrast, the phrase “post transitionally” does not appear anywhere in the 226 Patent specification and is meaningless in the context of claim 4. As such, this error is “a mistake of a clerical or typographical nature, [and] of minor character,” which qualifies for a Certificate of Correction under 35 U.S.C. § 255.

Patentee does not believe any additional fees, other than the fee specified above, are due in conjunction with this filing. Further, if any additional fees are required in the present, patented application, including any fees for extensions of time, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter Kaye Scholer LLP Deposit Account No. 50-2387 referencing matter number 1050138.00033.

The Commissioner is invited to contact the patentee's undersigned representative at (202) 942-6195 to address any unresolved issues remaining in this patent.

Respectfully submitted,

/Xianfeng Xu/

David R. Marsh, Ph.D. (Reg. Atty. No. 41,408)
Xianfeng Xu, Ph.D. (Reg. Atty. No. 68,376)

Date: December 22, 2020

Arnold & Porter Kaye Scholer LLP
Attn: IP Docketing
601 Massachusetts Ave, NW
Washington, D.C. 20001
(202) 942-5000 telephone
(202) 942-5999 facsimile

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 10,406,226
DATED : September 10, 2019
INVENTOR(S) : Daniel B. DIX *et al.*

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

Col. 20, line 46, change "post transitionally" to --posttranslationally--

MAILING ADDRESS OF SENDER: Arnold & Porter Kaye Scholer LLP
Attn: IP Docketing
601 Massachusetts Avenue, N.W.
Washington, DC 20001

PATENT NO. 10,406,226

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

Electronic Patent Application Fee Transmittal				
Application Number:		15692893		
Filing Date:		31-Aug-2017		
Title of Invention:		METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS		
First Named Inventor/Applicant Name:		Daniel B. DIX		
Filer:		Xianfeng Xu/Angela Cox		
Attorney Docket Number:		REGN-023CON8		
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:				
CERTIFICATE OF CORRECTION	1811	1	160	160

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	41466922
Application Number:	15692893
International Application Number:	
Confirmation Number:	8858
Title of Invention:	METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS
First Named Inventor/Applicant Name:	Daniel B. DIX
Customer Number:	170744
Filer:	Xianfeng Xu
Filer Authorized By:	
Attorney Docket Number:	REGN-023CON8
Receipt Date:	22-DEC-2020
Filing Date:	31-AUG-2017
Time Stamp:	18:11:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment was successfully received in RAM	\$ 160
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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 37 CFR 1.17 (Patent application and reexamination processing fees)
 37 CFR 1.16 (National application filing, search, and examination fees)

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	Request2.pdf	167328	no	3
			27d8e2b25e32ddd7f8746b63c6951283892c4ed4		
Warnings:					
Information:					
2	Request for Certificate of Correction	COC2.pdf	146578	no	1
			73a729a800db5e6e8e641b019471621bb811bd53		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30447	no	2
			df07e3ce19ff7562e728d1e875d93976229c4bd8		
Warnings:					
Information:					
Total Files Size (in bytes):			344353		

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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.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,406,226 B2
APPLICATION NO. : 15/692893
DATED : September 10, 2019
INVENTOR(S) : Daniel B. Dix et al.

Page 1 of 1

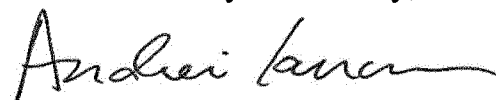
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 20, Line 45, change "1" to --3--

Column 20, Line 46, change "post transitionally" to --posttranslationally--

Signed and Sealed this
Nineteenth Day of January, 2021



Andrei Iancu
Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been
filed in the U.S. District Court Northern District of West Virginia on the following

☐ Trademarks or ☒ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO. 1:22-cv-61	DATE FILED 8/2/2022	U.S. DISTRICT COURT Northern District of West Virginia
PLAINTIFF REGENERON PHARMACEUTICALS, INC.		DEFENDANT MYLAN PHARMACEUTICALS, INC.
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 See attached		
2		
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading		
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK	
1			
2			
3			
4			
5			

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK CHERYL DEAN RILEY	(BY) DEPUTY CLERK /s/ D. Kinsey	DATE 8/3/2022
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Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
7,070,959	July 4, 2006	Regeneron Pharmaceuticals, Inc.
9,222,106	December 29, 2015	Regeneron Pharmaceuticals, Inc.
9,254,338	February 9, 2016	Regeneron Pharmaceuticals, Inc.
9,669,069	June 6, 2017	Regeneron Pharmaceuticals, Inc.
9,816,110	November 14, 2017	Regeneron Pharmaceuticals, Inc.
10,130,681	November 20, 2018	Regeneron Pharmaceuticals, Inc.
10,406,226	September 10, 2019	Regeneron Pharmaceuticals, Inc.
10,415,055	September 17, 2019	Regeneron Pharmaceuticals, Inc.
10,464,992	November 5, 2019	Regeneron Pharmaceuticals, Inc.
10,669,594	June 2, 2020	Regeneron Pharmaceuticals, Inc.
10,857,205	December 8, 2020	Regeneron Pharmaceuticals, Inc.
10,888,601	January 12, 2021	Regeneron Pharmaceuticals, Inc.
10,927,342	February 23, 2021	Regeneron Pharmaceuticals, Inc.
10,973,879	April 13, 2021	Regeneron Pharmaceuticals, Inc.
11,053,280	July 6, 2021	Regeneron Pharmaceuticals, Inc.
11,066,458	July 20, 2021	Regeneron Pharmaceuticals, Inc.
11,084,865	August 10, 2021	Regeneron Pharmaceuticals, Inc.
11,104,715	August 31, 2021	Regeneron Pharmaceuticals, Inc.
11,174,283	November 16, 2021	Regeneron Pharmaceuticals, Inc.
11,186,625	November 30, 2021	Regeneron Pharmaceuticals, Inc.
11,253,572	February 22, 2022	Regeneron Pharmaceuticals, Inc.
11,299,532	April 12, 2022	Regeneron Pharmaceuticals, Inc.
11,306,135	April 19, 2022	Regeneron Pharmaceuticals, Inc.
11,332,771	May 17, 2022	Regeneron Pharmaceuticals, Inc.