



APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/149,468	06/03/2014	8741963	PAT050279-US-CNT	1536

1095 7590 05/14/2014
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

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 21 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):

Peter C. Hiestand, Allschwil, SWITZERLAND;
Christian Schnell, Hesingue, FRANCE;

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Receipt date: 09/29/2011

13149468 PTO/S&B (07/09)

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Substitute for form 1449/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>		Application Number	13/149468
		Filing Date	May 31, 2011
		First Named Inventor	Hiestand, Peter C. et al.
		Art unit	
		Examiner Name	Spivack
		Attorney Docket Number	PAT050279-US-CNT
Sheet	1	of	2

U.S. PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Document Number		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code ² (if known)			
/P.S./		US-2006/0046979		03-02-2006	Carolyn Ann Foster et al.	
		US-				
		US-				
		US-				
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		US-				

Change(s) applied

to document,

FOREIGN PATENT DOCUMENTS							
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	†
		Country Code ³	Number ⁴ Kind Code ⁵ (if known)				
/A.E.M./		WO 2004/028521		04-08-2005	Novartis AG 2004		<input type="checkbox"/>
3/27/2011	/P.S./	WO 2003/099192		12-04-2003	Novartis AG		<input type="checkbox"/>
Change(s) applied	/P.S./	WO 2003/097028		11-27-2003	Novartis AG		<input type="checkbox"/>
to document,	/P.S./	WO 2004/050073		06-17-2004	Doosan Corporation		<input type="checkbox"/>
/A.E.M./		WO 2005/123104		12/2005			<input type="checkbox"/>
3/26/2011	/P.S./						<input type="checkbox"/>
Change(s) applied							<input type="checkbox"/>

3/27/2011

Change(s) applied

to document,

/A.E.M./

3/26/2011

Change(s) applied

to document,

/S.X.S./

Examiner Signature	/Phyllis Spivack/	Date Considered	03/24/2012
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3/17/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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

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

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1095 7590 01/21/2014
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ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

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.

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/149,468	05/31/2011	Peter C. Hiestand	PAT050279-US-CNT	1536

TITLE OF INVENTION: S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	04/21/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEDDINGTON, KEVIN E	1629	514-667000

<p>1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).</p> <p><input type="checkbox"/> Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.</p> <p><input type="checkbox"/> "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.</p>	<p>2. For printing on the patent front page, list</p> <p>(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,</p> <p>(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.</p> <p>1 <u>Andrew Holmes</u></p> <p>2 _____</p> <p>3 _____</p>
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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

(A) NAME OF ASSIGNEE **Novartis AG**

(B) RESIDENCE: (CITY and STATE OR COUNTRY) **Basel, CH**

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

<p>4a. The following fee(s) are submitted:</p> <p><input checked="" type="checkbox"/> Issue Fee</p> <p><input checked="" type="checkbox"/> Publication Fee (No small entity discount permitted)</p> <p><input type="checkbox"/> Advance Order - # of Copies _____</p>	<p>4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)</p> <p><input type="checkbox"/> A check is enclosed.</p> <p><input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.</p> <p><input checked="" type="checkbox"/> The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number <u>190134</u> (enclose an extra copy of this form).</p>
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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 / Andrew Holmes / Date April 21, 2014

Typed or printed name Andrew Holmes Registration No. 51813

Electronic Patent Application Fee Transmittal

Application Number:	13149468
Filing Date:	31-May-2011
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Filer:	Andrew K. Holmes/Angel Matos
Attorney Docket Number:	PAT050279-US-CNT

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960

Extension-of-Time:

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Total in USD (\$)				960

Electronic Acknowledgement Receipt

EFS ID:	18814595
Application Number:	13149468
International Application Number:	
Confirmation Number:	1536
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	1095
Filer:	Andrew K. Holmes/Angel Matos
Filer Authorized By:	Andrew K. Holmes
Attorney Docket Number:	PAT050279-US-CNT
Receipt Date:	21-APR-2014
Filing Date:	31-MAY-2011
Time Stamp:	14:55:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$960
RAM confirmation Number	1125
Deposit Account	190134
Authorized User	

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

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

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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)	SIGNED_PAT050279-US-CNT-Issue-Fee-Trans.pdf	90796 458d49fc74828ddb254d364de5380e850bf772	no	1

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30328 bdb6837c1ca1bd1faab2924fbf12be490e3a9130	no	2
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Warnings:

Information:

Total Files Size (in bytes): 121124

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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.

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13149468-PTO/Rele (of 8) 10/29

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				Art unit	
				Examiner Name	Spivack
Attorney Docket Number	PAT050279-US-CNT				
Sheet	1	of	2		

U.S. PATENT DOCUMENTS						
Examiner Initials*	Cite No.†	Document Number		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code‡ of Invention	Kind Code‡ of Document			
/P.S./		US-2006/0046979		03-02-2006	Carolyn Ann Foster et al.	
		US-				
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FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No.†	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	7
		Country Code‡	Number‡	Kind Code‡ of Invention				
/P.S./		WO	2004/028521		04-08-2008	Novartis AG		<input type="checkbox"/>
/P.S./		WO	2003/099192		12-04-2003	Novartis AG		<input type="checkbox"/>
/P.S./		WO	2003/097028		11-27-2003	Novartis AG		<input type="checkbox"/>
/P.S./		WO	2004/080073		06-17-2004	Doosan Corporation		<input type="checkbox"/>
/P.S./		WO	2005/123104					<input type="checkbox"/>
								<input type="checkbox"/>

Examiner Signature	/Phyllis Spivack/	Date Considered	03/24/2012
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Application Number	13/149468
				Filing Date	May 31, 2011
				First Named Inventor	Hiestand, Peter C. et al.
				Art unit	
				Examiner Name	
Sheet	2	of	2	Attorney Docket Number	PAT050279-US-CNT

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.	†
		Mecchikewski M.D. Pharmaceuticals, Moscow, Newsja Weins, 2001, in 2 volumes, vol.1 p.11	<input type="checkbox"/>
/P.S./		LaMontagne K „Antagonism of Sphingosine-1-Phosphate Receptors by FTY720 Inhibits Angiogenesis..“ Cancer Research, Jan 2006, 66, 221-231.	<input type="checkbox"/>
/P.S./		Hla. T. „Physiological and pathological actions of sphingosine 1-phosphate“ Seminars in Cell & Developmental Biology, Oct 2004, 15(5), 513-520.	<input type="checkbox"/>
/P.S./		Kappos L et al. „FTY720 in relapsing MS...“ 23.06.2005 online (found 02.06.2011) URL: http://www.ms-in-europe.com/printversion/index.php?an=105&cnr=4/	<input type="checkbox"/>
/P.S./		Ho J.W et al. „Effects of a novel immunomodulating agent..“ Molecular cancer therapeutics, 2005 Set, 4(9), 1430-1439.	<input type="checkbox"/>
/P.S./		Virely D.J. „Developing therapeutics for the treatment of multiple sclerosis.“ Journal of American Society for Experimental Neuro Therapeutics. Oct 2005, 2, 638-649. http://pubget.com/paper/16489371	<input type="checkbox"/>
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Examiner Signature	/Phyllis Spivack/	Date Considered	03/24/2012
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13149468 PTO/S&B/06a (7/09) 09

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/P.S./		US-2006/0046979		03-02-2006	Carolyn Ann Foster et al.	
		US-				
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Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³	Number ⁴ Kind Code ⁵ if known				
/P.S./		WO	2004/028521	04-08-2008	Novartis AG		<input type="checkbox"/>
/P.S./		WO	2003/099192	12-04-2003	Novartis AG		<input type="checkbox"/>
/P.S./		WO	2003/087028	11-27-203	Novartis AG		<input type="checkbox"/>
/P.S./		WO	2004/050073	06-17-2004	Doosan Corporation		<input type="checkbox"/>
/P.S./		WO	2006/123104				<input type="checkbox"/>
							<input type="checkbox"/>

Examiner Signature	/Phyllis Spivack/	Date Considered	03/24/2012
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13149468 PTD/SEP08 (7/09)9

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

Substitute for form 1449/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>		Application Number	13/149468
		Filing Date	May 31, 2011
		First Named Inventor	Hiestand, Peter C. et al.
		Art unit	
		Examiner Name	
		Attorney Docket Number	PAT050279-US-CNT
Sheet	2	of	2

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cita No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Mecchekowalij M.D. Pharmaceuticals, Moscow, Nowaja Wolna, 2001, in 2 volumes, vol. 1 p. 11	<input type="checkbox"/>
/P.S./		LaMontagne K. „Antagonism of Sphingosine-1-Phosphate Receptors by FTY720 Inhibits Angiogenesis..“ Cancer Research, Jan 2006, 66, 221-231.	<input type="checkbox"/>
/P.S./		Hla. T. „Physiological and pathological actions of sphingosine 1-phosphate“ Seminars in Cell & Developmental Biology, Oct 2004, 15(5), 513-520.	<input type="checkbox"/>
/P.S./		Kappos L et al. „FTY720 in relapsing MS....“ 23.06.2005 online (found 02.06.2011) URL: http://www.ms-in-europe.com/printversion/index.php?anr=105&cnr=4/	<input type="checkbox"/>
/P.S./		Ho J.W et al. „ Effects of a novel immunomodulating agent..“ Molecular cancer therapeutics, 2005 Set, 4(9), 1430-1438. Found:	<input type="checkbox"/>
/P.S./		Virely D.J. „Developing therapeutics for the treatment of multiple sclerosis.“ Journal of American Society for Experimental Neuro Therapeutics. Oct 2005, 2, 638-649. http://pubget.com/paper/16489371	<input type="checkbox"/>
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Examiner Signature	/Phyllis Spivack/	Date Considered	03/24/2012
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.
¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.
 This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
 If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.



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

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
13/149,468 05/31/2011 Peter C. Hiestand PAT050279-US-CNT 1536

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER
WEDDINGTON, KEVIN E

ART UNIT PAPER NUMBER

1629

DATE MAILED: 03/24/2014

PRIORITY ACKNOWLEDGMENT

- 1. Receipt is acknowledged of priority papers submitted under 35 U.S.C. 119. The papers have been placed of record in the file.
2. Applicant's claim for priority, based on papers filed in parent Application Number 12/303,765 submitted under 35 U.S.C. 119, is acknowledged.
3. The priority papers, submitted, after payment of the issue fee are
4. For utility and plant applications filed on or after November 29, 2000, the priority claim is not entered because the claim was not presented within the time limit required by 37 CFR 1.55(a)(1).

Handwritten signature
571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management



NOTICE OF ALLOWANCE AND FEE(S) DUE

1095 7590 01/21/2014
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

Table with 2 columns: EXAMINER (WEDDINGTON, KEVIN E), ART UNIT (1629), PAPER NUMBER (1536)

DATE MAILED: 01/21/2014

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.

13/149,468 05/31/2011 Peter C. Hiestand PAT050279-US-CNT 1536

TITLE OF INVENTION: S1P RECEPTOR MODULATORS FOR TREATING MULTIPLE SCLEROSIS

Table with 7 columns: APPLN. TYPE, ENTITY STATUS, ISSUE FEE DUE, PUBLICATION FEE DUE, PREV. PAID ISSUE FEE, TOTAL FEE(S) DUE, DATE DUE

nonprovisional UNDISCOUNTED \$960 \$0 \$0 \$960 04/21/2014

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

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

PART B - FEE(S) TRANSMITTAL

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

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

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

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.

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EAST HANOVER, NJ 07936-1080

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/149,468	05/31/2011	Peter C. Hiestand	PAT050279-US-CNT	1536

TITLE OF INVENTION: S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	04/21/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEDDINGTON, KEVIN E	1629	514-667000

<p>1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).</p> <p><input type="checkbox"/> Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.</p> <p><input type="checkbox"/> "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.</p>	<p>2. For printing on the patent front page, list</p> <p>(1) The names of up to 3 registered patent attorneys or agents OR, alternatively, _____ 1</p> <p>(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</p> <p>_____ 3</p>
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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

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

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

<p>4a. The following fee(s) are submitted:</p> <p><input type="checkbox"/> Issue Fee</p> <p><input type="checkbox"/> Publication Fee (No small entity discount permitted)</p> <p><input type="checkbox"/> Advance Order - # of Copies _____</p>	<p>4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)</p> <p><input type="checkbox"/> A check is enclosed.</p> <p><input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.</p> <p><input type="checkbox"/> The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).</p>
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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

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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
13/149,468 05/31/2011 Peter C. Hiestand PAT050279-US-CNT 1536

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EAST HANOVER, NJ 07936-1080

EXAMINER

WEDDINGTON, KEVIN E

ART UNIT PAPER NUMBER

1629

DATE MAILED: 01/21/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 78 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 78 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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

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

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

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 13/149,468	Applicant(s) HIESTAND ET AL.	
	Examiner KEVIN E. WEDDINGTON	Art Unit 1629	AIA (First Inventor to File) Status No

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

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 December 30, 2013.
 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 12-14, 16, 17, 21-23 and 25; renumbered respectively 1, 7, 2, 3, 9, 8 and 4-6. 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. <input type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 2. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 6. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. <input type="checkbox"/> Other _____. |
| 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date <u>12/30/2013</u> . | |

/KEVIN E WEDDINGTON/
Primary Examiner, Art Unit 1629

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

EXAMINER'S AMENDMENT

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

Authorization for this examiner's amendment was given in a telephone interview with Mr. Andrew Holmes on December 30, 2013.

The application has been amended as follows:

In the Claims:

Cancel claim 24.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KEVIN E. WEDDINGTON whose telephone number is (571)272-0587. The examiner can normally be reached on 12:30 pm -9:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery S. Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1629

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.

KEVIN E WEDDINGTON
Primary Examiner
Art Unit 1629

/KEVIN E WEDDINGTON/
Primary Examiner, Art Unit 1629

Applicant-Initiated Interview Summary	Application No. 13/149,468	Applicant(s) HIESTAND ET AL.	
	Examiner KEVIN E. WEDDINGTON	Art Unit 1629	

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

(1) KEVIN E. WEDDINGTON. (3)_____.

(2) Andrew Holmes. (4)_____.

Date of Interview: 30 December 2013.

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: Claim 24.

Identification of prior art discussed: NONE.

Substance of Interview

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

The attorney of record, Mr. Holmes, authorized the cancellation of claim 24.

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

/KEVIN E WEDDINGTON/
Primary Examiner, Art Unit 1629

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 examiner's 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 applicant's 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 applicant's 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 examiner's 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 examiner's initials.

Index of Claims 	Application/Control No. 13149468	Applicant(s)/Patent Under Reexamination HIESTAND ET AL.
	Examiner KEVIN E WEDDINGTON	Art Unit 1629

✓	Rejected
=	Allowed


-	Cancelled
÷	Restricted

N	Non-Elected
I	Interference

A	Appeal
O	Objected

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

CLAIM		DATE							
Final	Original	09/24/2013	12/30/2013						
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4	22	=	=						
5	23	=	=						
	24	✓	-						
6	25	=	=						

Search Notes 	Application/Control No. 13149468	Applicant(s)/Patent Under Reexamination HIESTAND ET AL.
	Examiner KEVIN E WEDDINGTON	Art Unit 1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	667	9/24/2013	KEW
514	903	9/24/2013	KEW

SEARCH NOTES		
Search Notes	Date	Examiner
CAS-ONLINE search with REGISTRY and USPATALL	9/24/2013	KEW
EAST and PALM for Inventors' Names for Related Applications for ODP	9/24/2013	KEW
Updated CAS-ONLINE search with REGISTRY and USPATALL	12/30/2013	KEW
Updated EAST and PALM for Inventors' Names for Related Applications for ODP	12/30/2013	KEW

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	667	12/30/2013	KEW
514	903	12/30/2013	KEW


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BIB DATA SHEET
CONFIRMATION NO. 1536

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
13/149,468	05/31/2011	514	1629	PAT050279-US-CNT		
APPLICANTS INVENTORS Peter C. Hiestand, Allschwil, SWITZERLAND; Christian Schnell, Hesingue, FRANCE; ** CONTINUING DATA ***** This application is a CON of 12/303,765 12/08/2008 ABN which is a 371 of PCT/EP2007/005597 06/25/2007 ** FOREIGN APPLICATIONS ***** UNITED KINGDOM 0612721.1 06/27/2006 ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 06/15/2011						
Foreign Priority claimed	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		SWITZERLAND	0	10	3
Verified and	/KEVIN E WEDDINGTON/ Examiner's Signature	Initials				
ADDRESS NOVARTIS PHARMACEUTICAL CORPORATION INTELLECTUAL PROPERTY DEPARTMENT ONE HEALTH PLAZA 101/2 EAST HANOVER, NJ 07936-1080 UNITED STATES						
TITLE S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS						
FILING FEE RECEIVED 1480	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			<input type="checkbox"/> All Fees		
				<input type="checkbox"/> 1.16 Fees (Filing)		
				<input type="checkbox"/> 1.17 Fees (Processing Ext. of time)		
				<input type="checkbox"/> 1.18 Fees (Issue)		
				<input type="checkbox"/> Other _____		
			<input type="checkbox"/> Credit			

Issue Classification 	Application/Control No. 13149468	Applicant(s)/Patent Under Reexamination HIESTAND ET AL.
	Examiner KEVIN E WEDDINGTON	Art Unit 1629

<input type="checkbox"/> Claims renumbered in the same order as presented by applicant		<input type="checkbox"/> CPA		<input type="checkbox"/> T.D.		<input type="checkbox"/> R.1.47									
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
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	2		18												
	3		19												
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	11														
1	12														
7	13														
2	14														
	15														
3	16														

NONE		Total Claims Allowed:	
		9	
(Assistant Examiner)	(Date)	O.G. Print Claim(s)	O.G. Print Figure
/KEVIN E WEDDINGTON/ Primary Examiner.Art Unit 1629	12/30/2013	1	NONE
(Primary Examiner)	(Date)		



PRIORITY DOCUMENT EXCHANGE

FAILURE STATUS REPORT

An attempt by the Office to electronically retrieve, under the Priority Document Exchange programs (PDX and DAS), 0612721.1 to which priority is claimed has FAILED on 01/13/2014.

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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
13/149,468 05/31/2011 Peter C. Hiestand PAT050279-US-CNT 1536

1095 7590 09/30/2013
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER

WEDDINGTON, KEVIN E

ART UNIT PAPER NUMBER

1629

NOTIFICATION DATE DELIVERY MODE

09/30/2013

ELECTRONIC

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

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

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

phip.patents@novartis.com

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

Claims 12-14, 16, 17 and 21-25 are presented for examination.

Applicants' request for continued examination, amendment and response filed February 18, 2013; and the information disclosure statement filed April 18, 2013 have been received and entered.

Accordingly, the rejection made under 35 USC 103(a) as being unpatentable over Virley, D.D., Journal of the American Society for Experimental NeuroTherapeutics, in view of LaMontagne et al., Cancer Research, and further in view of Kovarik et al., WO 06/058316 as set forth in the previous Office action dated November 16, 2012 at pages 2-3 as applied to claims 12-21 is hereby withdrawn because the applicants amendment the independent claims and the prior art does not read on applicants' newly limitation.

Allowable Subject Matter

Claims 12-14, 16, 17, 21-23 and 25 are allowable.

Claim Rejections - 35 USC § 112

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

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

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

Claim 24 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

Art Unit: 1629

subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 24 depends on a cancelled claim 15.

Claim 24 is not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KEVIN E. WEDDINGTON whose telephone number is (571)272-0587. The examiner can normally be reached on 12:30 pm -9:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery S. Lundgren can be reached on (571)272-5541. 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.

KEVIN E WEDDINGTON
Primary Examiner
Art Unit 1629

Application/Control Number: 13/149,468
Art Unit: 1629

Page 4

/KEVIN E WEDDINGTON/
Primary Examiner, Art Unit 1629

Index of Claims 	Application/Control No. 13149468	Applicant(s)/Patent Under Reexamination HIESTAND ET AL.
	Examiner KEVIN E WEDDINGTON	Art Unit 1629

✓	Rejected
=	Allowed

-	Cancelled
÷	Restricted

N	Non-Elected
I	Interference

A	Appeal
O	Objected

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

CLAIM		DATE							
Final	Original	09/24/2013							
	1	-							
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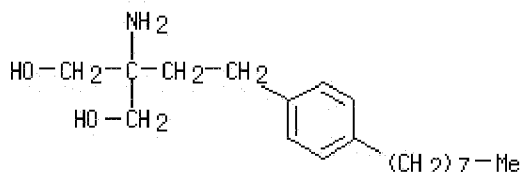
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OTHER NAMES:
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CN  Fingolimod hydrochloride
CN  FTY 720
CN  FTY 720
CN  Gilenya
CN  Imusera
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 PATDPASPC, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
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 CRN (162359-55-9)



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970 REFERENCES IN FILE CA (1907 TO DATE)
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 980 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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SINCE FILE ENTRY	TOTAL SESSION
9.89	10.13

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 CA INDEXING COPYRIGHT (C) 2013 AMERICAN CHEMICAL SOCIETY (ACS)

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=> s l1

L2 256 L1

=> d 200-256

L2 ANSWER 200 OF 256 USPATFULL on STN

Full Text

AN 1998:17339 USPATFULL

TI 2-amino-1,3-propanediol compound and immunosuppressant

IN Fujita, Tetsuro, Kyoto, Japan

Sasaki, Shigeo, Hyogo, Japan

Yoneta, Masahiko, Hyogo, Japan

Mishina, Tadashi, Saitama, Japan

Adachi, Kunitomo, Saitama, Japan

Chiba, Kenji, Saitama, Japan

PA Yoshitomi Pharmaceutical Industries, Ltd., Osaka, Japan (non-U.S.)

corporation)
Taito Co., Ltd., Tokyo, Japan (non-U.S. corporation)

PI US 5719176 19980217
AI US 1996-725890 19961002 (8)
RLI Division of Ser. No. US 1994-244942, filed on 17 Jun 1994, now patented,
Pat. No. US 5604229
PRAI JP 1992-283281 19921021
JP 1993-179427 19930720
DT Utility
FS Granted
LN.CNT 10472
INCL INCLM: 514/440.000
INCLS: 514/459.000; 514/471.000; 514/561.000; 514/564.000; 564/123.000;
564/336.000; 564/340.000; 564/342.000; 564/346.000; 564/374.000;
564/383.000; 564/459.000
NCL NCLM: 514/440.000
NCLS: 514/459.000; 514/471.000; 514/561.000; 514/564.000; 564/123.000;
564/336.000; 564/340.000; 564/342.000; 564/346.000; 564/374.000;
564/383.000; 564/459.000
CPC CPCI C07D0207-325 [I]; C07C0215-10 [I]; C07C0215-18 [I]; C07C0215-20
[I]; C07C0215-24 [I]; C07C0215-26 [I]; C07C0215-28 [I];
C07C0215-34 [I]; C07C0215-42 [I]; C07C0215-54 [I]; C07C0215-56
[I]; C07C0215-68 [I]; C07C0217-28 [I]; C07C0217-30 [I];
C07C0217-34 [I]; C07C0217-48 [I]; C07C0217-52 [I]; C07C0217-64
[I]; C07C0217-72 [I]; C07C0217-76 [I]; C07C0219-06 [I];
C07C0219-24 [I]; C07C0219-30 [I]; C07C0225-04 [I]; C07C0225-06
[I]; C07C0225-10 [I]; C07C0225-14 [I]; C07C0225-16 [I];
C07C0229-22 [I]; C07C0229-38 [I]; C07C0229-46 [I]; C07C0233-18
[I]; C07C0233-31 [I]; C07C0233-35 [I]; C07C0233-36 [I];
C07C0233-41 [I]; C07C0233-43 [I]; C07C0233-47 [I]; C07C0237-06
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C07C0271-20 [I]; C07C0271-24 [I]; C07C0271-28 [I]; C07C0323-25
[I]; C07C0323-30 [I]; C07C0323-32 [I]; C07C0323-34 [I];
C07C0323-41 [I]; C07C2101-08; C07C2101-14; C07D0207-06 [I];
C07D0207-09 [I]; C07D0207-335 [I]; C07D0211-14 [I]; C07D0211-26
[I]; C07D0213-38 [I]; C07D0213-40 [I]; C07D0231-12 [I];
C07D0233-56 [I]; C07D0233-64 [I]; C07D0237-08 [I]; C07D0239-26
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C07D0263-32 [I]; C07D0265-30 [I]; C07D0275-02 [I]; C07D0277-28
[I]; C07D0279-12 [I]; C07D0295-13 [I]; C07D0295-135 [I];
C07D0307-52 [I]; C07D0309-32 [I]; C07D0317-28 [I]; C07D0333-20
[I]
IPC [6]
IPCI C07C0711-00 [ICM,6]; A01N0043-40 [ICS,6]; A01N0033-02 [ICS,6]
IPCR A01N0033-02 [I]; A01N0043-40 [I]; A01N0043-60 [I]; A01N0057-00
[I]; C07C0215-10 [I]; C07C0215-18 [I]; C07C0215-20 [I];
C07C0215-24 [I]; C07C0215-26 [I]; C07C0215-28 [I]; C07C0215-34
[I]; C07C0215-42 [I]; C07C0215-54 [I]; C07C0215-56 [I];
C07C0215-68 [I]; C07C0217-28 [I]; C07C0217-30 [I]; C07C0217-34
[I]; C07C0217-48 [I]; C07C0217-52 [I]; C07C0217-64 [I];
C07C0217-72 [I]; C07C0217-76 [I]; C07C0219-06 [I]; C07C0219-24
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C07C0225-10 [I]; C07C0225-14 [I]; C07C0225-16 [I]; C07C0229-22
[I]; C07C0229-38 [I]; C07C0229-46 [I]; C07C0233-18 [I];
C07C0233-31 [I]; C07C0233-35 [I]; C07C0233-36 [I]; C07C0233-41
[I]; C07C0233-43 [I]; C07C0233-47 [I]; C07C0237-06 [I];
C07C0237-24 [I]; C07C0237-30 [I]; C07C0251-38 [I]; C07C0271-20
[I]; C07C0271-24 [I]; C07C0271-28 [I]; C07C0323-25 [I];
C07C0323-30 [I]; C07C0323-32 [I]; C07C0323-34 [I]; C07C0323-41
[I]; C07D0207-06 [I]; C07D0207-09 [I]; C07D0207-32 [N];
C07D0207-325 [I]; C07D0207-335 [I]; C07D0211-14 [I]; C07D0211-26
[I]; C07D0213-38 [I]; C07D0213-40 [I]; C07D0233-54 [I];
C07D0237-08 [I]; C07D0239-26 [I]; C07D0241-12 [I]; C07D0261-08
[I]; C07D0263-32 [I]; C07D0265-30 [I]; C07D0275-02 [I];
C07D0277-28 [I]; C07D0279-12 [I]; C07D0295-13 [I]; C07D0295-135
[I]; C07D0307-52 [I]; C07D0309-32 [I]; C07D0317-28 [I];
C07D0333-20 [I]; C07D0521-00 [I]
EXF 514/440; 514/459; 514/471; 514/561; 514/564; 564/336; 564/340; 564/342;
564/346; 564/374; 564/383; 564/459; 564/123
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 201 OF 256 USPATFULL on STN

Full Text

AN 97:14705 USPATFULL
TI 2-amino-1,3-propanediol compound and immunosuppressant
IN Fujita, Tetsuro, Muko, Japan
Sasaki, Shigeo, Kobe, Japan
Yoneta, Masahiko, Kobe, Japan
Mishina, Tadashi, Iruma, Japan
Adachi, Kunitomo, Iruma, Japan
Chiba, Kenji, Iruma, Japan
PA Yoshitomi Pharmaceutical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
Taito Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 5604229 19970218
WO 9408943 19940428
AI US 1994-244942 19940617 (8)
WO 1993-JP1515 19931018
19940617 PCT 371 date
19940617 PCT 102(e) date
PRAI JP 1992-283281 19921021
JP 1993-179427 19930720
DT Utility
FS Granted
LN.CNT 10702
INCL INCLM: 514/255.000
INCLS: 514/357.000; 514/372.000; 514/403.000; 514/427.000; 514/438.000;
514/459.000; 514/471.000; 544/401.000; 546/246.000; 546/247.000;
546/334.000; 548/214.000; 548/373.100; 548/516.000; 549/075.000;
549/426.000; 549/495.000; 549/472.000; 564/336.000; 564/340.000;
564/342.000; 564/346.000; 564/374.000; 564/383.000; 564/454.000;
564/123.000
NCL NCLM: 514/252.100
NCLS: 514/357.000; 514/372.000; 514/403.000; 514/427.000; 514/438.000;
514/459.000; 514/471.000; 544/401.000; 546/246.000; 546/247.000;
546/334.000; 548/214.000; 548/373.100; 548/516.000; 549/075.000;
549/426.000; 549/472.000; 549/495.000; 564/123.000; 564/336.000;
564/340.000; 564/342.000; 564/346.000; 564/374.000; 564/383.000;
564/454.000
CPC CPCI C07D0207-325 [I]; C07C0215-10 [I]; C07C0215-18 [I]; C07C0215-20 [I];
C07C0215-24 [I]; C07C0215-26 [I]; C07C0215-28 [I];
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C07C0229-22 [I]; C07C0229-38 [I]; C07C0229-46 [I]; C07C0233-18 [I];
C07C0233-31 [I]; C07C0233-35 [I]; C07C0233-36 [I];
C07C0233-41 [I]; C07C0233-43 [I]; C07C0233-47 [I]; C07C0237-06 [I];
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C07C0271-20 [I]; C07C0271-24 [I]; C07C0271-28 [I]; C07C0323-25 [I];
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C07C0323-41 [I]; C07C2101-08; C07C2101-14; C07D0207-06 [I];
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C07D0213-38 [I]; C07D0213-40 [I]; C07D0231-12 [I];
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C07D0263-32 [I]; C07D0265-30 [I]; C07D0275-02 [I]; C07D0277-28 [I];
C07D0279-12 [I]; C07D0295-13 [I]; C07D0295-135 [I];
C07D0307-52 [I]; C07D0309-32 [I]; C07D0317-28 [I]; C07D0333-20 [I]
IPC [6]
IPCI C07C0211-00 [ICM,6]; C07D0333-20 [ICS,6]; A01N0043-40 [ICS,6];
A01N0033-02 [ICS,6]
IPCR A01N0033-02 [I]; A01N0043-40 [I]; A01N0043-60 [I]; A01N0057-00 [I];
C07C0215-10 [I]; C07C0215-18 [I]; C07C0215-20 [I];
C07C0215-24 [I]; C07C0215-26 [I]; C07C0215-28 [I]; C07C0215-34 [I];
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C07C0217-72 [I]; C07C0217-76 [I]; C07C0219-06 [I]; C07C0219-24 [I];
C07C0219-30 [I]; C07C0225-04 [I]; C07C0225-06 [I];
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[I]; C07C0229-38 [I]; C07C0229-46 [I]; C07C0233-18 [I];
C07C0233-31 [I]; C07C0233-35 [I]; C07C0233-36 [I]; C07C0233-41
[I]; C07C0233-43 [I]; C07C0233-47 [I]; C07C0237-06 [I];
C07C0237-24 [I]; C07C0237-30 [I]; C07C0251-38 [I]; C07C0271-20
[I]; C07C0271-24 [I]; C07C0271-28 [I]; C07C0323-25 [I];
C07C0323-30 [I]; C07C0323-32 [I]; C07C0323-34 [I]; C07C0323-41
[I]; C07D0207-06 [I]; C07D0207-09 [I]; C07D0207-32 [N];
C07D0207-325 [I]; C07D0207-335 [I]; C07D0211-14 [I]; C07D0211-26
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C07D0237-08 [I]; C07D0239-26 [I]; C07D0241-12 [I]; C07D0261-08
[I]; C07D0263-32 [I]; C07D0265-30 [I]; C07D0275-02 [I];
C07D0277-28 [I]; C07D0279-12 [I]; C07D0295-13 [I]; C07D0295-135
[I]; C07D0307-52 [I]; C07D0309-32 [I]; C07D0317-28 [I];
C07D0333-20 [I]; C07D0521-00 [I]
EXF 546/210; 546/246; 546/247; 546/334; 560/172; 562/11; 558/169; 514/114;
514/119; 514/357; 514/255; 514/372; 514/403; 514/427; 514/438; 514/459;
514/471; 564/336; 564/340; 564/342; 564/346; 564/374; 564/383; 564/454;
564/123; 549/75; 549/426; 549/495; 548/214; 548/373.1; 548/516; 544/401
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 202 OF 256 USPAT2 on STN

Full Text

AN 2012:324839 USPAT2
TI Compounds that modulate intracellular calcium
IN Velicelebi, Gonul, San Diego, CA, UNITED STATES
Stauderman, Kenneth A., San Diego, CA, UNITED STATES
Pleyner, David P. M., Auburndale, MA, UNITED STATES
Cheng, Soan, San Diego, CA, UNITED STATES
Whitten, Jeffrey P., Santee, CA, UNITED STATES
PA Calcimedica, Inc., La Jolla, CA, UNITED STATES (U.S. corporation)
PI US 8524765 B2 20130903
AI US 2012-553726 20120719 (13)
RLI Division of Ser. No. US 2008-192812, filed on 15 Aug 2008, Pat. No. US
8263641
PRAI US 2007-971161P 20070910 (60)
DT Utility
FS GRANTED
LN.CNT 6498
INCL INCLM: 514/447.000
INCLS: 549/069.000
NCL NCLM: 514/443.000
NCLS: 514/447.000
CPC CPC1 C07D0333-68 [I]; A61K0031-00 [I]; A61K0031-405 [I]
CPC1-2 C07D0333-68 [I]; A61K0031-00 [I]; A61K0031-405 [I]
IPC IPC1 A61K0031-381 [I]; A61P0013-12 [I]; A61P0027-02 [I]; A61P0001-16
[I]; A61P0011-00 [I]; A61P0019-02 [I]; A61P0017-06 [I];
A61P0001-00 [I]; A61P0009-00 [I]; A61P0017-00 [I]; A61P0021-00
[I]; A61P0011-02 [I]; A61P0015-02 [I]; A61P0019-10 [I];
A61P0037-06 [I]; A61P0003-10 [I]; A61P0037-00 [I]; A61P0021-04
[I]; A61P0007-06 [I]; A61P0011-06 [I]; A61P0025-00 [I];
A61P0029-00 [I]
IPC1-2 A61K0031-381 [I]; C07D0333-40 [I]
IPCR A61K0031-381 [I]; A61P0001-00 [I]; A61P0001-16 [I]; A61P0003-10
[I]; A61P0007-06 [I]; A61P0009-00 [I]; A61P0011-00 [I];
A61P0011-02 [I]; A61P0011-06 [I]; A61P0013-12 [I]; A61P0015-02
[I]; A61P0017-00 [I]; A61P0017-06 [I]; A61P0019-02 [I];
A61P0019-10 [I]; A61P0021-00 [I]; A61P0021-04 [I]; A61P0025-00
[I]; A61P0027-02 [I]; A61P0029-00 [I]; A61P0037-00 [I];
A61P0037-06 [I]
EXF 514/447; 549/69

L2 ANSWER 203 OF 256 USPAT2 on STN

Full Text

AN 2012:295859 USPAT2
TI Methods for modulating inflammatory and/or immune responses
IN Marshall, Vivienne S., San Antonio, TX, UNITED STATES
Banas, Richard A., Turtle Creek, PA, UNITED STATES
Trumpower, Catherine J., Pittsburgh, PA, UNITED STATES
PA Stemnion, Inc., Pittsburgh, PA, UNITED STATES (U.S. corporation)
PI US 8506949 B2 20130813
AI US 2012-483369 20120530 (13)
RLI Division of Ser. No. US 2009-448903, filed on 13 Jul 2009, Pat. No. US

8221741
PRAI US 2007-880745P 20070117 (60)
US 2007-902440P 20070221 (60)
US 2007-997604P 20071004 (60)
DT Utility
FS GRANTED
LN.CNT 1982
INCL INCLM: 424/093.210
INCLS: 424/093.700; 424/184.100; 424/141.100; 424/173.100
NCL NCLM: 424/093.210; 424/093.700
NCLS: 424/093.700; 424/141.100; 424/173.100; 424/184.100; 424/572.000;
435/002.000
CPC CPCI A61K0039-001 [I]; A61K0035-50 [I]; A61K2039-5158; C12N0005-0634
[I]; C12N2502-025
CPCI-2 A61K0039-001 [I]; A61K0035-50 [I]; A61K2039-5158; C12N0005-0634
[I]; C12N2502-025
IPC IPCI A61K0035-12 [I]; A61P0029-00 [I]; C12N0005-078 [I]
IPCI-2 A61K0039-00 [I]; A61K0035-12 [I]; A61K0038-21 [I]
IPCR A61K0035-12 [I]; A61P0029-00 [I]; C12N0005-078 [I]

L2 ANSWER 204 OF 256 USPAT2 on STN

Full Text

AN 2012:220564 USPAT2
TI Treatment for multiple sclerosis
IN Lukashov, Matvey E., Tewksbury, MA, UNITED STATES
O'Neill, Gilmore, Medford, MA, UNITED STATES
PA Biogen Idec MA Inc., Cambridge, MA, UNITED STATES (U.S. corporation)
PI US 8399514 B2 20130319
AI US 2012-372426 20120213 (13)
RLI Continuation of Ser. No. US 1900-526296, ABANDONED A 371 of
International Ser. No. WO 2008-US1602, filed on 7 Feb 2008
PRAI US 2007-888921P 20070208 (60)
DT Utility
FS GRANTED
LN.CNT 2560
INCL INCLM: 514/549.000
NCL NCLM: 514/549.000; 514/547.000
CPC CPCI G01N0033-502 [I]; G01N2333-90209; G01N2800-285
CPCI-2 G01N0033-502 [I]; G01N2333-90209; G01N2800-285
IPC IPCI A61K0031-225 [I]; A61P0025-00 [I]
IPCI-2 A61K0031-22 [I]
IPCR A61K0031-22 [I]

L2 ANSWER 205 OF 256 USPAT2 on STN

Full Text

AN 2012:152949 USPAT2
TI FTY720-derived anticancer agents
IN Chen, Ching-Shih, Upper Arlington, OH, UNITED STATES
Kulp, Samuel K., Hilliard, OH, UNITED STATES
Wang, Dasheng, Dublin, OH, UNITED STATES
Byrd, John C., Columbus, OH, UNITED STATES
Muthusamy, Natarajan, Galloway, OH, UNITED STATES
PA The Ohio State University Research Foundation, Columbus, OH, UNITED
STATES (U.S. corporation)
PI US 8309768 B2 20121113
AI US 2011-305927 20111129 (13)
PRAI US 2010-417566P 20101129 (61)
DT Utility
FS GRANTED
LN.CNT 2578
INCL INCLM: 564/355.000
INCLS: 564/336.000; 564/347.000
NCL NCLM: 564/355.000; 514/653.000
NCLS: 564/336.000; 564/347.000; 564/374.000
CPC CPCI C07C0217-74 [I]; C07C0217-64 [I]; C07C2101-02
CPCI-2 C07C0217-74 [I]; C07C0217-64 [I]; C07C2101-02
IPC IPCI A61K0031-137 [I]; A61P0035-00 [I]; C07C0215-28 [I]
IPCI-2 C07C0215-00 [I]; C07C0211-00 [I]; C07C0213-00 [I]
IPCR C07C0215-00 [I]; C07C0211-00 [I]; C07C0213-00 [I]
EXF 564/336; 564/347; 564/355

L2 ANSWER 206 OF 256 USPAT2 on STN

Full Text

AN 2011:348766 USPAT2
TI Tricyclic compounds
IN Wishart, Neil, Jefferson, MA, UNITED STATES
Frank, Kristine E., Worcester, MA, UNITED STATES
Friedman, Michael, Brookline, MA, UNITED STATES
George, Dawn M., Charlton, MA, UNITED STATES
Stewart, Kent D., Gurnee, IL, UNITED STATES
Wallace, Grier A., Sterling, MA, UNITED STATES
PA Abbott Laboratories, Abbott Park, IL, UNITED STATES (U.S. corporation)
PI US 8426411 B2 20130423
AI US 2010-958115 20101201 (12)
PRAI US 2009-265563P 20091201 (61)
US 2010-364116P 20100714 (61)
DT Utility
FS GRANTED
LN.CNT 22219
INCL INCLM: 514/250.000
NCL NCLM: 514/250.000; 424/085.200
NCLS: 424/085.100; 424/085.400; 424/085.500; 424/085.600; 424/085.700;
424/142.100; 424/158.100; 514/008.200; 514/009.100; 514/171.000;
514/210.210; 514/293.000; 544/346.000; 546/082.000
CPC CPCI C07D0487-14 [I]; A61K0031-437 [I]; A61K0031-4985 [I]; A61K0045-06
[I]; C07D0471-14 [I]; C07D0498-14 [I]; C07D0513-14 [I]
CPCI-2 C07D0487-14 [I]; A61K0031-437 [I]; A61K0031-4985 [I]; A61K0045-06
[I]; C07D0471-14 [I]; C07D0498-14 [I]; C07D0513-14 [I]
IPC IPCI A61K0031-4985 [I]; C07D0471-14 [I]; A61K0031-437 [I];
A61K0039-395 [I]; A61P0025-00 [I]; A61K0038-21 [I]; A61K0038-18
[I]; A61K0031-573 [I]; A61P0035-00 [I]; A61P0037-06 [I];
C07D0487-14 [I]; A61K0038-20 [I]
IPCI-2 A61K0031-50 [I]
IPCR A61K0031-4985 [I]; A61K0031-437 [I]; A61K0031-573 [I];
A61K0038-18 [I]; A61K0038-20 [I]; A61K0038-21 [I]; A61K0039-395
[I]; A61P0025-00 [I]; A61P0035-00 [I]; A61P0037-06 [I];
C07D0471-14 [I]; C07D0487-14 [I]
EXF 514/250

L2 ANSWER 207 OF 256 USPAT2 on STN

Full Text

AN 2011:328619 USPAT2
TI COMPOSITION AND METHOD FOR TREATMENT OF REPERFUSION INJURY AND TISSUE
DAMAGE
IN Heffernan, Mark, Dublin 8, IRELAND
O'Neill, Luke, Dublin, IRELAND
McGuirk, Peter, Dublin, IRELAND
Keogh, Brian, Dublin, IRELAND
Locher, Christopher, Lexington, MA, UNITED STATES
De Kleijn, Dominique, Utrecht, NETHERLANDS
Arslan, Fatih, Utrecht, NETHERLANDS
Pasterkamp, Gerard, Utrecht, NETHERLANDS
PA Opsona Therapeutics Ltd, Dublin 8, IRELAND (non-U.S. corporation)
PI US 20120141466 A9 20120607
AI US 2011-671810 A1 20080804 (12)
WO 2008-EP60249 20080804
20110816 PCT 371 date
PRAI IE 2007-558 20070803
US 2008-38555P 20080321 (61)
DT Utility
FS APPLICATION
LN.CNT 3095
INCL INCLM: 424/133.100
INCLS: 435/375.000; 424/172.100; 424/143.100; 424/139.100; 424/158.100
NCL NCLM: 424/133.100
NCLS: 424/139.100; 424/143.100; 424/158.100; 424/172.100; 435/375.000
CPC CPCI A61K0045-06 [I]; A61K0031-00 [I]; A61K0031-7088 [I]; A61K0038-177
[I]; C07K0016-2896 [I]; C12N0015-1138 [I]; G01N0033-567 [I];
G01N2500-00
CPCI-2 A61K0045-06 [I]; A61K0031-00 [I]; A61K0031-7088 [I]; A61K0038-177
[I]; C07K0016-2896 [I]; C12N0015-1138 [I]; G01N0033-567 [I];
G01N2500-00
IPC IPCI A61K0039-395 [I]; A61P0039-06 [I]; A61P0007-02 [I]; A61P0009-00
[I]; A61P0009-10 [I]; A61P0009-06 [I]; A61P0009-04 [I];

A61P0009-12 [I]; C12N0005-071 [I]; A61P0007-10 [I]
IPCI-2 A61K0039-395 [I]; A61P0039-06 [I]; A61P0007-02 [I]; A61P0009-00
[I]; A61P0009-10 [I]; A61P0009-06 [I]; A61P0009-04 [I];
A61P0009-12 [I]; C12N0005-071 [I]; A61P0007-10 [I]
IPCR A61K0039-395 [I]; A61P0007-02 [I]; A61P0007-10 [I]; A61P0009-00
[I]; A61P0009-04 [I]; A61P0009-06 [I]; A61P0009-10 [I];
A61P0009-12 [I]; A61P0039-06 [I]; C12N0005-071 [I]; C12N0015-113
[I]

L2 ANSWER 208 OF 256 USPAT2 on STN

Full Text

AN 2011:237523 USPAT2
TI Cycloundecadepsipeptide compounds and use of said compounds as a
medicament
IN Wenger, Roland, Riehen, SWITZERLAND
Mutter, Manfred, Belmont-Sur-Lausanne, SWITZERLAND
Garrouste, Patrick, Saxon, SWITZERLAND
Lysek, Robert, Martigny, SWITZERLAND
Turpin, Olivier, Martigny, SWITZERLAND
Vuagniaux, Gregoire, Lausanne, SWITZERLAND
Nicolas, Valerie, St-Prex, SWITZERLAND
Novaroli Zanolari, Laura, Lausanne, SWITZERLAND
Crabbe, Rafael, Bursins, SWITZERLAND
PA Debio Recherche Pharmaceutique S.A., Martigny, SWITZERLAND (non-U.S.
corporation)
PI US 8501683 B2 20130806
WO 2010052559 20100514
AI US 2011-998588 20091106 (12)
WO 2009-IB7361 20091106
20110505 PCT 371 date
PRAI WO 2008-IB2982 20081106
DT Utility
FS GRANTED
LN.CNT 1819
INCL INCLM: 514/004.300
INCLS: 514/021.100
NCL NCLM: 514/004.300; 424/085.700
NCLS: 514/021.100; 424/094.500; 530/317.000
CPC CPCI C07K0011-02 [I]; A61K0038-212 [I]
CPCI-2 C07K0011-02 [I]; A61K0038-212 [I]
IPC IPCI A61K0038-21 [I]; C07K0011-02 [I]; A61K0038-15 [I]; A61K0038-45
[I]; A61P0031-14 [I]
IPCI-2 A61K0038-12 [I]
IPCR A61K0038-21 [I]; A61K0038-15 [I]; A61K0038-45 [I]; A61P0031-14
[I]; C07K0011-02 [I]

L2 ANSWER 209 OF 256 USPAT2 on STN

Full Text

AN 2011:91679 USPAT2
TI Selective inhibitors of histone deacetylase
IN Verner, Erik, Belmont, CA, UNITED STATES
Balasubramanian, Sriram, San Carlos, CA, UNITED STATES
Buggy, Joseph J., Mountain View, CA, UNITED STATES
PA Pharmacyclics, Inc., Sunnyvale, CA, UNITED STATES (U.S. corporation)
PI US 8466193 B2 20130618
WO 2009129335 20091022
AI US 2010-988271 20090415 (12)
WO 2009-US40709 20090415
20101201 PCT 371 date
PRAI US 2008-45198P 20080415 (61)
DT Utility
FS GRANTED
LN.CNT 7428
INCL INCLM: 514/427.000
INCLS: 548/561.000
NCL NCLM: 514/427.000; 424/450.000
NCLS: 548/561.000; 424/085.200; 424/133.100; 514/019.300; 514/043.000;
514/049.000; 514/114.000; 514/235.500; 514/383.000; 544/141.000
CPC CPCI C07D0207-337 [I]; C07D0209-08 [I]; C07D0235-06 [I]; C07D0307-79
[I]; C07D0307-80 [I]; C07D0333-54 [I]; C07D0333-56 [I];
C07D0401-06 [I]; C07D0401-12 [I]; C07D0405-06 [I]; C07D0409-06
[I]; C07D0471-04 [I]

CPCI-2 C07D0207-337 [I]; C07D0209-08 [I]; C07D0235-06 [I]; C07D0307-79 [I]; C07D0307-80 [I]; C07D0333-54 [I]; C07D0333-56 [I]; C07D0401-06 [I]; C07D0401-12 [I]; C07D0405-06 [I]; C07D0409-06 [I]; C07D0471-04 [I]

IPC IPCI A61K0009-127 [I]; C07D0207-337 [I]; C07D0413-12 [I]; A61K0031-40 [I]; A61K0031-5377 [I]; A61K0038-08 [I]; A61K0038-20 [I]; A61K0039-395 [I]; A61K0031-661 [I]; A61K0031-4196 [I]; A61K0031-706 [I]; A61K0031-7068 [I]; A61P0019-02 [I]; A61P0019-06 [I]; A61P0017-06 [I]; A61P0029-00 [I]; A61P0011-06 [I]; A61P0007-06 [I]; A61P0011-00 [I]

IPCI-2 A01N0043-36 [I]

IPCR A61K0009-127 [I]; A61K0031-40 [I]; A61K0031-4196 [I]; A61K0031-5377 [I]; A61K0031-661 [I]; A61K0031-706 [I]; A61K0031-7068 [I]; A61K0038-08 [I]; A61K0038-20 [I]; A61K0039-395 [I]; A61P0007-06 [I]; A61P0011-00 [I]; A61P0011-06 [I]; A61P0017-06 [I]; A61P0019-02 [I]; A61P0019-06 [I]; A61P0029-00 [I]; C07D0207-337 [I]; C07D0413-12 [I]

EXF 548/561; 514/427

L2 ANSWER 210 OF 256 USPAT2 on STN

Full Text

AN 2010:348825 USPAT2

TI Treatment of inflammatory diseases

IN Soliven, Betty C., Chicago, IL, UNITED STATES

PA The University of Chicago, Chicago, IL, UNITED STATES (U.S. corporation)

PI US 8258150 B2 20120904
WO 2008021532 20080221

AI US 2010-377736 20070817 (12)
WO 2007-US18331 20070817
20100825 PCT 371 date

PRAI US 2006-838222P 20060817 (60)

DT Utility

FS GRANTED

LN.CNT 1138

INCL INCLM: 514/291.000
INCLS: 424/283.100

NCL NCLM: 514/291.000; 424/130.100
NCLS: 424/283.100; 514/017.700; 514/090.000; 514/114.000; 514/171.000; 514/364.000; 514/653.000

CPC CPCI A61K0031-133 [I]; A61K0031-138 [I]; A61K0031-4245 [I]; A61K0031-56 [I]; A61K0031-661 [I]; A61K0045-06 [I]

CPCI-2 A61K0031-133 [I]; A61K0031-138 [I]; A61K0031-4245 [I]; A61K0031-56 [I]; A61K0031-661 [I]; A61K0045-06 [I]

IPC IPCI A61K0031-137 [I]; A61K0031-661 [I]; A61K0031-4245 [I]; A61K0039-395 [I]; A61K0031-56 [I]; A61K0038-13 [I]; A61K0031-675 [I]; A61P0025-02 [I]; A61P0037-02 [I]

IPCI-2 A61K0031-137 [I]

IPCR A61K0031-137 [I]

L2 ANSWER 211 OF 256 USPAT2 on STN

Full Text

AN 2010:342740 USPAT2

TI Compounds that modulate intracellular calcium

IN Velicelebi, Gonul, San Diego, CA, UNITED STATES
Stauderman, Kenneth A., San Diego, CA, UNITED STATES
King, Frank, Bishops Stortford, UNITED KINGDOM
Pei, Yazhong, San Diego, CA, UNITED STATES
Whitten, Jeffrey P., Santee, CA, UNITED STATES

PA Calcimedica, Inc., La Jolla, CA, UNITED STATES (U.S. corporation)

PI US 8389567 B2 20130305
WO 2009076454 20090618

AI US 2010-747604 20081210 (12)
WO 2008-US86254 20081210
20100817 PCT 371 date

PRAI US 2007-13227P 20071212 (61)

DT Utility

FS GRANTED

LN.CNT 6878

INCL INCLM: 514/447.000

NCL NCLM: 514/447.000
NCLS: 544/333.000; 546/256.000; 546/272.100; 546/275.400; 546/279.100; 548/245.000; 548/372.100; 548/532.000; 549/069.000

CPC CPCI C07D0403-04 [I]; A61K0031-381 [I]; A61K0031-415 [I];
A61K0031-4436 [I]; A61K0031-4439 [I]; A61K0031-444 [I];
A61K0031-5025 [I]; A61K0031-506 [I]; A61K0045-06 [I];
C07D0207-456 [I]; C07D0213-55 [I]; C07D0213-80 [I]; C07D0231-38
[I]; C07D0231-40 [I]; C07D0261-18 [I]; C07D0333-38 [I];
C07D0333-68 [I]; C07D0333-74 [I]; C07D0401-04 [I]; C07D0401-12
[I]; C07D0401-14 [I]; C07D0409-12 [I]; C07D0413-04 [I];
C07D0413-14 [I]; C07D0495-04 [I]
CPCI-2 C07D0403-04 [I]; A61K0031-381 [I]; A61K0031-415 [I];
A61K0031-4436 [I]; A61K0031-4439 [I]; A61K0031-444 [I];
A61K0031-5025 [I]; A61K0031-506 [I]; A61K0045-06 [I];
C07D0207-456 [I]; C07D0213-55 [I]; C07D0213-80 [I]; C07D0231-38
[I]; C07D0231-40 [I]; C07D0261-18 [I]; C07D0333-38 [I];
C07D0333-68 [I]; C07D0333-74 [I]; C07D0401-04 [I]; C07D0401-12
[I]; C07D0401-14 [I]; C07D0409-12 [I]; C07D0413-04 [I];
C07D0413-14 [I]; C07D0495-04 [I]
IPC IPCI A61K0031-381 [I]; C07D0261-18 [I]; C07D0413-14 [I]; C07D0231-38
[I]; C07D0413-04 [I]; C07D0401-04 [I]; C07D0403-04 [I];
C07D0401-14 [I]; C07D0207-50 [I]; C07D0333-36 [I]; A61P0029-00
[I]; A61P0013-12 [I]; A61P0001-16 [I]; A61P0011-00 [I];
A61P0001-00 [I]; A61P0017-00 [I]; A61P0019-10 [I]; A61P0003-10
[I]; A61P0007-06 [I]; A61P0011-02 [I]; A61P0037-08 [I];
A61P0037-02 [I]; A61P0027-02 [I]; A61P0017-06 [I]; A61P0025-00
[I]
IPCI-2 A61K0031-381 [I]
IPCR A61K0031-381 [I]
EXF 514/447; 549/69

L2 ANSWER 212 OF 256 USPAT2 on STN

Full Text

AN 2010:188549 USPAT2
TI Heterocyclic substituted pyridine compounds with CXCR3 antagonist
activity
IN Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
Shih, Neng-Yang, Lexington, MA, UNITED STATES
McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
Hobbs, Douglas W., Chesterfield, MS, UNITED STATES
PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
Pharmacoepia, Inc., Princeton, NJ, UNITED STATES (U.S. corporation)
PI US 8017616 B2 20110913
AI US 2009-642931 20091221 (12)
RLI Continuation of Ser. No. US 2007-688014, filed on 19 Mar 2007, Pat. No.
US 7786124
PRAI US 2006-784504P 20060321 (60)
DT Utility
FS GRANTED
LN.CNT 3250
INCL INCLM: 514/253.090
INCLS: 514/253.100; 544/364.000
NCL NCLM: 514/253.090; 514/253.100
NCLS: 514/253.100; 544/364.000
CPC CPCI C07D0401-14 [I]; C07D0413-14 [I]
CPCI-2 C07D0401-14 [I]; C07D0413-14 [I]
IPC IPCI A61K0031-496 [I]; C07D0413-14 [I]; C07D0401-14 [I]; C07D0417-14
[I]; A61P0019-02 [I]; A61P0017-06 [I]; A61P0011-00 [I]
IPCI-2 A61K0031-496 [I]; C07D0413-14 [I]
IPCR A61K0031-496 [I]; C07D0413-14 [I]

L2 ANSWER 213 OF 256 USPAT2 on STN

Full Text

AN 2010:76378 USPAT2
TI Methods for modulating inflammatory and/or immune responses
IN Marshall, Vivienne S., Glenshaw, PA, UNITED STATES
Banas, Richard A., Turtle Creek, PA, UNITED STATES
Trumpower, Catherine J., Pittsburgh, PA, UNITED STATES
PI US 8221741 B2 20120717
WO 2008088738 20080724
AI US 2009-448903 20080111 (12)
WO 2008-US396 20080111
PRAI US 2007-880745P 20090713 PCT 371 date
20070117 (60)

US 2007-902440P 20070221 (60)
 US 2007-997604P 20071004 (60)
 DT Utility
 FS GRANTED
 LN.CNT 1978
 INCL INCLM: 424/093.210
 INCLS: 424/093.700; 424/184.100; 424/141.100; 424/173.100
 NCL NCLM: 424/093.210; 424/085.400
 NCLS: 424/093.700; 424/141.100; 424/173.100; 424/184.100
 CPC CPCI C12N0005-0636 [I]; C12N0005-0605 [I]; C12N2501-23; C12N2502-02
 CPCI-2 C12N0005-0636 [I]; C12N0005-0605 [I]; C12N2501-23; C12N2502-02
 IPC IPCI A61K0039-395 [I]; A61K0035-12 [I]; A61K0038-21 [I]; A61P0037-06
 [I]; A61P0029-00 [I]
 IPCI-2 A61K0039-00 [I]; A61K0035-12 [I]; A61K0038-21 [I]
 IPCR A61K0039-00 [I]; A61K0035-12 [I]; A61K0038-21 [I]; C12N0005-073
 [I]; C12N0005-0783 [I]

L2 ANSWER 214 OF 256 USPAT2 on STN

Full Text

AN 2009:362673 USPAT2
 TI Fc receptor binding proteins
 IN TenHoor, Christopher, Hopkinton, MA, UNITED STATES
 Muruganandam, Arumugam, Bangalore, INDIA
 Ladner, Robert Charles, Ijamsville, MD, UNITED STATES
 Wood, Clive, Boston, MA, UNITED STATES
 Bitonti, Alan J., Acton, MA, UNITED STATES
 Stattel, James, Hagerstown, MD, UNITED STATES
 McDonnell, Kevin, Waltham, MA, UNITED STATES
 Liu, Liming, Upper Dublin, PA, UNITED STATES
 Dumont, Jennifer, Groton, MA, UNITED STATES
 Sato, Aaron, Richmond, CA, UNITED STATES
 PA Dyax Corp., Burlington, MA, UNITED STATES (U.S. corporation)
 Syntonix Pharmaceuticals, Inc., Waltham, MA, UNITED STATES (U.S.
 corporation)
 PI US 8273351 B2 20120925
 AI US 2009-429529 20090424 (12)
 PRAI US 2008-48152P 20080425 (61)
 US 2008-48500P 20080428 (61)
 DT Utility
 FS GRANTED
 LN.CNT 6646
 INCL INCLM: 424/133.100
 INCLS: 530/389.100
 NCL NCLM: 424/133.100; 424/172.100
 NCLS: 530/389.100; 436/501.000; 536/023.530
 CPC CPCI C07K0016-283 [I]; A61K2039-505; C07K2317-21; C07K2317-56;
 C07K2317-565; G01N0033-68 [I]
 CPCI-2 C07K0016-283 [I]; A61K2039-505; C07K2317-21; C07K2317-56;
 C07K2317-565; G01N0033-68 [I]
 IPC IPCI A61K0039-395 [I]; C07K0016-00 [I]; C07H0021-00 [I]; G01N0033-53
 [I]; A61P0037-00 [I]
 IPCI-2 A61K0039-395 [I]; C07K0016-00 [I]; C07H0021-00 [N]; G01N0033-53
 [N]
 IPCR A61K0039-395 [I]; C07H0021-00 [N]; C07K0016-00 [I]; G01N0033-53
 [N]
 EXF 424/133.1; 530/389.1

L2 ANSWER 215 OF 256 USPAT2 on STN

Full Text

AN 2009:225737 USPAT2
 TI Immunomodulation by altering sphingosine 1-phosphate lyase (SPL)
 activity
 IN Saba, Julie D., Oakland, CA, UNITED STATES
 PA Children's Hospital & Research Center at Oakland, Oakland, CA, UNITED
 STATES (U.S. corporation)
 PI US 8124111 B2 20120228
 WO 2006135862 20061221
 AI US 2008-917029 20060608 (11)
 WO 2006-US22805 20060608
 20080908 PCT 371 date
 PRAI US 2005-689611P 20050610 (60)
 DT Utility

FS GRANTED
LN.CNT 2310
INCL INCLM: 424/278.100
INCLS: 514/009.000
NCL NCLM: 424/278.100; 424/139.100
NCLS: 514/021.200; 424/094.500; 514/345.000; 514/558.000
CPC CPC1 C12N0009-88 [I]; A01K2267-03; C12N2799-022
CPC1-2 C12N0009-88 [I]; A01K2267-03; C12N2799-022
IPC IPC1 A61K0039-395 [I]; A61K0031-7105 [I]; A61K0031-4415 [I];
A61K0031-164 [I]; A61K0031-711 [I]; A61K0038-45 [I]; A61P0037-00
[I]
IPC1-2 A61K0039-00 [I]; C12N0009-88 [N]
IPCR A61K0039-00 [I]; C12N0009-88 [N]

L2 ANSWER 216 OF 256 USPAT2 on STN

Full Text

AN 2009:219334 USPAT2
TI Oligodendrocyte precursor cell composition and methods of use
IN Bieberich, Erhard, Augusta, GA, UNITED STATES
PA Georgia Health Sciences University, Augusta, GA, UNITED STATES (U.S.
corporation)
PI US 7985586 B2 20110726
AI US 2009-365381 20090204 (12)
PRAI US 2008-63315P 20080204 (61)
DT Utility
FS GRANTED
LN.CNT 2359
INCL INCLM: 435/366.000
INCLS: 435/325.000; 435/374.000
NCL NCLM: 435/366.000; 424/093.700
NCLS: 435/325.000; 435/374.000; 435/368.000; 435/378.000
CPC CPC1 C12N0005-0622 [I]; A61K0031-164 [I]; A61K0035-30 [I];
C12N0005-0081 [I]; C12N0005-0623 [I]; C12N2500-36; C12N2501-48;
C12N2506-02
CPC1-2 C12N0005-0622 [I]; A61K0031-164 [I]; A61K0035-30 [I];
C12N0005-0081 [I]; C12N0005-0623 [I]; C12N2500-36; C12N2501-48;
C12N2506-02
IPC IPC1 A61K0035-30 [I]; C12N0005-08 [I]; A61P0025-28 [I]; C12N0005-02
[I]
IPC1-2 C12N0005-00 [I]
IPCR C12N0005-00 [I]; C12N0005-079 [I]; C12N0005-0797 [I]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 217 OF 256 USPAT2 on STN

Full Text

AN 2009:173940 USPAT2
TI Aminopropanol derivatives
IN Albert, Rainer, Basel, SWITZERLAND
Francotte, Eric, Nuglar, SWITZERLAND
Zecri, Frederic, Bartenheim, FRANCE
Zollinger, Markus, Mohlin, SWITZERLAND
PA Novartis AG, Basel, SWITZERLAND (non-U.S. corporation)
PI US 7902175 B2 20110308
AI US 2009-391298 20090224 (12)
RLI Division of Ser. No. US 1900-569696, Pat. No. US 7528120 A 371 of
International Ser. No. WO 2004-EP9589, filed on 27 Aug 2004
PRAI GB 2003-20196 20030828
GB 2003-24206 20031015
DT Utility
FS GRANTED
LN.CNT 1168
INCL INCLM: 514/080.000
INCLS: 514/114.000; 548/414.000; 564/015.000
NCL NCLM: 514/080.000
NCLS: 514/114.000; 548/414.000; 564/015.000
CPC CPC1 C07F0009-5728 [I]; C07D0209-46 [I]; C07D0263-14 [I]; C07F0009-094
[I]; C07F0009-653 [I]
CPC1-2 C07F0009-5728 [I]; C07D0209-46 [I]; C07D0263-14 [I]; C07F0009-094
[I]; C07F0009-653 [I]
IPC IPC1 A61K0031-675 [I]; C07F0009-547 [I]; C07F0009-06 [I]; A61K0031-66
[I]
IPC1-2 A61K0031-675 [I]; A61K0031-661 [I]; C07F0009-572 [I]; C07F0009-06

[I]
IPCR A61K0031-675 [I]; A61K0031-661 [I]; A61P0037-02 [I]; C07D0209-46
[I]; C07D0263-14 [I]; C07F0009-06 [I]; C07F0009-09 [I];
C07F0009-572 [I]; C07F0009-653 [I]
EXF 514/114; 564/15
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 218 OF 256 USPAT2 on STN

Full Text

AN 2009:152815 USPAT2
TI Compounds that modulate intracellular calcium
IN Velicelebi, Gonul, San Diego, CA, UNITED STATES
Stauderman, Kenneth A., San Diego, CA, UNITED STATES
Pleyne, David P. M., San Diego, CA, UNITED STATES
Cheng, Soan, San Diego, CA, UNITED STATES
Whitten, Jeffrey P., Santee, CA, UNITED STATES
PA Calcimedica, Inc., La Jolla, CA, UNITED STATES (U.S. corporation)
PI US 8263641 B2 20120911
AI US 2008-192812 20080815 (12)
PRAI US 2007-971161P 20070910 (60)
DT Utility
FS GRANTED
LN.CNT 6562
INCL INCLM: 514/447.000
INCLS: 549/069.000
NCL NCLM: 514/447.000; 514/443.000
NCLS: 549/069.000; 435/375.000; 549/057.000
CPC CPC1 C07D0333-68 [I]; A61K0031-00 [I]; A61K0031-405 [I]
CPC1-2 C07D0333-68 [I]; A61K0031-00 [I]; A61K0031-405 [I]
IPC IPC1 A61K0031-381 [I]; C12N0005-06 [I]; C07D0409-12 [I]; C07D0333-36
[I]
IPC1-2 A61K0031-381 [I]; C07D0333-36 [I]
IPCR A61K0031-381 [I]; C07D0333-36 [I]
EXF 549/69; 514/447

L2 ANSWER 219 OF 256 USPAT2 on STN

Full Text

AN 2009:32548 USPAT2
TI Use of S1P receptor agonists in heart diseases
IN Brinkmann, Volker, Freiburg, GERMANY, FEDERAL REPUBLIC OF
Feutren, Gilles, Mulhouse, FRANCE
Hof, Robert Paul, Gelterkinden, SWITZERLAND
PA Novartis AG, Basel, SWITZERLAND (non-U.S. corporation)
PI US 7910626 B2 20110322
AI US 2008-244422 20081002 (12)
RLI Continuation of Ser. No. US 1900-521297, ABANDONED A 371 of
International Ser. No. WO 2003-EP8085, filed on 23 Jul 2003
PRAI GB 2002-17152 20020724
DT Utility
FS GRANTED
LN.CNT 517
INCL INCLM: 514/646.000
INCLS: 514/653.000; 558/169.000
NCL NCLM: 514/646.000; 514/020.100
NCLS: 514/653.000; 558/169.000; 514/114.000; 514/357.000; 514/408.000;
514/649.000; 514/651.000
CPC CPC1 A61K0045-06 [I]; A61K0031-13 [I]; A61K0031-137 [I]; A61K0038-2242
[I]; A61K0038-556 [I]
CPC1-2 A61K0045-06 [I]; A61K0031-13 [I]; A61K0031-137 [I]; A61K0038-2242
[I]; A61K0038-556 [I]
IPC IPC1 A61K0038-17 [I]; A61K0031-66 [I]; A61K0031-137 [I]; A61P0009-04
[I]; A61P0009-10 [I]; A61P0009-06 [I]; A61K0031-44 [I];
A61K0031-40 [I]
IPC1-2 A01N0033-02 [I]; A61K0031-135 [I]
IPCR A01N0033-02 [I]; C07D0333-56 [I]; A61K0031-13 [I]; A61K0031-135
[I]; A61K0031-137 [I]; A61K0031-381 [I]; A61K0031-661 [I];
A61K0038-22 [I]; A61K0038-55 [I]; A61K0045-00 [I]; A61K0045-06
[I]; A61P0009-00 [I]; A61P0009-04 [I]; A61P0009-06 [I];
A61P0009-10 [I]; A61P0043-00 [I]
EXF 514/183
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 220 OF 256 USPAT2 on STN

Full Text

AN 2008:333414 USPAT2
TI Heterocyclic substituted pyridine or phenyl compounds with CXCR3 antagonist activity
IN Anilkumar, Gopinadhan N., Edison, NJ, UNITED STATES
Zeng, Qingbei, Edison, NJ, UNITED STATES
Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
Hobbs, Douglas W., Chesterfield, MO, UNITED STATES
PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
Pharmacoepia Drug Discovery, Inc., Princeton, NJ, UNITED STATES (U.S. corporation)
PI US 7799789 B2 20100921
AI US 2008-147140 20080626 (12)
RLI Division of Ser. No. US 2006-353609, filed on 14 Feb 2006, Pat. No. US 7417045
PRAI US 2005-653332P 20050216 (60)
DT Utility
FS GRANTED
LN.CNT 3391
INCL INCLM: 514/253.010
INCLS: 514/253.100; 544/360.000
NCL NCLM: 514/253.010; 424/085.600
NCLS: 514/253.100; 544/360.000; 424/133.100; 514/001.100; 514/002.400; 514/161.000; 514/252.180; 514/253.090; 544/295.000; 544/364.000
CPC CPC I C07D0417-14 [I]; C07D0401-04 [I]; C07D0401-14 [I]; C07D0413-14 [I]
CPCI-2 C07D0417-14 [I]; C07D0401-04 [I]; C07D0401-14 [I]; C07D0413-14 [I]
IPC IPC I A61K0038-21 [I]; C07D0401-14 [I]; A61K0031-496 [I]; A61K0038-13 [I]; A61K0031-573 [I]; A61P0029-00 [I]; A61K0031-505 [I]; A61K0031-606 [I]
IPC I-2 A61K0031-497 [I]; C07D0401-00 [I]
IPCR A61K0031-497 [I]; C07D0401-00 [I]
EXF 514/253.1; 514/253.09; 544/360
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 221 OF 256 USPAT2 on STN

Full Text

AN 2008:327426 USPAT2
TI Use of azapaullones for preventing and treating pancreatic autoimmune disorders
IN Mussmann, Rainer, Gottingen, GERMANY, FEDERAL REPUBLIC OF
Kunick, Conrad Peter, Hamburg, GERMANY, FEDERAL REPUBLIC OF
Stukenbrock, Hendrik, Braunschweig, GERMANY, FEDERAL REPUBLIC OF
Geese, Marcus, Gottingen, GERMANY, FEDERAL REPUBLIC OF
Kegel, Simone, Uslar, GERMANY, FEDERAL REPUBLIC OF
Burk, Ulrike, Gottingen, GERMANY, FEDERAL REPUBLIC OF
PA Develogen Atkiengesellschaft, Goettingen, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)
Technische Universitaet Carolo-Wilhelmina Zu Braunschweig, Braunschweig, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)
PI US 7968535 B2 20110628
WO 2006117221 20061109
AI US 2008-913486 20060504 (11)
WO 2006-EP4186 20060504
20080603 PCT 371 date
PRAI EP 2005-9846 20050504
EP 2005-15986 20050722
EP 2005-23168 20051024
EP 2006-1327 20060123
DT Utility
FS GRANTED
LN.CNT 1719
INCL INCLM: 514/212.060
INCLS: 540/521.000
NCL NCLM: 514/212.060; 514/215.000
NCLS: 540/521.000
CPC CPC I C07D0471-14 [I]; A61K0031-55 [I]; A61K0045-00 [I]; A61K0045-06 [I]

CPCI-2 C07D0471-14 [I]; A61K0031-55 [I]; A61K0045-00 [I]; A61K0045-06 [I]
IPC IPCI A61K0031-55 [I]; C07D0487-14 [I]; A61P0005-48 [I]; A61P0001-18 [I]; A61P0003-10 [I]; A61P0025-28 [I]
IPCI-2 C07D0471-14 [I]; A61K0031-55 [I]
IPCR C07D0471-14 [I]; A61K0031-55 [I]
EXF 540/521; 514/212.06
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 222 OF 256 USPAT2 on STN

Full Text

AN 2008:66423 USPAT2
TI Heterocyclic substituted piperazine compounds with CXCR3 antagonist activity
IN Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
Shih, Neng-Yang, Warren, NJ, UNITED STATES
McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
Hobbs, Douglas W., Chesterfield, MO, UNITED STATES
PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
Pharmacoepia, Inc., Princeton, NJ, UNITED STATES (U.S. corporation)
PI US 7902199 B2 20110308
AI US 2007-776901 20070712 (11)
PRAI US 2006-831053P 20060714 (60)
DT Utility
FS GRANTED
LN.CNT 2698
INCL INCLM: 514/253.130
INCLS: 544/364.000
NCL NCLM: 514/253.130; 514/253.010
NCLS: 544/364.000; 544/360.000
CPC CPCI C07D0401-14 [I]
CPCI-2 C07D0401-14 [I]
IPC IPCI A61K0031-497 [I]; A61P0025-00 [I]; C07D0401-02 [I]
IPCI-2 A61K0031-496 [I]; C07D0401-12 [I]; C07D0401-14 [I]
IPCR A61K0031-496 [I]; C07D0401-12 [I]; C07D0401-14 [I]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 223 OF 256 USPAT2 on STN

Full Text

AN 2008:44907 USPAT2
TI Methods of inhibiting vascular permeability and apoptosis
IN Hla, Timothy, Avon, CT, UNITED STATES
Sanchez, Teresa, West Hartford, CT, UNITED STATES
Claffey, Kevin Patrick, Burlington, CT, UNITED STATES
Paik, Ji-Hye, New Britain, CT, UNITED STATES
PA University of Connecticut, Farmington, CT, UNITED STATES (U.S. corporation)
PI US 7838562 B2 20101123
WO 2005002559 20050113
AI US 2007-562305 20040618 (10)
WO 2004-US19420 20040618
20070309 PCT 371 date
DT Utility
FS GRANTED
LN.CNT 1036
INCL INCLM: 514/646.000
INCLS: 514/653.000; 558/169.000
NCL NCLM: 514/646.000; 514/667.000
NCLS: 514/653.000; 558/169.000
CPC CPCI A61K0031-133 [I]; A61K0031-00 [I]
CPCI-2 A61K0031-133 [I]; A61K0031-00 [I]
IPC IPCI A61K0031-131 [I]; A61P0007-04 [I]; A61P0009-10 [I]
IPCI-2 A01N0033-02 [I]; A61K0031-135 [I]
IPCR A01N0033-02 [I]; A61K0031-00 [I]; A61K0031-133 [I]; A61K0031-135 [I]; A61P0009-00 [I]
EXF 514/183
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 224 OF 256 USPAT2 on STN

Full Text

AN 2008:44851 USPAT2

TI Heterocyclic substituted pyridine compounds with CXCR3 antagonist activity
IN Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
Shih, Neng-Yang, Warren, NJ, UNITED STATES
McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
Hobbs, Douglas W., Yardley, PA, UNITED STATES
PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
PI US 7786124 B2 20100831
AI US 2007-688014 20070319 (11)
PRAI US 2006-784504P 20060321 (60)
DT Utility
FS GRANTED
LN.CNT 3164
INCL INCLM: 514/253.090
INCLS: 514/253.100; 544/364.000
NCL NCLM: 514/253.090; 514/253.010
NCLS: 514/253.100; 544/364.000; 544/360.000
CPC CPCI C07D0401-14 [I]; C07D0413-14 [I]
CPCI-2 C07D0401-14 [I]; C07D0413-14 [I]
IPC IPCI A61K0031-497 [I]; A61P0029-00 [I]; C07D0401-02 [I]
IPCI-2 C07D0413-14 [I]; A61K0031-496 [I]
IPCR C07D0413-14 [I]; A61K0031-496 [I]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 225 OF 256 USPAT2 on STN

Full Text

AN 2007:322602 USPAT2
TI Indole derivatives as inhibitors of histone deacetylase
IN Buggy, Joseph J., Mountain View, CA, UNITED STATES
Balasubramanian, Sriram, San Carlos, CA, UNITED STATES
Verner, Erik, San Mateo, CA, UNITED STATES
Tai, Vincent W. F., San Mateo, CA, UNITED STATES
Lee, Chang-Sun, Belle Mead, NJ, UNITED STATES
PA Pharmacylics, Inc., Sunnyvale, CA, UNITED STATES (U.S. corporation)
PI US 8338416 B2 20121225
AI US 2007-687565 20070316 (11)
PRAI US 2006-783287P 20060316 (60)
DT Utility
FS GRANTED
LN.CNT 7187
INCL INCLM: 514/235.200
INCLS: 514/320.000; 514/415.000; 544/143.000; 546/201.000; 548/452.000
NCL NCLM: 514/235.200
NCLS: 514/320.000; 514/415.000; 544/143.000; 546/201.000; 548/452.000
CPC CPCI A61K0031-405 [I]; A61K0031-55 [I]; A61K0045-06 [I]; C07D0209-08 [I]; C07D0209-12 [I]; C07D0209-14 [I]
CPCI-2 A61K0031-405 [I]; A61K0031-55 [I]; A61K0045-06 [I]; C07D0209-08 [I]; C07D0209-12 [I]; C07D0209-14 [I]
IPC IPCI C07D0209-04 [I]; A61K0031-404 [I]; A61K0031-4523 [I]; A61K0031-5377 [I]; C07D0413-02 [I]; C07D0401-02 [I]; A61P0035-00 [I]; A61P0035-02 [I]
IPCI-2 C07D0401-02 [I]; C07D0209-04 [I]; C07D0413-02 [I]; A61K0031-404 [I]; A61K0031-4523 [I]; A61K0031-5377 [I]; A61P0035-00 [I]; A61P0035-02 [I]
IPCR C07D0401-02 [I]; A61K0031-404 [I]; A61K0031-4523 [I]; A61K0031-5377 [I]; A61P0035-00 [I]; A61P0035-02 [I]; C07D0209-04 [I]; C07D0413-02 [I]

L2 ANSWER 226 OF 256 USPAT2 on STN

Full Text

AN 2007:191244 USPAT2
TI Compound capable of binding S1P receptor and pharmaceutical use thereof
IN Nakade, Shinji, Tsukuba, JAPAN
Mizuno, Hirotaka, Tsukuba, JAPAN
Ono, Takeji, Tsukuba, JAPAN
Minami, Masashi, Tsukuba, JAPAN
Saga, Hiroshi, Tsukuba, JAPAN
Hagiya, Hiroshi, Tsukuba, JAPAN
Komiya, Takaki, Tsukuba, JAPAN
Habashita, Hiromu, Mishima-gun, JAPAN
Kurata, Haruto, Mishima-gun, JAPAN

Ohtsuki, Kazuhiro, Mishima-gun, JAPAN
 Kusumi, Kensuke, Mishima-gun, JAPAN
 PA Ono Pharmaceutical Co., Ltd., Osaka, JAPAN (non-U.S. corporation)
 PI US 7825109 B2 20101102
 WO 2005020882 20050310
 AI US 2006-569831 20040827 (10)
 WO 2004-JP12768 20040827
 20060228 PCT 371 date
 PRAI JP 2003-306088 20030829
 JP 2004-110573 20040402
 JP 2004-169958 20040608
 JP 2004-198523 20040705
 DT Utility
 FS GRANTED
 LN.CNT 7161
 INCL INCLM: 514/210.170
 INCLS: 548/953.000
 NCL NCLM: 514/210.170
 NCLS: 548/953.000; 514/319.000; 514/419.000; 514/567.000; 546/205.000;
 548/495.000; 562/444.000
 CPC CPCI C07D0205-04 [I]; C07C0229-14 [I]; C07C0229-22 [I]; C07C0229-36
 [I]; C07C0233-47 [I]; C07C0255-16 [I]; C07C0255-41 [I];
 C07C0271-22 [I]; C07C0323-12 [I]; C07C2101-08; C07C2101-14;
 C07D0211-70 [I]; C07D0217-04 [I]
 CPCI-2 C07D0205-04 [I]; C07C0229-14 [I]; C07C0229-22 [I]; C07C0229-36
 [I]; C07C0233-47 [I]; C07C0255-16 [I]; C07C0255-41 [I];
 C07C0271-22 [I]; C07C0323-12 [I]; C07C2101-08; C07C2101-14;
 C07D0211-70 [I]; C07D0217-04 [I]
 IPC IPCI A61K0031-445 [I]; A61K0031-405 [I]; A61K0031-197 [I];
 A61K0031-397 [I]; A61K0031-198 [I]
 IPCI-2 C07D0205-00 [I]; A61K0031-397 [I]
 IPCR C07D0205-00 [I]; A61K [I]; A61K0031-11 [I]; A61K0031-135 [I];
 A61K0031-197 [I]; A61K0031-198 [I]; A61K0031-222 [I]; A61K0031-27
 [I]; A61K0031-277 [I]; A61K0031-397 [I]; A61K0031-472 [I];
 A61K0045-00 [I]; A61P0037-06 [I]; A61P0037-08 [I]; A61P0043-00
 [I]; C07C0229-14 [I]; C07C0229-22 [I]; C07C0229-36 [I];
 C07C0233-47 [I]; C07C0255-16 [I]; C07C0255-41 [I]; C07C0271-22
 [I]; C07D0205-04 [I]; C07D0211-04 [I]; C07D0217-04 [I];
 C07D0405-06 [I]

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 227 OF 256 USPAT2 on STN

Full Text

AN 2007:95211 USPAT2
 TI Substituted heterocyclic compounds with CXCR3 antagonist activity
 IN Kim, Seong Heon, Livingston, NJ, UNITED STATES
 Shankar, Bandarpalle B., Branchburg, NJ, UNITED STATES
 Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
 Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
 Shih, Neng-Yang, Warren, NJ, UNITED STATES
 PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
 PI US 7781437 B2 20100824
 AI US 2006-545201 20061010 (11)
 PRAI US 2005-725483P 20051011 (60)
 DT Utility
 FS GRANTED
 LN.CNT 2367
 INCL INCLM: 514/252.110
 INCLS: 544/359.000; 544/405.000; 544/408.000; 546/207.000; 546/245.000;
 548/131.000; 548/215.000; 548/250.000; 548/255.000; 548/311.100
 NCL NCLM: 514/252.110
 NCLS: 544/359.000; 544/405.000; 544/408.000; 546/207.000; 546/245.000;
 548/131.000; 548/215.000; 548/250.000; 548/255.000; 548/311.100;
 514/253.010; 544/357.000; 544/364.000
 CPC CPCI C07D0401-14 [I]; C07D0401-08 [I]; C07D0413-14 [I]
 CPCI-2 C07D0401-14 [I]; C07D0401-08 [I]; C07D0413-14 [I]
 IPC IPCI A61K0031-497 [I]; A61K0031-496 [I]; C07D0403-14 [I]
 IPCI-2 A61K0031-497 [I]
 IPCR A61K0031-497 [I]
 EXF 544/359

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 228 OF 256 USPAT2 on STN

Full Text

AN 2007:62774 USPAT2
TI Pyrazinyl substituted piperazine-piperidines with CXCR3 antagonist activity
IN Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
Kim, Seong Heon, Livingston, NJ, UNITED STATES
Zeng, Qingbei, Edison, NJ, UNITED STATES
Wong, Michael K. C., North Brunswick, NJ, UNITED STATES
Anilkumar, Gopinadhan N., Edison, NJ, UNITED STATES
Jiang, Yueheng, Whitehouse Station, NJ, UNITED STATES
Yu, Wensheng, Edison, NJ, UNITED STATES
Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
Shih, Neng-Yang, Warren, NJ, UNITED STATES
Shankar, Bandarpalle B., Branchburg, NJ, UNITED STATES
McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
Dong, Guizhen, Dayton, NJ, UNITED STATES
Zawacki, Lisa Guise, Yardley, PA, UNITED STATES
Hobbs, Douglas W., Yardley, PA, UNITED STATES
Baldwin, John J., Gwynedd Valley, PA, UNITED STATES
Shao, Yuefei, Princeton, NJ, UNITED STATES
PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
PI US 7868005 B2 20110111
AI US 2006-354138 20060214 (11)
PRAI US 2005-653338P 20050216 (60)
DT Utility
FS GRANTED
LN.CNT 3899
INCL INCLM: 514/252.110
INCLS: 544/357.000; 544/229.000; 514/063.000
NCL NCLM: 514/252.110
NCLS: 514/063.000; 544/229.000; 544/357.000
CPC CPCI C07D0405-14 [I]; C07D0401-12 [I]; C07D0401-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
CPCI-2 C07D0405-14 [I]; C07D0401-12 [I]; C07D0401-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
IPC IPCI A61K0031-497 [I]; C07D0403-14 [I]
IPCI-2 C07D0241-04 [I]; C07D0401-14 [I]; A61K0031-443 [I]; A61K0031-4433 [I]; A61K0031-4439 [I]; A61K0031-444 [I]; A61K0031-4436 [I]; A61K0031-695 [I]; C07F0007-18 [I]; A61P0025-28 [N]; A61P0035-00 [N]; A61P0029-00 [N]
IPCR C07D0241-04 [I]; A61K0031-443 [I]; A61K0031-4433 [I]; A61K0031-4436 [I]; A61K0031-4439 [I]; A61K0031-444 [I]; A61K0031-695 [I]; A61P0025-28 [N]; A61P0029-00 [N]; A61P0035-00 [N]; C07D0401-14 [I]; C07F0007-18 [I]
EXF 514/252.11; 544/357
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 229 OF 256 USPAT2 on STN

Full Text

AN 2007:36890 USPAT2
TI Peptides and peptide mimetics to treat pathologies characterized by an inflammatory response
IN Fogelman, Alan M., Beverly Hills, CA, UNITED STATES
Navab, Mohamad, Los Angeles, CA, UNITED STATES
Anantharamaiah, Gattadahalli M., Birmingham, AL, UNITED STATES
PA The Regents of the University of California, Oakland, CA, UNITED STATES (U.S. corporation)
The UAB Research Foundation, Birmingham, AL, UNITED STATES (U.S. corporation)
PI US 7723303 B2 20100525
AI US 2006-407390 20060418 (11)
RLI Continuation-in-part of Ser. No. US 2003-423830, filed on 25 Apr 2003, Pat. No. US 7199102, issued on 3 Apr 2007 Continuation-in-part of Ser. No. US 2002-273386, filed on 16 Oct 2002, Pat. No. US 7166578, issued on 23 Jan 2007 Continuation-in-part of Ser. No. US 2002-187215, filed on 28 Jun 2002, Pat. No. US 7144862, issued on 5 Dec 2006 Continuation-in-part of Ser. No. US 2001-896841, filed on 29 Jun 2001, Pat. No. US 6933279, issued on 23 Aug 2005 Continuation-in-part of Ser. No. US 2000-645454, filed on 24 Aug 2000, Pat. No. US 6664230, issued on 16 Dec 2003
PRAI US 2005-697495P 20050707 (60)
US 2005-676431P 20050429 (60)

DT Utility
 FS GRANTED
 LN.CNT 11426
 INCL INCLM: 514/013.000
 INCLS: 424/424.000; 530/326.000; 623/001.420
 NCL NCLM: 435/006.160
 NCLS: 424/424.000; 514/001.400; 514/001.500; 514/001.900; 514/002.100;
 514/002.400; 514/003.200; 514/003.800; 514/007.300; 514/013.200;
 514/015.400; 514/016.400; 514/016.800; 514/016.900; 514/017.800;
 514/017.900; 514/018.200; 514/019.400; 530/326.000; 623/001.420
 CPC CPCI A61L0031-16 [I]; A61K0038-00; A61L2300-25; A61L2300-40;
 C07K0007-08 [I]; C07K0014-775 [I]
 CPCI-2 A61L0031-16 [I]; A61K0038-00; A61L2300-25; A61L2300-40;
 C07K0007-08 [I]; C07K0014-775 [I]
 IPC IPCI A61K0038-10 [I]; C07K0007-08 [I]
 IPCI-2 A61F0002-82 [I]; A61K0038-10 [I]; C07K0007-08 [I]
 IPCR A61F0002-82 [I]; A61K0038-10 [I]; C07K0007-08 [I]
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 230 OF 256 USPAT2 on STN

Full Text

AN 2007:29810 USPAT2
 TI Pharmaceutical co-crystal compositions
 IN Almarsson, Orn, Shrewsbury, MA, UNITED STATES
 Bourghol Hickey, Magali, Medford, MA, UNITED STATES
 Peterson, Matthew L., Framingham, MA, UNITED STATES
 Zaworotko, Michael J., Tampa, FL, UNITED STATES
 Moulton, Brian, Providence, RI, UNITED STATES
 Rodriguez-Hornedo, Nair, Ann Arbor, MI, UNITED STATES
 PA University of South Florida, Tampa, FL, UNITED STATES (U.S. corporation)
 The Regents of the University of Michigan, Ann Arbor, MI, UNITED STATES
 (U.S. corporation)
 Transform Pharmaceuticals, Inc., Lexington, MA, UNITED STATES (U.S.
 corporation)
 PI US 7927613 B2 20110419
 AI US 2003-660202 20030911 (10)
 RLI Continuation-in-part of Ser. No. WO 2003-US27772, filed on 4 Sep 2003,
 PENDING Continuation-in-part of Ser. No. US 2003-378956, filed on 1 Mar
 2003, PENDING Continuation-in-part of Ser. No. US 1900-660022, PENDING
 Continuation-in-part of Ser. No. US 2003-637829, filed on 8 Aug 2003,
 ABANDONED Division of Ser. No. US 2002-295995, filed on 18 Nov 2002,
 Pat. No. US 6699840 Continuation of Ser. No. US 2002-232589, filed on 3
 Sep 2002, Pat. No. US 6559293 Continuation of Ser. No. US 1900-660202,
 PENDING Continuation-in-part of Ser. No. US 2003-601092, filed on 20 Jun
 2003, ABANDONED Continuation-in-part of Ser. No. US 2003-449307, filed
 on 30 May 2003, Pat. No. US 7078526
 PRAI US 2002-360768P 20020301 (60)
 US 2003-451213P 20030228 (60)
 US 2003-463962P 20030418 (60)
 US 2003-487064P 20030711 (60)
 US 2002-406974P 20020830 (60)
 US 2002-380288P 20020515 (60)
 US 2002-356764P 20020215 (60)
 US 2003-444315P 20030131 (60)
 US 2003-439282P 20030110 (60)
 US 2002-384152P 20020531 (60)

DT Utility
 FS GRANTED
 LN.CNT 23308
 INCL INCLM: 424/400.000
 INCLS: 514/217.000; 514/403.000
 NCL NCLM: 424/400.000; 424/489.000
 NCLS: 514/217.000; 514/403.000
 CPC CPCI A61K0009-145 [I]; A61K0009-0004; A61K0009-1617 [I]; A61K0009-1652
 [I]; A61K0009-2077 [I]; A61K0009-209; A61K0031-167 [I];
 A61K0031-192 [I]; A61K0031-4166 [I]; A61K0031-55 [I];
 A61K0031-616 [I]; A61K0047-10 [I]; A61K0047-32 [I]; C07C0051-412
 [I]; C07C0051-43 [I]; C07C0233-25 [I]; C07D0223-26 [I];
 C07D0233-74 [I]; C07D0495-04 [I]
 CPCI-2 A61K0009-145 [I]; A61K0009-0004; A61K0009-1617 [I]; A61K0009-1652
 [I]; A61K0009-2077 [I]; A61K0009-209; A61K0031-167 [I];
 A61K0031-192 [I]; A61K0031-4166 [I]; A61K0031-55 [I];

A61K0031-616 [I]; A61K0047-10 [I]; A61K0047-32 [I]; C07C0051-412 [I]; C07C0051-43 [I]; C07C0233-25 [I]; C07D0223-26 [I]; C07D0233-74 [I]; C07D0495-04 [I]
IPC IPCI A61K0009-14 [I]
IPCI-2 A61K0009-00 [I]; A01N0043-46 [I]; A01N0043-56 [I]
IPCR A61K0009-00 [I]; A01N0043-46 [I]; A01N0043-56 [I]
EXF 424/400; 514/217; 514/403
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 231 OF 256 USPAT2 on STN

Full Text

AN 2007:24566 USPAT2
TI Pyridyl and phenyl substituted piperazine-piperidines with CXCR3 antagonist activity
IN McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
Anilkumar, Gopinadhan N., Edison, NJ, UNITED STATES
Kim, Seong Heon, Livingston, NJ, UNITED STATES
Shih, Neng-Yang, Warren, NJ, UNITED STATES
Jenh, Chung-Her, Annandale, NJ, UNITED STATES
Zavodny, Paul J., Mountainside, NJ, UNITED STATES
Hobbs, Douglas W., Yardley, PA, UNITED STATES
Dong, Guizhen, Dayton, NJ, UNITED STATES
Shao, Yuefei, Princeton, NJ, UNITED STATES
Zawacki, Lisa Guise, Yardley, PA, UNITED STATES
Yang, Cangmeng, Highland Park, NJ, UNITED STATES
Carroll, Carolyn Dilanni, Yardley, PA, UNITED STATES
PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
PI US 7776862 B2 20100817
AI US 2006-353697 20060214 (11)
PRAI US 2005-653337P 20050216 (60)
DT Utility
FS GRANTED
LN.CNT 4037
INCL INCLM: 514/253.010
INCLS: 514/253.090; 514/253.100; 514/253.110; 514/253.130; 544/360.000
NCL NCLM: 514/253.010; 544/360.000
NCLS: 514/253.090; 514/253.100; 514/253.110; 514/253.130; 544/360.000
CPC CPCI C07D0401-12 [I]; C07D0211-58 [I]; C07D0401-14 [I]; C07D0405-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
CPCI-2 C07D0401-12 [I]; C07D0211-58 [I]; C07D0401-14 [I]; C07D0405-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
IPC IPCI C07D0401-00 [I]
IPCI-2 A61K0031-497 [I]; C07D0401-00 [I]
IPCR A61K0031-497 [I]; C07D0401-00 [I]
EXF 514/253.11; 514/253.13; 514/253.01; 514/253.09; 514/253.1; 544/360
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 232 OF 256 USPAT2 on STN

Full Text

AN 2007:18124 USPAT2
TI Pharmaceutical propylene glycol solvate compositions
IN Tawa, Mark, Brighton, MA, UNITED STATES
Almarsson, Orn, Shrewsbury, MA, UNITED STATES
Remenar, Julius, Framingham, MA, UNITED STATES
PA McNeil-PPC, Inc., Skillman, NJ, UNITED STATES (U.S. corporation)
PI US 7790905 B2 20100907
AI US 2003-747742 20031229 (10)
PRAI US 2003-486713P 20030711 (60)
US 2003-459501P 20030401 (60)
US 2003-456608P 20030321 (60)
US 2003-456027P 20030318 (60)
US 2003-441335P 20030121 (60)
US 2002-437516P 20021230 (60)
DT Utility
FS GRANTED
LN.CNT 17727
INCL INCLM: 548/375.100
INCLS: 514/406.000
NCL NCLM: 548/375.100; 514/738.000
CPC CPCI C07D0495-04 [I]

CPCI-2 C07D0495-04 [I]
IPC IPCI A61K0031-045 [I]
IPCI-2 C07D0231-12 [I]; A61K0031-415 [I]
IPCR C07D0231-12 [I]; A61K0031-415 [I]
EXF 424/246; 514/220; 514/557; 514/406; 548/375.1
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 233 OF 256 USPAT2 on STN

Full Text

AN 2007:11103 USPAT2
TI Methods for treating immune disorders associated with graft
transplantation with soluble CTLA4 mutant molecules
IN Hagerty, David, Pennington, NJ, UNITED STATES
Rusnak, James, Newtown, PA, UNITED STATES
PA Bristol-Myers Squibb Company, Princeton, NJ, UNITED STATES (U.S.
corporation)
PI US 7482327 B2 20090127
AI US 2006-399666 20060406 (11)
PRAI US 2005-668774P 20050406 (60)
DT Utility
FS GRANTED
LN.CNT 4097
INCL INCLM: 514/012.000
INCLS: 424/134.100
NCL NCLM: 514/001.100; 424/133.100
NCLS: 424/134.100; 424/185.100
CPC CPCI A61K0031-00 [I]; A61K0009-0019; A61K0031-436 [I]; A61K0031-5377
[I]; A61K0031-573 [I]; A61K0038-1774 [I]; A61K0039-395 [I];
C07K2319-30
CPCI-2 A61K0031-00 [I]; A61K0009-0019; A61K0031-436 [I]; A61K0031-5377
[I]; A61K0031-573 [I]; A61K0038-1774 [I]; A61K0039-395 [I];
C07K2319-30
IPC IPCI A61K0039-395 [I]; A61K0039-00 [I]
IPCI-2 A61K0038-16 [I]
IPCR A61K0038-16 [I]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 234 OF 256 USPAT2 on STN

Full Text

AN 2006:327552 USPAT2
TI Modulation of NKG2D for treating or preventing solid organ allograft
rejection
IN Kang, Sang-Mo, San Francisco, CA, UNITED STATES
Lanier, Lewis L., San Francisco, CA, UNITED STATES
PA The Regents of the University of California, Oakland, CA, UNITED STATES
(U.S. corporation)
PI US 7998481 B2 20110816
AI US 2006-429354 20060505 (11)
RLI Continuation-in-part of Ser. No. WO 2005-US11487, filed on 5 Apr 2005,
PENDING
PRAI US 2005-659678P 20050307 (60)
US 2004-576242P 20040601 (60)
US 2004-559919P 20040405 (60)
DT Utility
FS GRANTED
LN.CNT 3392
INCL INCLM: 424/139.100
INCLS: 424/577.000; 514/885.000
NCL NCLM: 424/139.100; 424/204.100
NCLS: 424/577.000; 514/885.000; 424/130.100
CPC CPCI C07K0016-2851 [I]; A61K2039-505; C07K2316-96; C07K2317-73;
Y10S0514-885
CPCI-2 C07K0016-2851 [I]; A61K2039-505; C07K2316-96; C07K2317-73;
Y10S0514-885
IPC IPCI A61K0039-395 [I]; A61K0039-12 [I]
IPCI-2 A61K0039-40 [I]; A61K0035-28 [I]; A01N0025-00 [I]
IPCR A61K0039-40 [I]; A01N0025-00 [I]; A61K0035-28 [I]

L2 ANSWER 235 OF 256 USPAT2 on STN

Full Text

AN 2006:322435 USPAT2
TI Amine-linked pyridyl and phenyl substituted piperazine-piperidines with

CXCR3 antagonist activity

IN Wong, Michael K. C., North Brunswick, NJ, UNITED STATES
 Shu, Youheng, Blue Bell, PA, UNITED STATES
 Yu, Wensheng, Edison, NJ, UNITED STATES
 Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
 Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
 McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
 Shao, Yuefei, Princeton, NJ, UNITED STATES
 Hobbs, Douglas W., Yardley, PA, UNITED STATES

PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
 Pharmacoepia Drug Discovery, Inc., Princeton, NJ, UNITED STATES (U.S. corporation)

PI US 7566718 B2 20090728
 AI US 2006-354328 20060214 (11)
 PRAI US 2005-653339P 20050216 (60)
 DT Utility
 FS GRANTED
 LN.CNT 3775
 INCL INCLM: 514/253.010
 INCLS: 544/360.000; 544/364.000
 NCL NCLM: 514/253.010
 NCLS: 544/360.000; 544/364.000
 CPC CPCI C07D0401-14 [I]; C07D0211-58 [I]; C07D0401-12 [I]; C07D0405-14 [I]; C07D0409-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
 CPCI-2 C07D0401-14 [I]; C07D0211-58 [I]; C07D0401-12 [I]; C07D0405-14 [I]; C07D0409-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
 IPC IPCI A61K0031-496 [I]; C07D0403-14 [I]
 IPCI-2 A61K0031-497 [I]; C07D0401-00 [I]; C07D0403-00 [I]; C07D0405-00 [I]; C07D0409-00 [I]
 IPCR A61K0031-497 [I]; C07D0401-00 [I]; C07D0403-00 [I]; C07D0405-00 [I]; C07D0409-00 [I]
 EXF 514/253.01; 544/364
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 236 OF 256 USPAT2 on STN

Full Text

AN 2006:322434 USPAT2

TI Heterocyclic substituted piperazines with CXCR3 antagonist activity

IN Kim, Seong Heon, Livingston, NJ, UNITED STATES
 Anilkumar, Gopinadhan N., Edison, NJ, UNITED STATES
 Wong, Michael K. C., North Brunswick, NJ, UNITED STATES
 Zeng, Qingbei, Edison, NJ, UNITED STATES
 Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
 Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
 Shao, Yuefei, Princeton, NJ, UNITED STATES
 McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
 Hobbs, Douglas W., Yardley, PA, UNITED STATES

PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
 Pharmacoepia Drug Discovery, Inc., Princeton, NJ, UNITED STATES (U.S. corporation)

PI US 7868006 B2 20110111
 AI US 2006-353641 20060214 (11)
 PRAI US 2005-653309P 20050216 (60)
 DT Utility
 FS GRANTED
 LN.CNT 3895
 INCL INCLM: 514/252.120
 INCLS: 544/357.000
 NCL NCLM: 514/252.120
 NCLS: 544/357.000
 CPC CPCI C07D0401-12 [I]; C07D0401-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
 CPCI-2 C07D0401-12 [I]; C07D0401-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]
 IPC IPCI A61K0031-497 [I]; C07D0413-14 [I]; C07D0403-14 [I]
 IPCI-2 A61K0031-497 [I]; C07D0241-02 [I]
 IPCR A61K0031-497 [I]; C07D0241-02 [I]
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 237 OF 256 USPAT2 on STN

Full Text

AN 2006:322412 USPAT2

TI Piperazine-piperidines with CXCR3 antagonist activity
 IN Yu, Wensheng, Edison, NJ, UNITED STATES
 Kim, Seong Heon, Livingston, NJ, UNITED STATES
 Anilkumar, Gopinadhan N., Edison, NJ, UNITED STATES
 Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
 Shankar, Bandarpalle B., Branchburg, NJ, UNITED STATES
 McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
 Hobbs, Douglas W., Yardley, PA, UNITED STATES
 Shao, Yuefei, Princeton, NJ, UNITED STATES
 PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
 PI US 7763616 B2 20100727
 AI US 2006-353806 20060214 (11)
 PRAI US 2005-653378P 20050216 (60)
 DT Utility
 FS GRANTED
 LN.CNT 2577
 INCL INCLM: 514/249.000
 INCLS: 540/460.000; 540/502.000; 540/557.000; 544/350.000; 544/258.000;
 544/357.000; 544/229.000; 544/393.000; 544/360.000; 544/364.000;
 544/354.000; 514/253.010; 514/183.000; 514/221.000; 514/220.000;
 514/253.090
 NCL NCLM: 514/249.000; 514/221.000
 NCLS: 514/183.000; 514/220.000; 514/221.000; 514/253.010; 514/253.090;
 540/460.000; 540/502.000; 540/557.000; 544/229.000; 544/258.000;
 544/350.000; 544/354.000; 544/357.000; 544/360.000; 544/364.000;
 544/393.000; 514/251.000; 544/256.000
 CPC CPCI C07D0487-04 [I]; C07D0401-12 [I]
 CPCI-2 C07D0487-04 [I]; C07D0401-12 [I]
 IPC IPCI A61K0031-551 [I]; A61K0031-498 [I]; A61K0031-496 [I];
 A61K0031-525 [I]; C07D0487-02 [I]; C07D0475-02 [I]
 IPCI-2 A61K0031-5025 [I]; A61K0031-4985 [I]; C07D0245-02 [I];
 C07D0255-02 [I]; C07D0257-08 [I]; C07D0259-00 [I]; C07D0239-04
 [I]; C07D0239-70 [I]; C07D0471-04 [I]; C07D0487-04 [I];
 A61K0031-497 [N]; C07D0241-36 [N]; C07D0401-14 [N]; C07D0403-14
 [N]; C07D0405-14 [N]; C07D0409-14 [N]; A61P0029-00 [N];
 A61P0017-06 [N]; A61P0019-02 [N]; A61P0003-10 [N]; A61P0031-08
 [N]
 IPCR A61K0031-5025 [I]; A61K0031-497 [N]; A61K0031-4985 [I];
 A61P0003-10 [N]; A61P0017-06 [N]; A61P0019-02 [N]; A61P0029-00
 [N]; A61P0031-08 [N]; C07D0239-04 [I]; C07D0239-70 [I];
 C07D0241-36 [N]; C07D0245-02 [I]; C07D0255-02 [I]; C07D0257-08
 [I]; C07D0259-00 [I]; C07D0401-14 [N]; C07D0403-14 [N];
 C07D0405-14 [N]; C07D0409-14 [N]; C07D0471-04 [I]; C07D0487-04
 [I]
 EXF 514/249; 514/183; 514/221; 514/220; 540/460; 540/501; 540/502; 540/557;
 544/350; 544/249; 544/258
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 238 OF 256 USPAT2 on STN

Full Text

AN 2006:322403 USPAT2
 TI Heteroaryl substituted pyrazinyl-piperazine-piperidines with CXCR3
 antagonist activity
 IN Zeng, Qingbei, Edison, NJ, UNITED STATES
 Yang, De-Yi, Morris Plains, NJ, UNITED STATES
 Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
 Wong, Michael K. C., North Brunswick, NJ, UNITED STATES
 Anilkumar, Gopinadhan N., Edison, NJ, UNITED STATES
 Kim, Seong Heon, Livingston, NJ, UNITED STATES
 Yu, Wensheng, Edison, NJ, UNITED STATES
 Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
 Shih, Neng-Yang, Warren, NJ, UNITED STATES
 McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
 Zawacki, Lisa Guise, Yardley, PA, UNITED STATES
 Hobbs, Douglas W., Yardley, PA, UNITED STATES
 PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
 Pharmacoepia Drug Discovery, Inc., Princeton, NJ, UNITED STATES (U.S.
 corporation)
 PI US 7879838 B2 20110201
 AI US 2006-353474 20060214 (11)
 PRAI US 2005-653477P 20050216 (60)
 DT Utility

FS GRANTED
LN.CNT 3361
INCL INCLM: 514/210.200
INCLS: 514/235.500; 514/252.110; 544/120.000; 544/295.000; 544/357.000
NCL NCLM: 514/210.200
NCLS: 514/235.500; 514/252.110; 544/120.000; 544/295.000; 544/357.000
CPC CPCI C07D0401-12 [I]; C07D0401-14 [I]; C07D0405-14 [I]; C07D0409-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]; C07D0487-04 [I]
CPCI-2 C07D0401-12 [I]; C07D0401-14 [I]; C07D0405-14 [I]; C07D0409-14 [I]; C07D0413-14 [I]; C07D0417-14 [I]; C07D0487-04 [I]
IPC IPCI A61K0031-5377 [I]; A61K0031-506 [I]; A61K0031-497 [I]; C07D0413-14 [I]; C07D0403-14 [I]
IPCI-2 A01N0043-00 [I]; A61K0031-00 [I]; A61K0031-535 [I]; A61K0031-497 [I]; C07D0413-00 [I]; C07D0403-00 [I]; C07D0241-02 [I]
IPCR A01N0043-00 [I]; A61K0031-00 [I]; A61K0031-497 [I]; A61K0031-535 [I]; C07D0241-02 [I]; C07D0403-00 [I]; C07D0413-00 [I]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 239 OF 256 USPAT2 on STN

Full Text

AN 2006:308790 USPAT2
TI Aminopropanol derivatives
IN Albert, Rainer, Basel, SWITZERLAND
Francotte, Eric, Nuglar, SWITZERLAND
Zecri, Frederic, Bartenheim, FRANCE
Zollinger, Markus, Mohlin, SWITZERLAND
PA Novartis AG, Basel, SWITZERLAND (non-U.S. corporation)
PI US 7528120 B2 20090505
WO 2005021503 20050310
AI US 2006-569696 20040827 (10)
WO 2004-EP9589 20040827
PRAI GB 2003-20196 20060227 PCT 371 date
GB 2003-24206 20030828
20031015
DT Utility
FS GRANTED
LN.CNT 1100
INCL INCLM: 514/080.000
INCLS: 548/414.000
NCL NCLM: 514/080.000
NCLS: 548/414.000
CPC CPCI C07F0009-5728 [I]; C07D0209-46 [I]; C07D0263-14 [I]; C07F0009-094 [I]; C07F0009-653 [I]
CPCI-2 C07F0009-5728 [I]; C07D0209-46 [I]; C07D0263-14 [I]; C07F0009-094 [I]; C07F0009-653 [I]
IPC IPCI A61K0031-675 [I]; C07F0009-547 [I]
IPCI-2 A61K0031-675 [I]; C07F0009-572 [I]
IPCR A61K0031-675 [I]; A61P0037-02 [I]; C07D0209-46 [I]; C07D0263-14 [I]; C07F0009-09 [I]; C07F0009-572 [I]; C07F0009-653 [I]
EXF 548/414; 548/470; 548/472; 514/80
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 240 OF 256 USPAT2 on STN

Full Text

AN 2006:254936 USPAT2
TI Heterocyclic substituted pyridine or phenyl compounds with CXCR3 antagonist activity
IN Anilkumar, Gopinadhan N., Edison, NJ, UNITED STATES
Zeng, Qingbei, Edison, NJ, UNITED STATES
Rosenblum, Stuart B., West Orange, NJ, UNITED STATES
Kozlowski, Joseph A., Princeton, NJ, UNITED STATES
McGuinness, Brian F., Plainsboro, NJ, UNITED STATES
Hobbs, Douglas W., Yardley, PA, UNITED STATES
PA Schering Corporation, Kenilworth, NJ, UNITED STATES (U.S. corporation)
Pharmacoepia Inc., Princeton, NJ, UNITED STATES (U.S. corporation)
PI US 7417045 B2 20080826
AI US 2006-353609 20060214 (11)
PRAI US 2005-653332P 20050216 (60)
DT Utility
FS GRANTED
LN.CNT 3506
INCL INCLM: 514/252.120

INCLS: 544/358.000; 544/359.000
NCL NCLM: 514/253.010
NCLS: 544/364.000
CPC CPCI C07D0417-14 [I]; C07D0401-04 [I]; C07D0401-14 [I]; C07D0413-14 [I]
IPC IPCI C07D0403-14 [I]; A61K0031-496 [I]
IPCR C07D0403-14 [I]; A61K0031-496 [I]
EXF 544/358; 544/359; 514/252.12
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 241 OF 256 USPAT2 on STN

Full Text

AN 2006:215518 USPAT2
TI Pharmaceutical composition consisting of rapamycine and gastrin 17(LEU15) and a method for treating diabetes
IN Brand, Stephen J., Lincoln, MA, UNITED STATES
Cruz, Antonio, Toronto, CANADA
PA Waratah Pharmaceuticals Inc., Toronto, Ontario, CANADA (non-U.S. corporation)
PI US 7560425 B2 20090714
WO 2003103701 20031218
AI US 2006-517135 20030609 (10)
WO 2003-US18377 20030609
20060217 PCT 371 date
DT Utility
FS GRANTED
LN.CNT 1920
INCL INCLM: 514/002.000
INCLS: 530/300.000; 530/309.000; 424/198.100; 524/026.000
NCL NCLM: 514/001.100; 514/009.600
NCLS: 424/198.100; 514/006.900; 514/012.300; 514/012.600; 524/026.000; 530/300.000; 530/309.000; 514/109.000; 514/171.000; 514/232.500; 514/251.000; 514/263.310; 514/291.000; 514/651.000
CPC CPCI A61K0038-2207 [I]; A61K0031-436 [I]; A61K0031-522 [I]; A61K0031-525 [I]; A61K0031-535 [I]; A61K0031-5377 [I]; A61K0031-573 [I]; A61K0031-663 [I]; A61K0038-1808 [I]; A61K0038-21 [I]; A61K0038-28 [I]; A61K0045-06 [I]
CPCI-2 A61K0038-2207 [I]; A61K0031-436 [I]; A61K0031-522 [I]; A61K0031-525 [I]; A61K0031-535 [I]; A61K0031-5377 [I]; A61K0031-573 [I]; A61K0031-663 [I]; A61K0038-1808 [I]; A61K0038-21 [I]; A61K0038-28 [I]; A61K0045-06 [I]
IPC IPCI A61K0038-18 [I]; A61K0038-13 [I]; A61K0031-522 [I]; A61K0031-5377 [I]; A61K0031-663 [I]; A61K0031-573 [I]; A61K0031-535 [I]; A61K0031-525 [I]
IPCI-2 A61K0038-00 [I]; A01N0045-00 [I]
IPCR A61K0038-00 [I]; A61K0045-06 [I]; A01N0045-00 [I]; A61K0031-133 [I]; A61K0031-135 [I]; A61K0031-136 [I]; A61K0031-14 [I]; A61K0031-343 [I]; A61K0031-436 [I]; A61K0031-519 [I]; A61K0031-52 [I]; A61K0031-573 [I]; A61K0031-675 [I]; A61K0038-18 [I]; A61K0038-21 [I]; A61K0038-22 [I]; A61K0038-28 [I]; A61K0039-395 [I]; A61K0048-00 [N]; A61P0003-10 [I]; A61P0037-06 [I]; A61P0043-00 [I]

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 242 OF 256 USPAT2 on STN

Full Text

AN 2005:268813 USPAT2
TI Medicinal compositions for preventing or treating viral myocarditis
IN Matsumori, Akira, Minoh, JAPAN
PA Mitsubishi Tanabe Pharma Corporation, Osaka, JAPAN (non-U.S. corporation)
PI US 7902261 B2 20110308
AI US 2005-139532 20050531 (11)
RLI Continuation of Ser. No. US 1900-19263, ABANDONED A 371 of International Ser. No. WO 2000-JP4286, filed on 28 Jun 2000
PRAI JP 1999-185297 19990630
DT Utility
FS GRANTED
LN.CNT 600
INCL INCLM: 514/727.000
NCL NCLM: 514/727.000; 514/651.000
CPC CPCI A61K0031-137 [I]

CPCI-2 A61K0031-137 [I]
IPC IPCI A61K0031-138 [ICM,7]
IPCI-2 A01N0033-18 [I]; A01N0033-24 [I]
IPCR A01N0033-18 [I]; A61K0031-133 [I]; A01N0033-24 [I]; A61K0031-137
[I]; A61P0009-04 [I]; A61P0031-12 [I]; A61P0031-14 [I];
A61P0031-16 [I]; A61P0031-22 [I]
EXF 514/726; 514/727
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 243 OF 256 USPAT2 on STN

Full Text

AN 2005:38064 USPAT2
TI Method for alleviating pain using sphingosine-1-phosphate and related
compounds, and assays for identifying such compounds
IN Michaelis, Martin, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
Geisslinger, Gerd, Bad Soden, GERMANY, FEDERAL REPUBLIC OF
Scholich, Klaus, Dreieich, GERMANY, FEDERAL REPUBLIC OF
PA Sanofi-Aventis Pharma GmbH, Frankfurt am Main, GERMANY, FEDERAL REPUBLIC
OF (non-U.S. corporation)
PI US 7691563 B2 20100406
AI US 2004-850586 20040520 (10)
PRAI EP 2003-12389 20030530
US 2003-520780P 20031117 (60)
DT Utility
FS GRANTED
LN.CNT 9286
INCL INCLM: 435/004.000
NCL NCLM: 435/004.000; 514/054.000
NCLS: 514/078.000
CPC CPCI A61K0031-661 [I]; A61K0031-685 [I]; C07F0009-113 [I];
G01N0033-5008 [I]; G01N0033-5023 [I]; G01N0033-5058 [I];
G01N0033-6896 [I]; G01N0033-92 [I]; G01N2333-988; G01N2500-02;
G01N2500-04; G01N2500-10
CPCI-2 A61K0031-661 [I]; A61K0031-685 [I]; C07F0009-113 [I];
G01N0033-5008 [I]; G01N0033-5023 [I]; G01N0033-5058 [I];
G01N0033-6896 [I]; G01N0033-92 [I]; G01N2333-988; G01N2500-02;
G01N2500-04; G01N2500-10
IPC IPCI A61K0031-685 [ICM,7]
IPCI-2 C12Q0001-00 [I]
IPCR C12Q0001-00 [I]; A61K0031-661 [I]; A61K0031-685 [I]; A61P0029-00
[I]; C07F0009-113 [I]; G01N0033-50 [I]; G01N0033-68 [I];
G01N0033-92 [I]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 244 OF 256 USPAT2 on STN

Full Text

AN 2004:320576 USPAT2
TI Methods of suppressing, treating, or preventing graft rejection with an
antibody or a portion thereof that binds to AILIM
IN Suzuki, legal representative, Atsuko, Tokyo, JAPAN
Isobe, Mitsuaki, Tokyo, JAPAN
Suzuki, Seiichi, United States deceased
Suzuki, Seiichi, Tokyo, JAPAN
PA Japan Tobacco, Inc., Tokyo, JAPAN (non-U.S. corporation)
PI US 7438905 B2 20081021
AI US 2004-793171 20040304 (10)
RLI Continuation-in-part of Ser. No. US 2002-451972, ABANDONED A 371 of
International Ser. No. WO 2002-JP930, filed on 5 Feb 2002
PRAI JP 2001-56209 20010301
JP 2001-56216 20010301
JP 2002-8028 20020116
DT Utility
FS GRANTED
LN.CNT 2032
INCL INCLM: 424/130.100
INCLS: 424/133.100; 424/135.100; 424/141.100; 424/142.100; 424/154.100;
530/387.100; 530/388.100; 530/388.150; 530/388.220
NCL NCLM: 424/130.100; 424/131.100
NCLS: 424/133.100; 424/135.100; 424/141.100; 424/142.100; 424/154.100;
530/387.100; 530/388.100; 530/388.150; 530/388.220; 514/020.500;
514/291.000
CPC CPCI C07K0016-2818 [I]; A61K0038-00; A61K2039-505; C07K0016-28 [I];

C07K2319-30
CPCI-2 C07K0016-2818 [I]; A61K0038-00; A61K2039-505; C07K0016-28 [I];
C07K2319-30
IPC IPCI A61K0039-395 [ICM,7]; A61K0038-13 [ICS,7]; A61K0031-4745 [ICS,7]
IPCI-2 A61K0039-395 [I]; C07K0016-00 [I]; C07K0016-28 [I]
IPCR A61K0038-02 [I]; A61K0039-395 [I]; A61K0031-7105 [I];
A61K0031-711 [I]; A61K0038-00 [I]; A61K0045-00 [I]; A61P0037-06
[I]; C07K0016-00 [I]; C07K0016-28 [I]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 245 OF 256 USPAT2 on STN

Full Text

AN 2004:315311 USPAT2
TI 2-amino-1,3-propanediol compounds for the treatment of acute pain
IN Michaelis, Martin, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
Geisslinger, Gerd, Bad Soden, GERMANY, FEDERAL REPUBLIC OF
Scholich, Klaus, Dreieich, GERMANY, FEDERAL REPUBLIC OF
PA Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, GERMANY, FEDERAL
REPUBLIC OF (non-U.S. corporation)
PI US 7524887 B2 20090428
AI US 2004-853761 20040525 (10)
PRAI EP 2003-12864 20030606
US 2003-510994P 20031014 (60)
DT Utility
FS GRANTED
LN.CNT 939
INCL INCLM: 514/653.000
INCLS: 514/667.000; 564/360.000; 564/503.000; 564/507.000
NCL NCLM: 514/653.000; 514/649.000
NCLS: 514/667.000; 564/360.000; 564/503.000; 564/507.000
CPC CPCI A61K0031-137 [I]
CPCI-2 A61K0031-137 [I]
IPC IPCI A61K0031-137 [ICM,7]
IPCI-2 A61K0031-137 [I]; A61K0031-131 [I]; A61K0031-132 [I]; C07C0215-10
[I]; C07C0215-20 [I]; C07C0217-28 [I]; C07C0217-44 [I];
C07C0219-06 [I]; C07C0219-04 [I]; C07C0219-18 [I]
IPCR A61K0031-137 [I]; A61K0031-131 [I]; A61K0031-132 [I]; C07C0215-10
[I]; C07C0215-20 [I]; C07C0217-28 [I]; C07C0217-44 [I];
C07C0219-04 [I]; C07C0219-06 [I]; C07C0219-18 [I]
EXF 514/255; 514/357; 514/427
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 246 OF 256 USPAT2 on STN

Full Text

AN 2004:165963 USPAT2
TI Method for treating diseases associated with abnormal kinase activity
IN Lyons, John, Moraga, CA, UNITED STATES
Rubinfeld, Joseph, Danville, CA, UNITED STATES
PA SuperGen.Inc., Dublin, CA, UNITED STATES (U.S. corporation)
PI US 6998391 B2 20060214
AI US 2002-206854 20020726 (10)
RLI Continuation-in-part of Ser. No. US 2002-71849, filed on 7 Feb 2002,
ABANDONED
DT Utility
FS GRANTED
LN.CNT 1784
INCL INCLM: 514/049.000
INCLS: 514/085.000; 514/269.000; 514/234.500; 514/300.000; 536/023.500;
536/023.100; 435/069.100; 435/325.000; 530/350.000; 424/045.000;
424/450.000
NCL NCLM: 514/049.000; 514/050.000
NCLS: 424/045.000; 424/450.000; 435/069.100; 435/325.000; 514/085.000;
514/234.500; 514/269.000; 514/300.000; 530/350.000; 536/023.100;
536/023.500
CPC CPCI A61K0031-7068 [I]; A61K0031-00 [I]; A61K0031-706 [I]; A61K0045-06
[I]
CPCI-2 A61K0031-7068 [I]; A61K0031-00 [I]; A61K0031-706 [I]; A61K0045-06
[I]
IPC IPCI A61K0031-7072 [ICM,7]
IPCI-2 A61K0031-7072 [I]
IPCR A61K0031-7072 [I]; A61K0031-00 [I]; A61K0031-706 [I];
A61K0031-7068 [I]

EXF 514/49; 514/65; 514/269; 514/234.5; 514/300; 536/23.5; 536/23.1;
435/69.1; 435/325; 530/350; 424/45; 424/450
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 247 OF 256 USPAT2 on STN

Full Text

AN 2003:325269 USPAT2
TI Production of 2-amino-2-[2-(4-alkylphenyl) ethyl] propane-1, 3-diols
IN Abel, Stephan, Weil, GERMANY, FEDERAL REPUBLIC OF
Fujita, Tetsuro, Kyoto, JAPAN
Hirose, Ryoji, Hyogo, JAPAN
Jordine, Guido, Freiburg, GERMANY, FEDERAL REPUBLIC OF
Mishina, Tadashi, Osaka, JAPAN
PA Novartis AG, Basel, SWEDEN (non-U.S. corporation)
PI US 7026522 B2 20060411
AI US 2003-464294 20030618 (10)
RLI Division of Ser. No. US 2001-850851, filed on 8 May 2001, Pat. No. US
6605744 Continuation of Ser. No. WO 1999-EP8577, filed on 9 Nov 1999,
PENDING
PRAI GB 1998-24705 19981111
GB 1998-24706 19981111
DT Utility
FS GRANTED
LN.CNT 639
INCL INCLM: 570/195.000
INCLS: 570/194.000; 570/201.000
NCL NCLM: 570/195.000; 564/355.000
NCLS: 570/194.000; 570/201.000
CPC CPCI C07C0233-47 [I]; C07C0017-16 [I]; C07C0017-208 [I]; C07C0017-35
[I]; C07C0022-04 [I]; C07C0029-00 [I]; C07C0045-46 [I];
C07C0045-63 [I]; C07C0213-00 [I]; C07C0215-28 [I]
CPCI-2 C07C0233-47 [I]; C07C0017-16 [I]; C07C0017-208 [I]; C07C0017-35
[I]; C07C0022-04 [I]; C07C0029-00 [I]; C07C0045-46 [I];
C07C0045-63 [I]; C07C0213-00 [I]; C07C0215-28 [I]
IPC IPCI C07C0215-28 [ICM,7]
IPCI-2 C07C0022-00 [I]
IPCR C07C0022-00 [I]; C07C0017-16 [I]; C07C0017-20 [I]; C07C0017-35
[I]; C07C0022-04 [I]; C07C0029-00 [I]; C07C0045-46 [I];
C07C0045-63 [I]; C07C0213-00 [I]; C07C0213-02 [I]; C07C0215-28
[N]; C07C0215-34 [I]; C07C0231-12 [I]; C07C0233-05 [I];
C07C0233-47 [I]
EXF 570/195; 570/194; 570/201
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 248 OF 256 USPAT2 on STN

Full Text

AN 2003:201813 USPAT2
TI Delivery of therapeutic capable agents
IN Sirhan, Motasim, Sunnyvale, CA, UNITED STATES
Yan, John, Los Gatos, CA, UNITED STATES
PA Avantec Vascular Corporation, Sunnyvale, CA, UNITED STATES (U.S.
corporation)
PI US 7083642 B2 20060801
AI US 2002-206853 20020725 (10)
RLI Continuation-in-part of Ser. No. US 2001-2595, filed on 1 Nov 2001,
PENDING Continuation-in-part of Ser. No. US 2001-783253, filed on 13 Feb
2001, Pat. No. US 6939375 Continuation-in-part of Ser. No. US
2001-782927, filed on 13 Feb 2001, Pat. No. US 6471980
Continuation-in-part of Ser. No. US 2001-783254, filed on 13 Feb 2001,
PENDING Continuation-in-part of Ser. No. US 2001-782804, filed on 13 Feb
2001, PENDING Continuation-in-part of Ser. No. US 2001-206853, PENDING
Continuation-in-part of Ser. No. US 2001-17500, filed on 14 Dec 2001,
PENDING
PRAI US 2002-370703P 20020406 (60)
US 2002-355317P 20020207 (60)
US 2002-347473P 20020110 (60)
US 2001-308381P 20010726 (60)
US 2000-258024P 20001222 (60)
DT Utility
FS GRANTED
LN.CNT 1239
INCL INCLM: 623/001.420

INCLS: 623/001.150
NCL NCLM: 623/001.420; 623/001.150
NCLS: 623/001.150
CPC CPCI A61L0027-54 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2002-91558; A61F2250-0067; A61F2250-0071;
A61L0031-16 [I]; A61L2300-416; A61L2300-602
CPCI-2 A61L0027-54 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2002-91558; A61F2250-0067; A61F2250-0071;
A61L0031-16 [I]; A61L2300-416; A61L2300-602
IPC IPCI A61F0002-06 [ICM,7]
IPCI-2 A61F0002-06 [I]
IPCR A61F0002-06 [I]; A61F0002-00 [N]; A61F0002-84 [N]; A61F0002-90
[I]; A61L0027-54 [I]; A61L0031-16 [I]
EXF 623/1.39-1.48; 623/23.29; 623/23.3
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 249 OF 256 USPAT2 on STN

Full Text

AN 2003:121162 USPAT2
TI Apparatus and methods for variably controlled substance delivery from
implanted prostheses
IN Sirhan, Motasim, Sunnyvale, CA, UNITED STATES
Yan, John, Los Gatos, CA, UNITED STATES
PA Avantec Vascular Corporation, Sunnyvale, CA, UNITED STATES (U.S.
corporation)
PI US 7077859 B2 20060718
AI US 2001-17500 20011214 (10)
RLI Continuation-in-part of Ser. No. US 2001-2595, filed on 1 Nov 2001,
PENDING Continuation-in-part of Ser. No. US 2001-783253, filed on 13 Feb
2001, PENDING Continuation-in-part of Ser. No. US 2001-782927, filed on
13 Feb 2001, Pat. No. US 6471980 Continuation-in-part of Ser. No. US
2001-783254, filed on 13 Feb 2001, PENDING Continuation-in-part of Ser.
No. US 2001-782804, filed on 13 Feb 2001, PENDING
PRAI US 2001-308381P 20010726 (60)
US 2000-258024P 20001222 (60)
DT Utility
FS GRANTED
LN.CNT 2448
INCL INCLM: 623/001.150
INCLS: 623/001.420
NCL NCLM: 623/001.150; 604/891.100
NCLS: 623/001.420
CPC CPCI A61L0027-54 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2002-91558; A61F2002-91583; A61F2250-0067;
A61F2250-0068; A61L0031-16 [I]; A61L2300-416; A61L2300-602
CPCI-2 A61L0027-54 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2002-91558; A61F2002-91583; A61F2250-0067;
A61F2250-0068; A61L0031-16 [I]; A61L2300-416; A61L2300-602
IPC IPCI A61F0002-06 [ICM,7]
IPCI-2 A61F0002-06 [I]
IPCR A61F0002-06 [I]; A61K0009-00 [I]; A61F0002-00 [N]; A61F0002-82
[I]; A61F0002-84 [N]; A61F0002-90 [I]; A61L0027-54 [I];
A61L0031-00 [I]; A61L0031-16 [I]
EXF 623/1.13; 623/1.39; 623/1.4-1.48
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 250 OF 256 USPAT2 on STN

Full Text

AN 2003:23354 USPAT2
TI Intravascular delivery of mycophenolic acid
IN Sirhan, Motasim, Sunnyvale, CA, United States
Yan, John, Los Gatos, CA, United States
PA Avantec Vascular Corporation, Sunnyvale, CA, United States (U.S.
corporation)
PI US 6858221 B2 20050222
AI US 2002-242334 20020911 (10)
RLI Division of Ser. No. US 2001-782927, filed on 13 Feb 2001, now patented,
Pat. No. US 6471980
PRAI US 2000-258024P 20001222 (60)
DT Utility
FS GRANTED
LN.CNT 1119

INCL INCLM: 424/423.000
INCLS: 424/424.000; 424/425.000; 424/426.000; 623/001.100; 623/001.420
NCL NCLM: 424/423.000; 424/426.000
NCLS: 424/424.000; 424/425.000; 424/426.000; 623/001.100; 623/001.420;
514/171.000; 514/251.000; 514/291.000; 514/470.000
CPC CPCI A61F0002-90 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2250-0067; A61L0027-54 [I]; A61L0031-16 [I];
A61L2300-416; A61L2300-602
CPCI-2 A61F0002-90 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2250-0067; A61L0027-54 [I]; A61L0031-16 [I];
A61L2300-416; A61L2300-602
IPC [7]
IPCI A61K0031-573 [ICM,7]; A61K0031-525 [ICS,7]; A61K0031-4745
[ICS,7]; A61F0002-00 [ICS,7]; A61K0031-365 [ICS,7]
IPCI-2 A61F0002-02 [ICM,7]; A61F0002-06 [ICS,7]
IPCR A61F0002-00 [N]; A61F0002-06 [I]; A61F0002-84 [N]; A61F0002-90
[I]; A61L0027-54 [I]; A61L0031-16 [I]
EXF 424/423; 424/424; 424/425; 424/426; 623/1.1; 623/1.42
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 251 OF 256 USPAT2 on STN

Full Text

AN 2002:213450 USPAT2
TI Intravascular delivery of mycophenolic acid
IN Sirhan, Motasim, Sunnyvale, CA, United States
Yan, John, Los Gatos, CA, United States
PA Avantec Vascular Corporation, Sunnyvale, CA, United States (U.S.
corporation)
PI US 6471980 B2 20021029
AI US 2001-782927 20010213 (9)
PRAI US 2000-258024P 20001222 (60)
DT Utility
FS GRANTED
LN.CNT 1071
INCL INCLM: 424/423.000
INCLS: 424/424.000; 424/425.000; 424/426.000
NCL NCLM: 424/423.000
NCLS: 424/424.000; 424/425.000; 424/426.000; 514/470.000
CPC CPCI A61F0002-90 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2250-0067; A61L0027-54 [I]; A61L0031-16 [I];
A61L2300-416; A61L2300-602
CPCI-2 A61F0002-90 [I]; A61F0002-91 [I]; A61F0002-915 [I]; A61F0002-95;
A61F2002-91533; A61F2250-0067; A61L0027-54 [I]; A61L0031-16 [I];
A61L2300-416; A61L2300-602
IPC [7]
IPCI A61F0002-00 [ICM,7]; A61K0031-365 [ICS,7]
IPCI-2 A61F0002-02 [ICM,7]
IPCR A61F0002-00 [N]; A61F0002-06 [I]; A61F0002-84 [N]; A61F0002-90
[I]; A61L0027-54 [I]; A61L0031-16 [I]
EXF 424/423; 424/424; 424/425; 424/426
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 252 OF 256 USPAT2 on STN

Full Text

AN 2002:191216 USPAT2
TI Compositions and methods of using compositions with accelerated
lymphocyte homing immunosuppressive properties
IN Chiba, Kenji, Fukuoka, JAPAN
Adachi, Kunitomo, Fukuoka, JAPAN
PA Mitsubishi Pharma Corporation, Osaka, JAPAN (non-U.S. corporation)
PI US 6667025 B2 20031223
AI US 1999-334213 19990615 (9)
RLI Division of Ser. No. US 1997-933738, filed on 23 Sep 1997, now patented,
Pat. No. US 6004565
PRAI JP 1997-237273 19970902
DT Utility
FS GRANTED
LN.CNT 1499
INCL INCLM: 424/009.100
INCLS: 424/009.200; 424/093.700; 424/278.100; 435/002.000; 435/029.000;
514/885.000
NCL NCLM: 424/009.100; 424/278.100

NCLS: 424/009.200; 424/093.700; 424/278.100; 435/002.000; 435/029.000;
514/885.000; 514/472.000; 514/487.000; 514/546.000; 514/653.000
CPC CPCI A61K0031-135 [I]; Y10S0514-885
CPCI-2 A61K0031-135 [I]; Y10S0514-885
IPC [7]
IPCI A61K0045-00 [ICM,7]; A61K0047-00 [ICS,7]; A61K0031-34 [ICS,7];
A01N0043-08 [ICS,7]; A61K0031-27 [ICS,7]; A01N0047-10 [ICS,7];
A61K0031-22 [ICS,7]; A01N0037-02 [ICS,7]; A61K0031-135 [ICS,7];
A01N0033-02 [ICS,7]
IPCI-2 A61K0049-00 [ICM,7]; A61K0045-00 [ICS,7]; A01N0001-02 [ICS,7]
IPCR G01N0033-49 [I]; A61K0031-13 [I]; A61K0031-135 [I]; A61K0045-00
[I]; A61P0037-06 [I]
EXF 424/278.1; 424/9.1; 424/9.2; 424/93.7; 514/472; 514/653; 514/487;
514/546; 514/885; 560/29; 560/163; 564/223; 564/355; 435/2; 435/29
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 253 OF 256 USPAT2 on STN

Full Text

AN 2002:172348 USPAT2
TI Phosphate derivatives as immunoregulatory agents
IN Mandala, Suzanne, Scotch Plains, NJ, United States
Bergstrom, James, Neshanic Station, NJ, United States
Hajdu, Richard, Old Bridge, NJ, United States
Rosen, Hugh, Springfield, NJ, United States
Parsons, William, Belle Mead, NJ, United States
Card, Deborah J., Somerset, NJ, United States
Maccoss, Malcolm, Freehold, NJ, United States
Kathleen, Rupprecht, Cranford, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 6437165 B2 20020820
AI US 2001-942411 20010830 (9)
PRAI US 2000-229438P 20000831 (60)
DT Utility
FS GRANTED
LN.CNT 1329
INCL INCLM: 558/169.000
INCLS: 558/070.000; 558/166.000; 514/114.000
NCL NCLM: 558/169.000; 514/114.000
NCLS: 558/070.000; 558/166.000; 514/118.000; 558/116.000
CPC CPCI C07F0009-094 [I]; C07F0009-3882 [I]
CPCI-2 C07F0009-094 [I]; C07F0009-3882 [I]
IPC [7]
IPCI A61K0031-66 [ICM,7]; C07F0009-24 [ICS,7]
IPCI-2 A61K0031-662 [ICM,7]
IPCR A61K0031-661 [I]; A61K0031-662 [I]; A61P0001-02 [I]; A61P0001-04
[I]; A61P0001-16 [I]; A61P0001-18 [I]; A61P0003-10 [I];
A61P0005-14 [I]; A61P0007-00 [I]; A61P0007-06 [I]; A61P0009-04
[I]; A61P0009-10 [I]; A61P0011-00 [I]; A61P0011-02 [I];
A61P0011-06 [I]; A61P0013-12 [I]; A61P0017-00 [I]; A61P0017-04
[I]; A61P0017-06 [I]; A61P0017-10 [I]; A61P0017-14 [I];
A61P0019-02 [I]; A61P0021-00 [I]; A61P0025-00 [I]; A61P0025-06
[I]; A61P0025-28 [I]; A61P0027-02 [I]; A61P0029-00 [I];
A61P0031-04 [I]; A61P0031-14 [I]; A61P0031-18 [I]; A61P0035-00
[I]; A61P0035-04 [I]; A61P0037-02 [I]; A61P0037-06 [I];
A61P0043-00 [I]; C07F0009-09 [I]; C07F0009-38 [I]
EXF 558/70; 558/166; 558/169; 514/114
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 254 OF 256 USPAT2 on STN

Full Text

AN 2002:158063 USPAT2
TI Intravascular delivery of methylprednisolone
IN Sirhan, Motasim, Sunnyvale, CA, UNITED STATES
Yan, John, Los Gatos, CA, UNITED STATES
PA Avantec Vascular Corporation, Sunnyvale, CA, UNITED STATES (U.S.
corporation)
PI US 7018405 B2 20060328
AI US 2001-782804 20010213 (9)
PRAI US 2000-258024P 20001222 (60)
DT Utility
FS GRANTED
LN.CNT 966

INCL INCLM: 623/001.420
INCLS: 623/001.450
NCL NCLM: 623/001.420; 623/001.150
NCLS: 623/001.450; 623/001.430
CPC CPCI A61F0002-90 [I]; A61F2250-0067; A61L0027-54 [I]; A61L0031-16 [I];
A61L2300-41; A61L2300-416; A61L2300-602
CPCI-2 A61F0002-90 [I]; A61F2250-0067; A61L0027-54 [I]; A61L0031-16 [I];
A61L2300-41; A61L2300-416; A61L2300-602
IPC IPCI A61F0002-06 [ICM,7]
IPCI-2 A61F0002-06 [I]
IPCR A61F0002-06 [I]; A61F0002-00 [N]; A61F0002-90 [I]; A61L0027-54
[I]; A61L0031-16 [I]
EXF 623/1.42; 623/1.43; 623/1.44; 623/1.45; 623/1.46; 623/1.47; 623/1.48
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 255 OF 256 USPAT2 on STN

Full Text

AN 2002:141646 USPAT2
TI Production of 2-amin-2-[2-(2-(40-C2-20-alkyl-phenyl)ethyl)propane-1,3-
diols
IN Abel, Stephan, Weil, GERMANY, FEDERAL REPUBLIC OF
Fujita, Tetsuro, Kyoto, JAPAN
Hirose, Ryoji, Hyogo, JAPAN
Jordine, Guido, Freiburg, GERMANY, FEDERAL REPUBLIC OF
Mishina, Tadashi, Osaka, JAPAN
PA Novartis AG, Basel, SWITZERLAND (non-U.S. corporation)
Taito Co. Ltd., Tokyo, JAPAN (non-U.S. corporation)
Mitsubishi Pharma Corp., Osaka, JAPAN (non-U.S. corporation)
PI US 6605744 B2 20030812
AI US 2001-850851 20010508 (9)
RLI Continuation of Ser. No. WO 1999-EP8577, filed on 9 Nov 1999
PRAI GB 1998-24705 19981111
GB 1998-24706 19981111

DT Utility

FS GRANTED

LN.CNT 743

INCL INCLM: 564/357.000
INCLS: 564/355.000; 564/356.000; 564/358.000
NCL NCLM: 564/357.000; 564/356.000
NCLS: 564/355.000; 564/356.000; 564/358.000
CPC CPCI C07C0233-47 [I]; C07C0017-16 [I]; C07C0017-208 [I]; C07C0017-35
[I]; C07C0022-04 [I]; C07C0029-00 [I]; C07C0045-46 [I];
C07C0045-63 [I]; C07C0213-00 [I]; C07C0215-28 [I]
CPCI-2 C07C0233-47 [I]; C07C0017-16 [I]; C07C0017-208 [I]; C07C0017-35
[I]; C07C0022-04 [I]; C07C0029-00 [I]; C07C0045-46 [I];
C07C0045-63 [I]; C07C0213-00 [I]; C07C0215-28 [I]
IPC [7]
IPCI C07C0215-56 [ICM,7]
IPCI-2 C07C0209-24 [ICM,7]
IPCR C07C0017-16 [I]; C07C0017-20 [I]; C07C0017-35 [I]; C07C0022-04
[I]; C07C0029-00 [I]; C07C0045-46 [I]; C07C0045-63 [I];
C07C0213-00 [I]; C07C0213-02 [I]; C07C0215-28 [N]; C07C0215-34
[I]; C07C0231-12 [I]; C07C0233-05 [I]; C07C0233-47 [I]
EXF 564/356; 564/355; 564/357; 564/358
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 256 OF 256 USPAT2 on STN

Full Text


AN 2001:114679 USPAT2
TI Process for preparing 2-amino malonic acid derivatives and
2-amino-1,3-propanediol derivatives, and intermediates for preparing the
same
IN Hirase, Susumu, Kobe, Japan
Sasaki, Shigeo, Kobe, Japan
Yoneta, Masahiko, Hadano, Japan
Hirose, Ryoji, Kobe, Japan
Fujita, Tetsuro, Muko, Japan
PA Taito Co., LTD, Tokyo, Japan (non-U.S. corporation)
Welfide Corporation, Osaka, Japan (non-U.S. corporation)
PI US 6284915 B2 20010904
AI US 1999-261342 19990303 (9)
RLI Continuation of Ser. No. WO 1998-JP2998, filed on 3 Jul 1998

PRAI JP 1997-2299 19970703
 DT Utility
 FS GRANTED
 LN.CNT 1061
 INCL INCLM: 560/039.000
 INCLS: 560/040.000; 568/031.000; 568/331.000; 568/336.000
 NCL NCLM: 560/039.000
 NCLS: 560/040.000; 568/031.000; 568/331.000; 568/336.000
 CPC CPCI C07C0309-73 [I]; C07C0045-63 [I]; C07C0045-673 [I]; C07C0213-08
 [I]; C07C0227-16 [I]; C07C0229-36 [I]; C07C0233-47 [I]
 CPCI-2 C07C0309-73 [I]; C07C0045-63 [I]; C07C0045-673 [I]; C07C0213-08
 [I]; C07C0227-16 [I]; C07C0229-36 [I]; C07C0233-47 [I]
 IPC [7]
 IPCI C07C0229-00 [ICM,7]
 IPCI-2 C07C0229-28 [ICM,7]
 IPCR C07C0045-63 [I]; C07C0045-67 [I]; C07C0213-08 [I]; C07C0215-28
 [N]; C07C0227-16 [I]; C07C0229-36 [I]; C07C0233-47 [I];
 C07C0309-73 [I]
 EXF 568/336; 568/331; 568/31; 560/39; 560/40
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	83.88	94.01

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Search Notes 	Application/Control No. 13149468	Applicant(s)/Patent Under Reexamination HIESTAND ET AL.
	Examiner KEVIN E WEDDINGTON	Art Unit 1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	667	9/24/2013	KEW
514	903	9/24/2013	KEW

SEARCH NOTES		
Search Notes	Date	Examiner
CAS-ONLINE search with REGISTRY and USPATALL	9/24/2013	KEW
EAST and PALM for Inventors' Names for Related Applications for ODP	9/24/2013	KEW

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

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET
CONFIRMATION NO. 1536

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
13/149,468	05/31/2011	514	1629	PAT050279-US-CNT		
APPLICANTS Peter C. Hiestand, Allschwil, SWITZERLAND; Christian Schnell, Hesingue, FRANCE;						
** CONTINUING DATA ***** This application is a CON of 12/303,765 12/08/2008 ABN which is a 371 of PCT/EP2007/005597 06/25/2007						
** FOREIGN APPLICATIONS ***** UNITED KINGDOM 0612721.1 06/27/2006						
** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 06/15/2011						
Foreign Priority claimed <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	35 USC 119(a-d) conditions met <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
Verified and /KEVIN E WEDDINGTON/ Examiner's Signature	Acknowledged	Initials	SWITZERLAND	0	10	3
ADDRESS NOVARTIS PHARMACEUTICAL CORPORATION INTELLECTUAL PROPERTY DEPARTMENT ONE HEALTH PLAZA 101/2 EAST HANOVER, NJ 07936-1080 UNITED STATES						
TITLE S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS						
FILING FEE RECEIVED 1480	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit			

Electronic Acknowledgement Receipt

EFS ID:	15550410
Application Number:	13149468
International Application Number:	
Confirmation Number:	1536
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	1095
Filer:	Karen DeBenedictis/Denise Cooper
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	PAT050279-US-CNT
Receipt Date:	18-APR-2013
Filing Date:	31-MAY-2011
Time Stamp:	11:15:06
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		50279.pdf	78442 <small>be0887518ee4346007557307dc58801c755f2643</small>	yes	2

Multipart Description/PDF files in .zip description			
	Document Description	Start	End
	Transmittal Letter	1	1
	Information Disclosure Statement (IDS) Form (SB08)	2	2

Warnings:

Information:

2	Non Patent Literature	Rammohan_FREEDOMS-II-Ext-Safety_AAN-2013March.pdf	995217 <small>7d9033da33c5e6be22b087a12eb32017a654315a</small>	no	1
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Warnings:

Information:

Total Files Size (in bytes):		1073659
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Art Unit: 1629

Hiestand, Peter C. et al.

Examiner:

APPLICATION NO: 13/149468

FILED: May 31, 2011

FOR: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

MS: Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

- before the mailing date of a first Office Action on the merits, and so under 37 C.F.R. §1.97(b)(3) no fees are required.

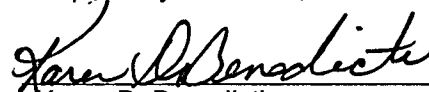
If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134 in the name of Novartis.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

- Copies of the references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s).

Respectfully submitted,



Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 862 7783785

Date: 4/17/13

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

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	13/149488
Filing Date	May 31, 2011
First Named Inventor	Hiestand, Peter C. et al.
Art unit	1629
Examiner Name	SPIVACK, PHYLLIS G
Attorney Docket Number	PAT050279-US-CNT

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application. Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant must request non-entry of such amendment(s).

- a. Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i. Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. Other _____
- b. Enclosed
- i. Amendment/Reply
- ii. Affidavit(s)/Declaration(s)
- iii. Information Disclosure Statement (IDS)
- iv. Other _____

2. **Miscellaneous**

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

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

- a. The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 19-0134 in the name of Novartis.
- i. RCE fee required under 37 CFR 1.17(e)
- ii. Extension of time fee (37 CFR 1.136 and 1.17)
- iii. Other _____
- b. Check in the amount of \$_____ enclosed
- c. Payment by credit card (Form PTO-2038 enclosed)

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

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Karen DeBenedictis /	Date	February 18, 2013
Name (Print/Type)	Karen DeBenedictis	Registration No.	32,977

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature		Date	
Name (Print/Type)			

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop RCE, 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Art Unit: 1629

Hiestand, Peter C. *et al.*

Examiner: Spivack, Phyllis G.

APPLICATION NO: 13/149468

Conf. No.: 1536

FILED: May 31, 2011

FOR: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Amendment is being submitted with a Request for Continued Examination pursuant to 37 CFR §1.114 in response to the Office Action in the above application that was mailed to Applicants' attorney on November 16, 2012 (the "Office Action"). A response to the Office Action is due by February 16, 2013.

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

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims:

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

Listing of Claims:

Claims 1 – 11. (Cancelled).

Claim 12. (Currently amended) A method for inhibiting or treating neo-angiogenesis associated with multiple sclerosis in a subject in need thereof, comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

Claim 13. (Currently amended) A method for reducing or alleviating relapses in primary progressive multiple sclerosis in a subject in need thereof, comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

Claim 14. (Currently amended) A method according to claim 12, wherein said multiple sclerosis is primary progressive relapsing-remitting multiple sclerosis, ~~for inhibiting or treating neo-angiogenesis associated with relapsing-remitting multiple sclerosis in a subject in need thereof,~~ comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg.

Claim 15. (Canceled)

Claim 16. (Currently amended) A method according to claim 12 or 13 wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered.

Claim 17. (Currently amended) A method for slowing progression of multiple sclerosis in a subject in the relapsing-remitting phase of primary progressive multiple sclerosis ~~in need thereof,~~ comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, absent an immediately preceding loading dose regimen.

Claim 18. (Canceled)

Claim 19. (Canceled)

Claim 20. (Canceled)

Claim 21. (Previously presented) A method according to claim 13, wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered.

Claim 22. (New) A method according to claim 16, wherein said multiple sclerosis is primary-progressive multiple sclerosis.

Claim 23. (New) A method according to claim 14, wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered.

Claim 24. (New) A method according to claim 15, wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered.

Claim 25. (New) A method according to claim 12, wherein said multiple sclerosis is relapsing-remitting multiple sclerosis.

REMARKS

Reconsideration of the above application is respectfully requested.

There are 10 claims pending in this application. They are claims 12 – 21. By the above amendments, Applicants have amended claims 12 – 14, 16 – 17, and 21, canceled claims 15, 18 and 20 and added new claims 22 through 25. Claim 19 was canceled in a previously submitted paper. Applicants maintain their position that the subject matter deleted from the claims via the above amendments is patentable over the cited art, and have made such amendments to advance prosecution of the remaining subject matter. They reserve their right to prosecute the above deleted subject matter in subsequent divisional applications. These amendments add no new matter to the application.

In the Office Action, the Examiner maintained her rejection of claims 12 – 18 and 20 - 21 under 35 U.S.C. 103(a) as being unpatentable over Virley, D.J., Journal of the American Society for NeuroTherapeutics ("Virley"), in view of LaMontagne *et al.*, Cancer Research ("LaMontagne"), and further in view of Kovarik *et al.*, WO06/058316 ("Kovarik"), all of record. The Examiner stated that LaMontagne was included in the rejection merely to establish the utility of FTY720 as an anti-angiogenic agent. She further stated that Kovarik teaches a method for treating an autoimmune disease, in a subject in need thereof, with FTY720 at a daily dosage of about 0.1 to 0.5 mg, and that Virley teaches the administration of FTY720 for the treatment of multiple sclerosis. For the following reasons, Applicants traverse this rejection, as applied to all pending claims, as amended, and respectfully request that it be withdrawn.

Applicants have amended all pending claims (or the claims from which they depend) to specify that the stated daily dosage of 0.5 mg cannot immediately follow a loading dose regimen. Applicants have made these amendments to further distinguish their claims from the disclosure of Kovarik. Applicants have also amended the pending claims to specify that the disorder being treated by a daily dosage of 0.5 mg is either primary progressive multiple sclerosis (which includes the relapsing-remitting phase of primary progressive multiple sclerosis) or angiogenesis associated with multiple sclerosis.

Kovarik's mention of a dosage of 0.5 mg is limited to the context of a dosage that follows, immediately, the loading dose regimen described therein. The Kovarik loading dose regimen involves raising stepwise the daily dosage of the S1P receptor or agonist over 3 to 6 days up to 3- to 21-fold the standard daily dosage for the purpose of attaining steady state blood levels of the drug in less than a week. This loading dosage allows patients to continue, immediately following such regimen, with a daily dosage that is the same or lower than the standard daily dosage. Kovarik indicates that when the dosage administered after the initial period is lower than the standard daily dosage, it can be from 1/50 to ½ the standard daily dosage. Kovarik also states that the daily dosage employed following a loading dose regimen can be 0.1 – 0.5 mg or can be much larger – 2.5 or 5.0 mg. Thus, Kovarik teaches that the daily dosage

administered after the initial period can vary substantially relative to the standard daily dosage and is dependent on the immediately preceding loading dose administered during the initial phase. In addition to being only one of a wide range of dosages that can be employed following a loading dose regimen of an S1P receptor modulator or agonist, the 0.5 mg daily dosage referenced in Kovarik is mentioned only in the context of a dosage employed following the conclusion of a loading dose regimen. In view of the above, Applicants submit that the skilled person reading Kovarik would attach no significance to the suitability of any daily dosage mentioned therein outside the context of an immediately preceding loading dose regimen.

Kovarik makes no mention of angiogenesis, and no endpoints relating to angiogenesis were measured in connection with any dosage of FTY720. Also, Kovarik makes no distinction between primary progressive multiple sclerosis, relapsing-remitting multiple sclerosis and the relapsing-remitting phase of primary progressive multiple sclerosis. In view of this, Applicants submit that the skilled person reading Kovarik, as of the priority filing date of this application, would not have been motivated to inhibit or treat, with a reasonable expectation of success, angiogenesis associated with multiple sclerosis, or to treat, with a reasonable expectation of success, primary progressive multiple sclerosis with the low daily dosage of 0.5 mg FTY720.

Applicants further submit that neither Virley nor Lamontagne would provide the skilled person with any guidance regarding a favorable human dosage, *i.e.*, favorable with respect to the balance of safety and efficacy, to use for any of the disorders mentioned in Applicants' claims. They simply refer to the use of FTY720 to treat, respectively, multiple sclerosis and angiogenesis. As Applicants mentioned in the prior Amendment they submitted in this case, LaMontagne reports that dosages of 0.3 and 3.0 mg/kg FTY720 were tested in an angiogenesis model in mice, and that the dosage of 0.3 mg/kg was less active in inhibiting angiogenesis than the dosage of 3.0 mg/kg. To the extent that this reference teaches anything about a favorable daily dosage of FTY720 for inhibiting angiogenesis, Applicants submit that it teaches away from the inventions of their pending claims, as amended. A dosage of 0.3 mg/kg corresponds to a dosage of 21.0 mg/day in an adult human weighing 70 kg, which is 42 times greater than the daily dosage of 0.5 mg/day that is a key feature of Applicants pending claims. Thus, Applicants respectfully submit that LaMontagne would not motivate the skilled person, and would not add anything to the disclosures of Kovarik and Lamontagne that would motivate the skilled person to treat angiogenesis associated with multiple sclerosis with a dosage of FTY720 as low as 0.5 mg, considering that the lower of the two FTY720 daily dosages mentioned in LaMontagne was stated therein to be not as effective as the higher of these two dosages, and the lower daily dosage was 42 times greater than 0.5 mg.

In view of the above, Applicants submit that all pending claims, as amended, comply fully

with 35 U.S.C. §103, and they respectfully request that such claims be allowed to issue.

Respectfully submitted,

/Karen DeBenedictis/

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 8627783785

Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Date: 2/18/13

Electronic Patent Application Fee Transmittal

Application Number:	13149468
Filing Date:	31-May-2011
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Filer:	Karen DeBenedictis/Andrea Jacquin
Attorney Docket Number:	PAT050279-US-CNT

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Request for continued examination	1801	1	930	930
Total in USD (\$)				930

Electronic Acknowledgement Receipt

EFS ID:	14982503
Application Number:	13149468
International Application Number:	
Confirmation Number:	1536
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	1095
Filer:	Karen DeBenedictis/Andrea Jacquin
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	PAT050279-US-CNT
Receipt Date:	18-FEB-2013
Filing Date:	31-MAY-2011
Time Stamp:	16:02:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$930
RAM confirmation Number	11800
Deposit Account	190134
Authorized User	

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

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		50279-US-CNT_RCE_Amendment_2013Feb18.pdf	2225762 05d8ff8d34b5f7138083956bd0954b24ed3e3e01	yes	7
Multipart Description/PDF files in .zip description					
Document Description			Start	End	
Request for Continued Examination (RCE)			1	1	
Amendment After Final			2	2	
Claims			3	4	
Applicant Arguments/Remarks Made in an Amendment			5	7	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30488 82fd9434d2de45f3781928c84d4b3041dd5bccc	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			2256250		
<p>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.</p> <p><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.</p> <p><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.</p> <p><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.</p>					

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/149,468	Filing Date 05/31/2011	<input type="checkbox"/> To be Mailed
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APPLICATION AS FILED – PART I			OTHER THAN SMALL ENTITY			
	(Column 1)	(Column 2)	SMALL ENTITY <input type="checkbox"/>	OR	SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A	N/A		N/A	
<input type="checkbox"/> SEARCH FEE <small>(37 CFR 1.16(k), (j), or (m))</small>	N/A	N/A	N/A		N/A	
<input type="checkbox"/> EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A	N/A		N/A	
TOTAL CLAIMS <small>(37 CFR 1.16(j))</small>	minus 20 =	*	X \$ =		X \$ =	
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	minus 3 =	*	X \$ =		X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).					
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT <small>(37 CFR 1.16(j))</small>						
			TOTAL		TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II					OTHER THAN SMALL ENTITY			
	(Column 1)	(Column 2)	(Column 3)		SMALL ENTITY	OR	SMALL ENTITY	
AMENDMENT	02/18/2013	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 10	Minus ** 20	= 0	X \$ =		OR X \$62=	0
	Independent (37 CFR 1.16(h))	* 3	Minus ***3	= 0	X \$ =		OR X \$250=	0
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))						OR	
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						OR	
					TOTAL ADD'L FEE		OR TOTAL ADD'L FEE	0

	(Column 1)	(Column 2)	(Column 3)		SMALL ENTITY	OR	SMALL ENTITY	
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	X \$ =		OR X \$ =	
	Independent (37 CFR 1.16(h))	*	Minus ***	=	X \$ =		OR X \$ =	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))						OR	
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						OR	
					TOTAL ADD'L FEE		OR TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
 ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
 *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

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

Legal Instrument Examiner:
 /Tina J. Barden/

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/149,468	05/31/2011	Peter C. Hiestand	PAT050279-US-CNT	1536
1095	7590	11/16/2012	EXAMINER	
NOVARTIS PHARMACEUTICAL CORPORATION INTELLECTUAL PROPERTY DEPARTMENT ONE HEALTH PLAZA 101/2 EAST HANOVER, NJ 07936-1080			SPIVACK, PHYLLIS G	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			11/16/2012	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):

phip.patents@novartis.com

Applicants' Amendment filed July 27, 2012 is acknowledged. Claim 19 is canceled. Claims 12-18, 20 and 21 remain under consideration.

Information Disclosure Statements (IDS) filed April 16, 2012 and July 19, 2012 are further acknowledged and have been reviewed to the extent each reference is provided. It is noted the actual document RU2199339C2, cited on the IDS filed April 16, 2012, has not been supplied.

A new Abstract and an amendment to page 12 of the specification are noted.

The objections set forth in the last Office Action are withdrawn. The following rejection constitutes the only rejection presently applied to the present claims.

In the last Office Action claims 12-21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Virley, D.J., Journal of the American Society for Experimental NeuroTherapeutics, in view of LaMontagne et al., Cancer Research, and further in view of Kovarik et al., WO 06/058316. It was asserted Virley teaches the administration of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-propane-1,3-diol, also known as FTY720, which is a sphingosine-1-phosphate receptor modulator, for the treatment of multiple sclerosis (MS). Virley distinguishes between the categories of relapsing-remitting MS and primary progressive MS. See the introduction on page 638, as well as the discussion of experimental models for MS on page 640. In order to provide predictive

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indices for clinical application, experimental autoimmune encephalomyelitis (EAE) models are discussed. LaMontagne teaches FTY720 to be an anti-angiogenic agent. The compound becomes phosphorylated *in vivo* and interacts with sphingosine-1-phosphate (S1P) receptors. The effect is on vascular permeability, an important aspect of angiogenesis. See the Abstract. Kovarik teaches dosage regimens involving S1P receptor agonists, of which FTY720 is clearly encompassed. On line 16, page 17, a daily dose of 0.5 mg is taught for the treatment of autoimmune diseases, of which MS is recited as an example, on lines 7-8 on page 14.

Applicants state FTY720 is efficacious for the treatment of multiple sclerosis as a fact, on page 6 of their Amendment. With respect to the LaMontagne reference, Applicants' argument is entirely directed to a dosage range disclosed therein for inhibiting angiogenesis. Applicants argue Kovarik makes no distinction among various immune disorders with respect to the dosages therein disclosed.

Applicants' arguments have been given careful consideration but are not found persuasive. The rejection of claims 12-18, 20 and 21 under 35 U.S.C. 103(a) as being unpatentable over Virley, D.J., Journal of the American Society for Experimental NeuroTherapeutics, in view of LaMontagne et al., Cancer Research, and further in view of Kovarik et al., WO 06/058316, is maintained. LaMontagne was included in the rejection of record merely to establish the utility of FTY720 as an anti-angiogenic agent. On page 17 in paragraph 2.5, Kovarik teaches a method for treating an autoimmune

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disease in a subject in need thereof, wherein a daily dosage of FTY720 of about 0.1 to 0.5 mg is disclosed. With such guidance, through no more than routine experimentation, one skilled in the immunology art would have readily determined an optimal dosage range for a subject suffering from multiple sclerosis. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) and MPEP §2144.05(II). The medical arts recognize that drug therapy may be optimized by designing regimens that account for the concentration of a drug, for example, to achieve a desired pharmacological response. Factors such as weight, age, gender, renal and hepatic status, *inter alia*, are always considered. Therefore, the determination of the optimum dosing regimen and dosage amounts would have been matters well within the purview of one of ordinary skill in the art, at the time of the invention, through no more than routine experimentation.

In view of the teachings of Virley, LaMontagne and Kovarik, one skilled in the neurology art would have been motivated to administer FTY720 with a reasonable expectation of success in inhibiting neo-angiogenesis associated multiple sclerosis, in alleviating relapses in MS and slowing the progression of MS. Such would have been obvious because FTY720 is a known anti-angiogenic agent that has been taught for use in the treatment of autoimmune diseases such as multiple sclerosis. A daily dosage of 0.5 mg is suggested by the prior art.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicants are 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.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Jeff Lundgren, can be reached 571-272-5541. 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.

Application/Control Number: 13/149,468

Page 6

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November 13, 2012

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1629

Receipt date: 04/16/2012

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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
Application Number	13/149468				
Filing Date	May 31, 2011				
First Named Inventor	Hiestand, Peter C. et al				
Art unit	1629				
Examiner Name	Spivack				
Attorney Docket Number	PAT050279-US-CNT				
Sheet	1	of	1		

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number Number-Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-			
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FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document Country Code ³ Number ⁴ Kind Code ⁵ (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		RU2199339C2	02-27-2003	TEKH; OOO BIO		<input type="checkbox"/>
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Examiner Signature	/Phyllis Spivack/	Date Considered	11/13/2012
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO <h2 style="text-align: center;">INFORMATION DISCLOSURE STATEMENT BY APPLICANT</h2> <p style="text-align: center;"><i>(Use as many sheets as necessary)</i></p>		Complete if Known	
		Application Number	13/149468
		Filing Date	May 31, 2011
		First Named Inventor	Hiestand, Peter C. et al.
		Art unit	1629
		Examiner Name	Spivack
		Attorney Docket Number	PAT050279-US-CNT
Sheet	1	of	2

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-			
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		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
/P.S./		WO 2006/066086	06-22-2006	GENENTECH, INC.		<input type="checkbox"/>
/P.S./		WO 2006/055809	05-26-2006	INCLONE SYSTEMS INCORPORATED		<input type="checkbox"/>
						<input type="checkbox"/>
						<input type="checkbox"/>
						<input type="checkbox"/>
						<input type="checkbox"/>

Examiner Signature	/Phyllis Spivack/	Date Considered	11/13/2012
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Art Unit: 1629

Hiestand, Peter C. et al.

Examiner:

APPLICATION NO: 13/149468

Conf. No.:

FILED: May 31, 2011

FOR: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Amendment is being submitted in response to the Office Action in the above application that was mailed to Applicants' attorney on May 3, 2012 ("Office Action") a response to which is due by August 3, 2012.

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

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

Remarks/Arguments begin on page 5 of this paper.

Amendments to the Specification:

On page 12, delete lines 22-23 and replace with:

--In particular, the S1P receptor modulators as described herein, e.g. FTY720, i.e. 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, are useful for treating PP-MS.--

Amendments to the Claims:

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

Listing of Claims:

Claims 1 – 11. (Cancelled).

Claim 12. (Previously presented) A method for inhibiting or treating neo-angiogenesis associated with multiple sclerosis in a subject in need thereof, comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg.

Claim 13. (Previously presented) A method for reducing or alleviating relapses in multiple sclerosis in a subject in need thereof, comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg.

Claim 14. (Previously presented) A method according to claim 12 for inhibiting or treating neo-angiogenesis associated with relapsing-remitting multiple sclerosis in a subject in need thereof, comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg.

Claim 15. (Previously presented) A method according to claim 13 for reducing or alleviating relapses in relapsing-remitting multiple sclerosis in a subject in need thereof, comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg.

Claim 16. (Previously presented) A method according to claim 12 or 13 wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered.

Claim 17. (Previously presented) A method for slowing progression of multiple sclerosis in a subject in need thereof, comprising administering to said subject 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg.

Claim 18. (Previously presented) A method according to claim 17 wherein the disease is relapsing-remitting multiple sclerosis.

Claim 19. (Cancelled)

Claim 20. (Previously presented) A method according to claim 17 wherein the disease is primary-progressive multiple sclerosis (PP-MS).

Claim 21. (Previously presented) A method according to claim 17, wherein 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol hydrochloride is administered.

REMARKS

Reconsideration of the above application is respectfully requested. There are 10 claims pending in this application. They are claims 12 – 21. By the above amendments, Applicants have amended the specification to correct a spelling error noted by the Examiner on page 12 and have cancelled claim 19. These amendments add no new matter to the application.

In the Office Action, the Examiner objected to the Abstract for being broader than the scope of claimed subject matter under consideration. Applicants have attached to this paper a replacement Abstract, which they submit corresponds to the claimed subject matter being prosecuted in this application.

The Examiner also objected to the disclosure because of a spelling error on page 12. By the above amendments, Applicants have corrected the spelling of the misspelled chemical name.

In the Office Action, the Examiner rejected claims 12 - 21 under 35 U.S.C. 103(a) as being unpatentable over Virley, D.J., Journal of the American Society for NeuroTherapeutics ("Virley"), in view of LaMontagne *et al.*, Cancer Research ("LaMontagne"), and further in view of Kovarik *et al.*, WO06/058316 ("Kovarik"), all of record. The Examiner took the position that, in view of Virley's disclosure of the use of 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol ("FTY720") to treat multiple sclerosis, LaMontagne's reference to FTY720 as an anti-angiogenic agent and Kovarik's reference to the treatment of an autoimmune disease such as multiple sclerosis with FTY720 at a daily dosage of 0.5 mg, the skilled person would have been motivated, as of the priority filing date of this application, to administer FTY720 at a daily dosage of 0.5 mg for inhibiting the neo-angiogenesis associated with multiple sclerosis with a reasonable expectation of success. For the following reasons, Applicants traverse this rejection, as applied to the pending claims, as amended, and respectfully request that it be withdrawn.

Applicants submit that Kovarik would not suggest anything to the skilled person regarding the daily dosage that would be efficacious or advantageous for the treatment or inhibition of angiogenesis associated with multiple sclerosis. Kovarik refers to a loading dose regimen for FTY720 that is aimed at reaching a steady state blood level of the drug in less than a week. This is accomplished by administering the S1P receptor modulator or agonist during the initial 3 – 6 days, preferably, the initial 4 days of treatment, at a daily dosage that is higher than the standard daily dosage (*i.e.*, the dosage necessary for a steady-state trough blood level of the drug providing effective treatment) and is preferably increased stepwise during such initial period, after which the drug is administered at a dosage that is less than or equal to the standard daily dosage. Kovarik indicates that when the dosage administered after the initial period is lower than the standard daily dosage, it can be from 1/50 and 1/2 the standard daily dosage. Thus, the dosage administered after the initial period can vary substantially relative to the standard daily dosage and is also dependent on the immediately preceding loading dose

administered during the initial phase. The reference to a daily dosage of 0.5 mg FTY720 on page 19 of Kovarik refers to a dosage that could be administered on day 5 of a treatment regimen following 4 days of administering the drug in accordance with the loading dose regimen set forth on page 18. Kovarik also states, on page 18, that the same loading dose regimen during days 1 – 4 can be followed by the administration of a daily dosage of 5.0 mg FTY720. Kovarik makes no mention of angiogenesis, and no endpoints relating to angiogenesis were measured in connection with any dosage of FTY720. Also, Kovarik makes no distinction between different immune disorders with respect to any of the dosages mentioned therein. In view of this, Applicants submit that the skilled person reading Kovarik, as of the priority filing date of this application, would not be motivated to inhibit or treat the angiogenesis associated with multiple sclerosis, or any other immune disorder or symptom thereof, with a daily dosage of 0.5 mg FTY720.

Applicants wish to draw the Examiner's attention to another reason that Kovarik would not suggest to the skilled person any efficacious or advantageous dosage for any particular immune disorder or symptom thereof. The skilled person would not expect the optimal dosage or dosing regimen for treating transplant patients to be indicative of the optimal dosage or dosing regimen for treating an immune disorder such as multiple sclerosis. When treating a transplant patient, it is important to deliver a very high dose very early in treatment to counter rejection of the transplanted tissue, a consideration that does not apply to chronic immune disorders such as multiple sclerosis, where the goal is to degrade the disease over the period of the patient's natural life. Therefore, Kovarik's general disclosure of dosing regimen's suitable for transplant patients and for any other immune disorder would not suggest to the skilled person any particular dosage for any particular disorder or symptom thereof.

The main reference cited by the Examiner, Virley, provides no teaching relevant to Applicants' pending claims other than the fact that FTY720 is efficacious for the treatment of multiple sclerosis. For the reasons stated above, Kovarik adds nothing to the teachings of Virley that would suggest to the skilled person the efficacy of FTY720 in treating or inhibiting angiogenesis associated with multiple sclerosis, let alone a particular dosage for doing so.

Applicants submit that LaMontagne fails to provide the teaching that, taken together with the teachings of Virley and Kovarik, would suggest the subject matter of Applicants' claims to the skilled person, specifically the treatment or inhibition of angiogenesis associated with multiple sclerosis by administering FTY720 at a daily dosage of 0.5 mg. Lamontagne reports that dosages of 0.3 and 3.0 mg/kg FY720 were tested in an angiogenesis model in mice, and that the dosage of 0.3 mg/kg was less active in inhibiting angiogenesis than the dosage of 3.0 mg/kg. However, a dosage of 0.3 mg/kg corresponds to a dosage of 21.0 mg/day in an adult human weighing 70 kg, which is 42 times greater than the daily dosage of 0.5 mg/day that is a feature of Applicants pending claims. Thus, Applicants respectfully submit that LaMontagne would not motivate the skilled person to treat angiogenesis associated with multiple sclerosis

with a dosage of FTY720 as low as 0.5 mg, considering that the lower of the two FTY720 daily dosages mentioned in LaMontagne was stated therein to be not as effective as the higher of these two dosages, and the lower daily dosage was 42 times greater than 0.5 mg.

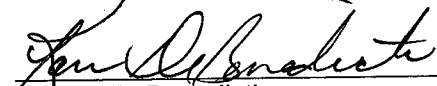
In view of the above, Applicants submit that all pending claims, as amended, comply fully with 35 U.S.C. §103, and they respectfully request that such claims be allowed to issue.

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 862 7783785

Date:

7/26/12

Respectfully submitted,



Karen DeBenedictis
Attorney for Applicant
Reg. No. 32,977

Abstract

The present invention relates to the use of the S1P receptor modulator 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, administered at a daily dosage of 0.5 mg, for inhibiting or treating neo-angiogenesis associated with multiple sclerosis.

Electronic Acknowledgement Receipt

EFS ID:	13355040
Application Number:	13149468
International Application Number:	
Confirmation Number:	1536
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	1095
Filer:	Karen DeBenedictis/Denise Cooper
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	PAT050279-US-CNT
Receipt Date:	27-JUL-2012
Filing Date:	31-MAY-2011
Time Stamp:	09:41:39
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		50279-US-CNT-Amendment. pdf	252323 <small>2b3a53b9ddb18aef4413e46d06636e9d36294fda</small>	yes	8

Multipart Description/PDF files in .zip description			
Document Description		Start	End
Amendment/Req. Reconsideration-After Non-Final Reject		1	7
Abstract		8	8

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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.

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Document code: WFEE

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APPLICATION AS FILED – PART I			OTHER THAN SMALL ENTITY			
	(Column 1)	(Column 2)	SMALL ENTITY <input type="checkbox"/>	OR	SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A	N/A		N/A	
<input type="checkbox"/> SEARCH FEE <small>(37 CFR 1.16(k), (j), or (m))</small>	N/A	N/A	N/A		N/A	
<input type="checkbox"/> EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A	N/A		N/A	
TOTAL CLAIMS <small>(37 CFR 1.16(j))</small>	minus 20 =	*	X \$ =	OR	X \$ =	
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	minus 3 =	*	X \$ =		X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).					
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT <small>(37 CFR 1.16(j))</small>						
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL		TOTAL	

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AMENDMENT	07/27/2012	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
	Total <small>(37 CFR 1.16(i))</small>	* 8	Minus ** 20	= 0	X \$ =		OR	X \$60= 0
	Independent <small>(37 CFR 1.16(h))</small>	* 3	Minus ***3	= 0	X \$ =		OR	X \$250= 0
	<input type="checkbox"/> Application Size Fee <small>(37 CFR 1.16(s))</small>						OR	
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>						OR	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE
							OR	0

	(Column 1)	(Column 2)	(Column 3)		SMALL ENTITY	OR	SMALL ENTITY	
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)
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	Independent <small>(37 CFR 1.16(h))</small>	*	Minus ***	=	X \$ =		OR	X \$ =
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Electronic Patent Application Fee Transmittal

Application Number:	13149468			
Filing Date:	31-May-2011			
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS			
First Named Inventor/Applicant Name:	Peter C. Hiestand			
Filer:	Karen DeBenedictis/Denise Cooper			
Attorney Docket Number:	PAT050279-US-CNT			
Filed as Large Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Total in USD (\$)				180

Electronic Acknowledgement Receipt

EFS ID:	13296073
Application Number:	13149468
International Application Number:	
Confirmation Number:	1536
Title of Invention:	S1P RECEPTOR MODULATORS FOR TREATING MUTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Peter C. Hiestand
Customer Number:	1095
Filer:	Karen DeBenedictis/Denise Cooper
Filer Authorized By:	Karen DeBenedictis
Attorney Docket Number:	PAT050279-US-CNT
Receipt Date:	19-JUL-2012
Filing Date:	31-MAY-2011
Time Stamp:	17:39:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$180
RAM confirmation Number	4606
Deposit Account	190134
Authorized User	

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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 June 2006 (22.06.2006)

PCT

(10) International Publication Number
WO 2006/066086 A1

(51) International Patent Classification:
C07K 16/22 (2006.01) A61K 39/395 (2006.01)

(21) International Application Number:
PCT/US2005/045600

(22) International Filing Date:
16 December 2005 (16.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/637,169 17 December 2004 (17.12.2004) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, 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.

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

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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

(54) Title: ANTIANGIOGENESIS THERAPY OF AUTOIMMUNE DISEASE IN PATIENTS WHO HAVE FAILED PRIOR THERAPY

(57) Abstract: The present application describes therapy with angiogenesis antagonists such as anti-VEGF antibodies. In particular, the application describes the use of such antagonists to treat autoimmune disease in a patient who has failed prior treatment such as treatment with DMARDs or TNF α -inhibitors.



WO 2006/066086 A1

ANTIANGIOGENESIS THERAPY OF AUTOIMMUNE DISEASE
IN PATIENTS WHO HAVE FAILED PRIOR THERAPY

Related Applications

This is a non-provisional application filed under 37 CFR §1.53(b), claiming priority under 35 U.S.C. §119(e) to U.S. Provisional Application Serial No. 60/637,169 filed on December 17, 2004, the entire contents of which is hereby incorporated by reference.

Field of the Invention

The present invention concerns therapy with angiogenesis antagonists, such as an anti-VEGF antibody. In particular, the invention concerns the use of such antagonists to treat autoimmune disease, particularly in a patient who has failed prior treatment.

Background of the Invention

Autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, vasculitis, and lupus, among others, remain clinically important diseases in humans. Collectively, autoimmune diseases affect about 5% of North Americans and Europeans, two-thirds of whom are women. As the name implies, autoimmune diseases wreak their havoc through the body's own immune system. The immune system, normally efficient in defeating external threats from the microbial world, at times directs its potent arsenal against the body's self-constituents, causing autoimmunity. While the pathological mechanisms differ among individual types of autoimmune diseases, one general mechanism involves the binding of certain antibodies (referred to herein as self-reactive antibodies or autoantibodies) present. The diseases often involve distinct anatomic regions. For example, the immune system attacks the synovial lining of the joints in rheumatoid arthritis (RA), the thyroid gland in thyroiditis, the insulin-secreting beta cells of the pancreas in type 1 diabetes mellitus (T1DM), and the myelin sheath of the brain and the spinal cord in multiple sclerosis (MS). In systemic lupus erythematosus (SLE), there are protean manifestations with involvement of skin, kidneys, joints, and brain.

Rheumatoid arthritis (RA) is a chronic autoimmune disorder of unknown etiology, typically characterized by symmetrical pain and swelling of the small joints of the hands and feet. Virtually any other joint in the body may become affected by inflammation, including the large joints, such as the shoulders, knees, and hips, jaws, and cervical spine. Persistent joint inflammation often produces articular cartilage and bone destruction as well as permanent deformities. The natural history of disease is described in years, but joint damage may occur as early as 3 to 6 months after onset. Although RA predominantly affects the joints, it is a systemic disease and may cause fatigue, low-grade fever, and involve other organ systems, including the eyes, lungs, and blood vessels. For example, RA may cause scleritis

(inflammatory eye disease), pleuritis, interstitial pulmonary fibrosis, and vasculitis. RA exacts a considerable toll on a patient's quality of life, causing pain and functional disability, with associated restrictions on household, family, and recreational activities. Limitations in work capacity and in some cases, unemployment, can have substantial economic ramifications for both individuals and society.

The diagnosis of RA is based on clinical manifestations and the results of selected laboratory tests. Approximately 75% of patients will test positive for rheumatoid factor (an autoantibody reactive with the Fc portion of immunoglobulin G [IgG]), but this finding may not be present during the first year of disease. Furthermore, rheumatoid factor is not specific for rheumatoid arthritis and is found in 5% of healthy individuals. The erythrocyte sedimentation rate is increased in most patients with RA, and C-reactive protein, another acute phase reactant, is typically elevated in patients with active disease. X-rays of the hands and feet, or possibly other joints, may be useful in some cases, demonstrating periarticular bony demineralization, joint space narrowing, and bony erosions.

Currently there is no cure for RA. Since the cause of the disease is unknown, current therapies are directed toward suppression of the inflammatory response. Like most chronic arthritides, the goal of treatment is to preserve joint function and limit disease progression. The medication list of a patient with active RA may include a nonsteroidal anti-inflammatory drug (NSAID), a low dose of prednisone, and one or more disease-modifying antirheumatic drugs (DMARDs). See "Guidelines for the management of rheumatoid arthritis" *Arthritis & Rheumatism* 46(2): 328-346 (February, 2002). The majority of patients with newly diagnosed RA are started with disease-modifying antirheumatic drug (DMARD) therapy within 3 months of diagnosis. DMARDs commonly used in RA are hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide, azathioprine, D-penicillamine, Gold (oral), Gold (intramuscular), minocycline, cyclosporine, and Staphylococcal protein A immunoadsorption. Recent studies indicate that patients with active RA develop significant joint damage during the first few years of disease. This knowledge has led to a more aggressive treatment approach using combinations of DMARDs. However, combination DMARD therapy does not completely abrogate disease activity and may result in serious drug-related complications. Moreover, most patients still develop joint erosions despite aggressive treatment.

Overactivity of the cytokine tumor necrosis factor (TNF) has been associated with synoviocyte proliferation, neo-angiogenesis, the recruitment of inflammatory cells, and the production of degradative enzymes. These findings have stimulated the development of anticytokine therapies. Further investigation has shown that the signs and symptoms of RA can be abrogated when certain proinflammatory cytokines, such as TNF and IL-1, are neutralized by monoclonal antibodies, naturally occurring cytokine antagonists, or cytokine receptor blockers.

Etanercept (ENBREL®) is an injectable drug approved in the US for therapy of active RA. Etanercept binds to TNF α and serves to remove most TNF α from joints and blood, thereby preventing TNF α from promoting inflammation and other symptoms of rheumatoid arthritis. Etanercept is an “immunoadhesin” fusion protein consisting of the extracellular ligand binding portion of the human 75 kD (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of a human IgG1. The drug has been associated with negative side effects including serious infections and sepsis, nervous system disorders such as multiple sclerosis (MS).

Infliximab, sold under the trade name REMICADE®, is an immune-suppressing drug prescribed to treat RA and Crohn's disease. Infliximab is a chimeric monoclonal antibody that binds to TNF α and reduces inflammation in the body by targeting and binding to TNF α which produces inflammation. Infliximab has been linked to fatal reactions such as heart failure and infections including tuberculosis as well as demyelination resulting in MS.

In December 2002, Abbott Laboratories received FDA approval to market adalimumab (HUMIRA™), previously known as D2E7. Adalimumab is a human monoclonal antibody that binds to TNF α and is approved for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately to severely active RA who have had insufficient response to one or more traditional disease modifying DMARDs.

Angiogenesis is an important cellular event in which vascular endothelial cells proliferate, prune and reorganize to form new vessels from preexisting vascular network. There are compelling evidences that the development of a vascular supply is essential for normal and pathological proliferative processes (Folkman and Klagsbrun (1987) *Science* 235:442-447). Delivery of oxygen and nutrients, as well as the removal of catabolic products, represent rate-limiting steps in the majority of growth processes occurring in multicellular organisms. Thus, it has been generally assumed that the vascular compartment is necessary, albeit but not sufficient, not only for organ development and differentiation during embryogenesis, but also for wound healing and reproductive functions in the adult.

Angiogenesis is also implicated in the pathogenesis of a variety of disorders, including but not limited to, proliferative retinopathies, age-related macular degeneration, tumors, autoimmune diseases such as rheumatoid arthritis (RA), and psoriasis. Angiogenesis is a cascade of process consisting of 1) degradation of the extracellular matrix of a local venue after the release of protease, 2) proliferation of capillary endothelial cells, and 3) migration of capillary tubules toward the angiogenic stimulus. Ferrara et al. (1992) *Endocrine Rev.* 13:18-32.

In view of the remarkable physiological and pathological importance of angiogenesis, much work has been dedicated to the elucidation of the factors capable of regulating this

process. It is suggested that the angiogenesis process is regulated by a balance between pro- and anti- angiogenic molecules, and is derailed in various diseases, especially cancer. Carmeliet and Jain (2000) *Nature* 407:249-257.

Vascular endothelial cell growth factor (VEGF), a potent mitogen for vascular endothelial cells, has been reported as a pivotal regulator of both normal and abnormal angiogenesis. Ferrara and Davis-Smyth (1997) *Endocrine Rev.* 18:4-25; Ferrara (1999) *J. Mol. Med.* 77:527-543. Compared to other growth factors that contribute to the processes of vascular formation, VEGF is unique in its high specificity for endothelial cells within the vascular system. Recent evidence indicates that VEGF is essential for embryonic vasculogenesis and angiogenesis. Carmeliet et al. (1996) *Nature* 380:435-439; Ferrara et al. (1996) *Nature* 380:439-442. Furthermore, VEGF is required for the cyclical blood vessel proliferation in the female reproductive tract and for bone growth and cartilage formation. Ferrara et al. (1998) *Nature Med.* 4:336-340; Gerber et al. (1999) *Nature Med.* 5:623-628.

In addition to being an angiogenic factor in angiogenesis and vasculogenesis, VEGF, as a pleiotropic growth factor, exhibits multiple biological effects in other physiological processes, such as endothelial cell survival, vessel permeability and vasodilation, monocyte chemotaxis and calcium influx. Ferrara and Davis-Smyth (1997), *supra*. Moreover, recent studies have reported mitogenic effects of VEGF on a few non-endothelial cell types, such as retinal pigment epithelial cells, pancreatic duct cells and Schwann cells. Guerrin et al. (1995) *J. Cell Physiol.* 164:385-394; Oberg-Welsh et al. (1997) *Mol. Cell. Endocrinol.* 126:125-132; Sondell et al. (1999) *J. Neurosci.* 19:5731-5740.

Substantial evidence also implicates VEGF's critical role in the development of conditions or diseases that involve pathological angiogenesis. The VEGF mRNA is overexpressed by the majority of human tumors examined (Berkman *et al. J Clin Invest* 91:153-159 (1993); Brown *et al. Human Pathol.*, 26:86-91 (1995); Brown *et al. Cancer Res.* 53:4727-4735 (1993); Mattern *et al. Brit. J. Cancer.* 73:931-934 (1996); and Dvorak *et al. Am J. Pathol.* 146:1029-1039 (1995)). Also, the concentration of VEGF in eye fluids are highly correlated to the presence of active proliferation of blood vessels in patients with diabetic and other ischemia-related retinopathies (Aiello *et al. N. Engl. J. Med.* 331:1480-1487 (1994)). Furthermore, recent studies have demonstrated the localization of VEGF in choroidal neovascular membranes in patients affected by AMD (Lopez *et al. Invest. Ophthalmol. Vis. Sci.* 37:855-868 (1996)).

The recognition of VEGF as a primary regulator of angiogenesis in pathological conditions has led to numerous attempts to block VEGF activities. Inhibitory anti-VEGF receptor antibodies, soluble receptor constructs, antisense strategies, RNA aptamers against VEGF and low molecular weight VEGF receptor tyrosine kinase (RTK) inhibitors have all been proposed for use in interfering with VEGF signaling (Siemeister *et al. Cancer*

Metastasis Rev. 17:241-248 (1998). Indeed, anti-VEGF neutralizing antibodies have been shown to suppress the growth of a variety of human tumor cell lines in nude mice (Kim *et al. Nature* 362:841-844 (1993); Warren *et al. J. Clin. Invest.* 95:1789-1797 (1995); Borgström *et al. Cancer Res.* 56:4032-4039 (1996); and Melnyk *et al. Cancer Res.* 56:921-924 (1996)) and also inhibit intraocular angiogenesis in models of ischemic retinal disorders (Adamis *et al. Arch. Ophthalmol.* 114:66-71 (1996)). Therefore, anti-VEGF monoclonal antibodies or other inhibitors of VEGF action are promising candidates for the treatment of solid tumors and various intraocular neovascular disorders. Although the VEGF molecule is upregulated in tumor cells, and its receptors are upregulated in tumor infiltrated vascular endothelial cells, the expression of VEGF and its receptors remain low in normal cells that are not associated with angiogenesis. Thus, such normal cells would not be affected by blocking the interaction between VEGF and its receptors to inhibit tumor angiogenesis, and therefore tumor growth and cancer metastasis.

Monoclonal antibodies are now commonly manufactured using recombinant DNA technology. Widespread use has been made of monoclonal antibodies, particularly those derived from rodents. However, nonhuman antibodies are frequently antigenic in humans. The art has attempted to overcome this problem by constructing "chimeric" antibodies in which a nonhuman antigen-binding domain is coupled to a human constant domain (Cabilly *et al.*, U.S. patent No. 4,816,567). The isotype of the human constant domain may be selected to tailor the chimeric antibody for participation in antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity. In a further effort to resolve the antigen binding functions of antibodies and to minimize the use of heterologous sequences in human antibodies, humanized antibodies have been generated for various antigens in which substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species have substituted rodent (CDR) residues for the corresponding segments of a human antibody to generate. In practice, humanized antibodies are typically human antibodies in which some complementarity determining region (CDR) residues and possibly some framework region (FR) residues are substituted by residues from analogous sites in rodent antibodies. Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature* 332:323-327 (1988); Verhoeyen *et al.*, *Science* 239:1534-1536 (1988).

Several humanized anti-human VEGF (hVEGF) antibodies have been successfully generated, and have shown significant hVEGF-inhibitory activities both *in vitro* and *in vivo*. Presta *et al.* (1997) *Cancer Research* 57:4593-4599; Chen *et al.* (1999) *J. Mol. Biol.* 293:865-881. One specific humanized anti-VEGF antibody, bevacizumab (Avastin®, Genentech, Inc.), has been approved in the US for use in combination with chemotherapeutic agents for treating metastatic colorectal cancer (CRC). The drug is currently used in several clinical trials for

treating various other cancers. Another high-affinity variant of the humanized anti-VEGF antibody is currently clinically tested for treating age-related macular degeneration (AMD).

There is increasing evidence to suggest that VEGF is associated with the pathogenesis of inflammatory joint diseases such as RA. VEGF has been identified in synovial tissues such as synovial lining cells, synovial lining macrophages, perivascular fibroblasts, and vascular smooth muscle cells in the inflamed joints of patients with RA. Nagashima et al (1995) *J. Rheumatol.* 22:1624-1630. VEGF levels in synovial fluid and serum are found to be significantly elevated in both adult and juvenile RA and to correlate with disease activity. Koch et al. (1994) *J. Immunol.* 152:4149-4156. Recently, it has been demonstrated that neutralization of VEGF can prevent collagen-induced arthritis and ameliorate established RA in mice. Sone et al. (2001) *Bioch. Bioph. Res. Comm.* 281:562-568.

Despite these developments, there remains a need for effective therapies of autoimmune diseases, especially therapies using angiogenesis antagonists.

Summary of the Invention

The present invention provides, in a first aspect, a method of treating an autoimmune disease in a mammal who has failed a prior treatment, comprising administering to the mammal a therapeutically effective amount of an angiogenesis antagonist.

For instance, the invention provides a method of treating rheumatoid arthritis in a mammal who has failed or experiences an inadequate response to a DMARD therapy such as MTX or a TNF α -inhibitor, comprising administering to the mammal a therapeutically effective amount of an antibody that binds to and blocks VEGF.

The invention also concerns a method of reducing the risk of a negative side effect selected from the group consisting of an infection, heart failure and demyelination, comprising administering to a mammal with an autoimmune disease a therapeutically effective amount of an angiogenesis antagonist.

Also provided are uses of angiogenesis antagonists such as anti-VEGF antibodies in the preparation of medicaments for the treatment of autoimmune diseases such as RA, in patients who have failed prior therapies.

Detailed Description of the Preferred Embodiments

I. Definitions

For the purposes herein, "angiogenesis antagonist" is a composition capable of blocking, inhibiting, abrogating, interfering or reducing pathological angiogenesis associated with a disease or disorder. Many angiogenesis antagonists have been identified and are known in the arts, including those listed by Carmeliet and Jain (2000). Generally, angiogenesis antagonist is a composition targeting a specific angiogenic factor or an angiogenesis pathway. In certain aspects, the angiogenesis antagonist is a protein

composition such as an antibody targeting an angiogenic factor. One of the most recognized angiogenic factors is VEGF, and one of the most potent angiogenesis antagonists is a neutralizing anti-VEGF antibody.

The terms "VEGF" and "VEGF-A" are used interchangeably to refer to the 165-amino acid vascular endothelial cell growth factor and related 121-, 189-, and 206- amino acid vascular endothelial cell growth factors, as described by Leung *et al. Science*, 246:1306 (1989), and Houck *et al. Mol. Endocrin.*, 5:1806 (1991), together with the naturally occurring allelic and processed forms thereof. The term "VEGF" is also used to refer to truncated forms of the polypeptide comprising amino acids 8 to 109 or 1 to 109 of the 165-amino acid human vascular endothelial cell growth factor. Reference to any such forms of VEGF may be identified in the present application, e.g., by "VEGF (8-109)," "VEGF (1-109)" or "VEGF₁₆₅." The amino acid positions for a "truncated" native VEGF are numbered as indicated in the native VEGF sequence. For example, amino acid position 17 (methionine) in truncated native VEGF is also position 17 (methionine) in native VEGF. The truncated native VEGF has binding affinity for the KDR and Flt-1 receptors comparable to native VEGF.

An "anti-VEGF antibody" is an antibody that binds to VEGF with sufficient affinity and specificity. Preferably, the anti-VEGF antibody of the invention can be used as a therapeutic agent in targeting and interfering with diseases or conditions wherein the VEGF activity is involved. An anti-VEGF antibody will usually not bind to other VEGF homologues such as VEGF-B or VEGF-C, nor other growth factors such as PlGF, PDGF or bFGF. A preferred anti-VEGF antibody is a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709. More preferably the anti-VEGF antibody is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta *et al. (1997) Cancer Res.* 57:4593-4599, including but not limited to the antibody known as bevacizumab (BV; Avastin[®]).

The anti-VEGF antibody "Bevacizumab (BV)", also known as "rhUMAb VEGF" or "Avastin[®]", is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta *et al. (1997) Cancer Res.* 57:4593-4599. It comprises mutated human IgG1 framework regions and antigen-binding complementarity-determining regions from the murine anti-hVEGF monoclonal antibody A.4.6.1 that blocks binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence of Bevacizumab, including most of the framework regions, is derived from human IgG1, and about 7% of the sequence is derived from the murine antibody A4.6.1. Bevacizumab has a molecular mass of about 149,000 daltons and is glycosylated.

A “VEGF antagonist” refers to a molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing or interfering with VEGF activities including its binding to one or more VEGF receptors. VEGF antagonists include anti-VEGF antibodies and antigen-binding fragments thereof, receptor molecules and derivatives which bind specifically to VEGF thereby sequestering its binding to one or more receptors, anti-VEGF receptor antibodies and VEGF receptor antagonists such as small molecule inhibitors of the VEGFR tyrosine kinases.

An “autoimmune disease” herein is a disease or disorder arising from and directed against an individual’s own tissues or a co-segregate or manifestation thereof or resulting condition therefrom. Examples of autoimmune diseases or disorders include, but are not limited to arthritis (rheumatoid arthritis, juvenile-onset rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and ankylosing spondylitis), psoriasis, dermatitis including atopic dermatitis, chronic idiopathic urticaria, including chronic autoimmune urticaria, polymyositis/dermatomyositis, toxic epidermal necrolysis, scleroderma (including systemic scleroderma), sclerosis such as progressive systemic sclerosis, inflammatory bowel disease (IBD) (for example, Crohn's disease, ulcerative colitis, autoimmune inflammatory bowel disease), pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, episcleritis), respiratory distress syndrome, including adult respiratory distress syndrome (ARDS), meningitis, IgE-mediated diseases such as anaphylaxis and allergic and atopic rhinitis, encephalitis such as Rasmussen's encephalitis, uveitis or autoimmune uveitis, colitis such as microscopic colitis and collagenous colitis, glomerulonephritis (GN) such as membranous GN (membranous nephropathy), idiopathic membranous GN, membranous proliferative GN (MPGN), including Type I and Type II, and rapidly progressive GN, allergic conditions, allergic reaction, eczema, asthma, conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, autoimmune myocarditis, leukocyte adhesion deficiency, systemic lupus erythematosus (SLE) such as cutaneous SLE, subacute cutaneous lupus erythematosus, lupus (including nephritis, cerebritis, pediatric, non-renal, discoid, alopecia), juvenile onset (Type I) diabetes mellitus, including pediatric insulin-dependent diabetes mellitus (IDDM), adult onset diabetes mellitus (Type II diabetes), multiple sclerosis (MS) such as spino-optical MS, immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, tuberculosis, sarcoidosis, granulomatosis including lymphomatoid granulomatosis, Wegener’s granulomatosis, agranulocytosis, vasculitis (including large vessel vasculitis (including polymyalgia rheumatica and giant cell (Takayasu’s) arteritis), medium vessel vasculitis (including Kawasaki’s disease and polyarteritis nodosa), CNS vasculitis, systemic necrotizing vasculitis, and ANCA-associated vasculitis, such as Churg-Strauss vasculitis or syndrome

(CSS)), temporal arteritis, aplastic anemia, Coombs positive anemia, Diamond Blackfan anemia, hemolytic anemia or immune hemolytic anemia including autoimmune hemolytic anemia (AIHA), pernicious anemia, pure red cell aplasia (PRCA), Factor VIII deficiency, hemophilia A, autoimmune neutropenia, pancytopenia, leukopenia, diseases involving leukocyte diapedesis, CNS inflammatory disorders, multiple organ injury syndrome, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, anti-phospholipid antibody syndrome, allergic neuritis, Bechet's or Behcet's disease, Castleman's syndrome, Goodpasture's syndrome, Reynaud's syndrome, Sjogren's syndrome, Stevens-Johnson syndrome, pemphigoid such as pemphigoid bullous, pemphigus (including vulgaris, foliaceus, and pemphigus mucus-membrane pemphigoid), autoimmune polyendocrinopathies, Reiter's disease, immune complex nephritis, chronic neuropathy such as IgM polyneuropathies or IgM-mediated neuropathy, thrombocytopenia (as developed by myocardial infarction patients, for example), including thrombotic thrombocytopenic purpura (TTP) and autoimmune or immune-mediated thrombocytopenia such as idiopathic thrombocytopenic purpura (ITP) including chronic or acute ITP, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, primary hypothyroidism, hypoparathyroidism, autoimmune endocrine diseases including thyroiditis such as autoimmune thyroiditis, chronic thyroiditis (Hashimoto's thyroiditis), or subacute thyroiditis, autoimmune thyroid disease, idiopathic hypothyroidism, Addison's disease, Grave's disease, polyglandular syndromes such as autoimmune polyglandular syndromes (or polyglandular endocrinopathy syndromes), paraneoplastic syndromes, including neurologic paraneoplastic syndromes such as Lambert-Eaton myasthenic syndrome or Eaton-Lambert syndrome, stiff-man or stiff-person syndrome, encephalomyelitis such as allergic encephalomyelitis, myasthenia gravis, cerebellar degeneration, limbic and/or brainstem encephalitis, neuromyotonia, opsoclonus or opsoclonus myoclonus syndrome (OMS), and sensory neuropathy, Sheehan's syndrome, autoimmune hepatitis, chronic hepatitis, lupoid hepatitis, chronic active hepatitis or autoimmune chronic active hepatitis, lymphoid interstitial pneumonitis, bronchiolitis obliterans (non-transplant) vs NSIP, Guillain-Barré syndrome, Berger's disease (IgA nephropathy), primary biliary cirrhosis, celiac sprue (gluten enteropathy), refractory sprue, dermatitis herpetiformis, cryoglobulinemia, amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), coronary artery disease, autoimmune inner ear disease (AIED); or autoimmune hearing loss, opsoclonus myoclonus syndrome (OMS), polychondritis such as refractory polychondritis, pulmonary alveolar proteinosis, amyloidosis, giant cell hepatitis, scleritis, a non-cancerous lymphocytosis, a primary lymphocytosis, which includes monoclonal B cell lymphocytosis (e.g., benign monoclonal gammopathy and monoclonal gammopathy of undetermined significance, MGUS), peripheral neuropathy, paraneoplastic syndrome, channelopathies such as epilepsy, migraine, arrhythmia, muscular

disorders, deafness, blindness, periodic paralysis, and channelopathies of the CNS, autism, inflammatory myopathy, focal segmental glomerulosclerosis (FSGS), endocrine ophthalmopathy, uveoretinitis, autoimmune hepatological disorder, fibromyalgia, multiple endocrine failure, Schmidt's syndrome, adrenalitis, gastric atrophy, presenile dementia, demyelinating diseases, Dressler's syndrome, alopecia arcata, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), male and female autoimmune infertility, ankylosing spondylitis, mixed connective tissue disease, Chagas' disease, rheumatic fever, recurrent abortion, farmer's lung, erythema multiforme, post-cardiotomy syndrome, Cushing's syndrome, bird-fancier's lung, Alport's syndrome, alveolitis such as allergic alveolitis and fibrosing alveolitis, interstitial lung disease, transfusion reaction, leprosy, malaria, leishmaniasis, kypanosomiasis, schistosomiasis, ascariasis, aspergillosis, Sampter's syndrome, Caplan's syndrome, dengue, endocarditis, endomyocardial fibrosis, endophthalmitis, erythema elevatum et diutinum, erythroblastosis fetalis, eosinophilic faciiitis, Shulman's syndrome, Felty's syndrome, flariasis, cyclitis such as chronic cyclitis, heterochronic cyclitis, or Fuch's cyclitis, Henoch-Schonlein purpura, human immunodeficiency virus (HIV) infection, echovirus infection, cardiomyopathy, Alzheimer's disease, parvovirus infection, rubella virus infection, post-vaccination syndromes, congenital rubella infection, Epstein-Barr virus infection, mumps, Evan's syndrome, autoimmune gonadal failure, Sydenham's chorea, post-streptococcal nephritis, thromboangitis ubiterans, thyrotoxicosis, tabes dorsalis, and giant cell polymyalgia.

A “tumor necrosis factor alpha (TNF α)” refers to a human TNF α molecule comprising the amino acid sequence as described in Pennica *et al.*, *Nature*, 312:721 (1984) or Aggarwal *et al.*, *JBC*, 260:2345 (1985).

A “TNF α inhibitor” herein is an agent that decreases, inhibits, blocks, abrogates or interferes a biological function of TNF α , generally through binding to TNF α and neutralizing its activity. Examples of TNF inhibitors specifically contemplated herein are Etanercept (ENBREL®), Infliximab (REMICADE®) and Adalimumab (HUMIRA™).

The term “inadequate response to a TNF α -inhibitor” refers to an inadequate response to previous or current treatment with a TNF α -inhibitor because of toxicity and/or inadequate efficacy. The inadequate response can be assessed by a clinician skilled in treating the disease in question.

A mammal who experiences “toxicity” from previous or current treatment with the TNF α -inhibitor experiences one or more negative side-effects associated therewith such as infection (especially serious infections), congestive heart failure, demyelination (leading to multiple sclerosis), hypersensitivity, neurologic events, autoimmunity, non-Hodgkin's lymphoma, tuberculosis (TB), autoantibodies, etc.

A mammal who has "failed prior treatment" or experiences "inadequate efficacy" continues to have active disease following previous or current treatment with a drug such as a DMARD or a TNF α -inhibitor. For instance, the patient may have active disease activity after 1 month or 3 months of therapy with the DMARD (such as MTX) or the TNF α -inhibitor.

A "B cell surface marker" herein is an antigen expressed on the surface of a B cell which can be targeted with an antagonist which binds thereto. Exemplary B cell surface markers include the CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD40, CD53, CD72, CD73, CD74, CDw75, CDw76, CD77, CDw78, CD79a, CD79b, CD80, CD81, CD82, CD83, CDw84, CD85 and CD86 leukocyte surface markers. The B cell surface marker of particular interest is preferentially expressed on B cells compared to other non-B cell tissues of a mammal and may be expressed on both precursor B cells and mature B cells. In one embodiment, the marker is one, like CD20 or CD19, which is found on B cells throughout differentiation of the lineage from the stem cell stage up to a point just prior to terminal differentiation into plasma cells. The preferred B cell surface markers herein is CD20.

The "CD20" antigen is a ~35 kDa, non-glycosylated phosphoprotein found on the surface of greater than 90% of B cells from peripheral blood or lymphoid organs. CD20 is expressed during early pre-B cell development and remains until plasma cell differentiation. CD20 is present on both normal B cells as well as malignant B cells. Other names for CD20 in the literature include "B-lymphocyte-restricted antigen" and "Bp35". The CD20 antigen is described in Clark *et al. PNAS (USA)* 82:1766 (1985), for example.

"Growth inhibitory" antagonists are those which prevent or reduce proliferation of a cell expressing an antigen to which the antagonist binds. For example, the antagonist may prevent or reduce proliferation of B cells *in vitro* and/or *in vivo*.

The term "antibody" herein is used in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.* bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

"Antibody fragments" comprise a portion of an intact antibody, preferably comprising the antigen-binding or variable region thereof. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

"Native antibodies" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each

light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains.

The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called hypervariable regions both in the light chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FRs). The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-binding sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and antigen-binding site. This region consists of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three hypervariable regions of each variable domain interact to define an antigen-binding site on the surface of the V_H - V_L dimer. Collectively, the six hypervariable regions confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three hypervariable regions specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for

Fab' in which the cysteine residue(s) of the constant domains bear at least one free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes. There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of antibodies are called α , δ , ϵ , γ , and μ , respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv see Plückthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H - V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993).

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being

obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.*, *Nature*, 256:495 (1975), or may be made by recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, *Nature*, 352:624-628 (1991) and Marks *et al.*, *J. Mol. Biol.*, 222:581-597 (1991), for example.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison *et al.*, *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (*e.g.* Old World Monkey, such as baboon, rhesus or cynomolgus monkey) and human constant region sequences (US Pat No. 5,693,780).

"Humanized" forms of non-human (*e.g.*, murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (*e.g.* residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain; Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (*e.g.* residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain; Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). "Framework" or "FR" residues are those variable domain residues other than the hypervariable region residues as herein defined.

An antagonist "which binds" an antigen of interest, *e.g.* VEGF, is one capable of binding that antigen with sufficient affinity and/or avidity such that the antagonist is useful as a therapeutic agent for targeting the antigen or a cell expressing the antigen.

An "isolated" antagonist is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antagonist, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antagonist will be purified (1) to greater than 95% by weight of antagonist as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antagonist includes the antagonist *in situ* within recombinant cells since at least one component of the antagonist's natural environment will not be present. Ordinarily, however, isolated antagonist will be prepared by at least one purification step.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, *etc.* Preferably, the mammal is human.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disease or disorder as well as those in which the disease or disorder is to be prevented. Hence, the mammal may have been diagnosed as having the disease or disorder or may be predisposed or susceptible to the disease.

The expression "therapeutically effective amount" refers to an amount of the antagonist which is effective for preventing, ameliorating or treating the autoimmune disease in question.

The term "immunosuppressive agent" as used herein for adjunct therapy refers to substances that act to suppress or mask the immune system of the mammal being treated herein. This would include substances that suppress cytokine production, downregulate or suppress self-antigen expression, or mask the MHC antigens. Examples of such agents include 2-amino-6-aryl-5-substituted pyrimidines (see U.S. Pat. No. 4,665,077, the disclosure of which is incorporated herein by reference); nonsteroidal antiinflammatory drugs (NSAIDs); azathioprine; cyclophosphamide; bromocryptine; danazol; dapsone; glutaraldehyde (which masks the MHC antigens, as described in U.S. Pat. No. 4,120,649); anti-idiotypic antibodies for MHC antigens and MHC fragments; cyclosporin A; steroids such as glucocorticosteroids, *e.g.*, prednisone, methylprednisolone, and dexamethasone; methotrexate (oral or subcutaneous); hydroxycloquine; sulfasalazine; leflunomide; cytokine or cytokine receptor antagonists including anti-interferon- γ , - β , or - α antibodies, anti-tumor necrosis factor- α antibodies (infliximab or adalimumab), anti-TNF α immunoahesin (etanercept), anti-tumor necrosis factor- β antibodies, anti-interleukin-2 antibodies and anti-IL-2 receptor antibodies; anti-LFA-1 antibodies, including anti-CD11a and anti-CD18 antibodies; anti-L3T4 antibodies; heterologous anti-lymphocyte globulin; pan-T antibodies, preferably anti-CD3 or anti-CD4/CD4a antibodies; soluble peptide containing a LFA-3 binding domain (WO 90/08187 published 7/26/90); streptokinase; TGF- β ; streptodornase; RNA or DNA from the host; FK506; RS-61443; deoxyspergualin; rapamycin; T-cell receptor (Cohen *et al.*, U.S. Pat. No. 5,114,721); T-cell receptor fragments (Offner *et al.*, *Science*, 251: 430-432 (1991); WO 90/11294; Ianeway, *Nature*, 341: 482 (1989); and WO 91/01133); and T cell receptor antibodies (EP 340,109) such as T10B9.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.* At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³² and radioactive isotopes of Lu), chemotherapeutic agents, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXANTM); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; nitrogen

mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, aethramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, encitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanol, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as froinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diazi quone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofiran; spirogermanium; tenuazonic acid; triazi quone; 2, 2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, *e.g.* paclitaxel (TAXOL®), Bristol-Myers Squibb Oncology, Princeton, NJ) and doxetaxel (TAXOTERE®, Rhône-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon- α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1 α , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12, IL-15; a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

The term "prodrug" as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active parent form. See, e.g., Wilman, "Prodrugs in Cancer Chemotherapy" *Biochemical Society Transactions*, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella *et al.*, "Prodrugs: A Chemical Approach to Targeted Drug Delivery," *Directed Drug Delivery*, Borchardt *et al.*, (ed.), pp. 247-267, Humana Press (1985). The prodrugs of this invention include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β -lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form for use in this invention include, but are not limited to, those chemotherapeutic agents described above.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as the antagonists disclosed herein and, optionally, a chemotherapeutic agent) to a mammal. The components of the

liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

The term "intravenous infusion" refers to introduction of a drug into the vein of an animal or human patient over a period of time greater than approximately 5 minutes, preferably between approximately 30 to 90 minutes, although, according to the invention, intravenous infusion is alternatively administered for 10 hours or less.

The term "intravenous bolus" or "intravenous push" refers to drug administration into a vein of an animal or human such that the body receives the drug in approximately 15 minutes or less, preferably 5 minutes or less.

The term "subcutaneous administration" refers to introduction of a drug under the skin of an animal or human patient, preferable within a pocket between the skin and underlying tissue, by relatively slow, sustained delivery from a drug receptacle. The pocket may be created by pinching or drawing the skin up and away from underlying tissue.

The term "subcutaneous infusion" refers to introduction of a drug under the skin of an animal or human patient, preferably within a pocket between the skin and underlying tissue, by relatively slow, sustained delivery from a drug receptacle for a period of time including, but not limited to, 30 minutes or less, or 90 minutes or less. Optionally, the infusion may be made by subcutaneous implantation of a drug delivery pump implanted under the skin of the animal or human patient, wherein the pump delivers a predetermined amount of drug for a predetermined period of time, such as 30 minutes, 90 minutes, or a time period spanning the length of the treatment regimen.

The term "subcutaneous bolus" refers to drug administration beneath the skin of an animal or human patient, where bolus drug delivery is preferably less than approximately 15 minutes, more preferably less than 5 minutes, and most preferably less than 60 seconds. Administration is preferably within a pocket between the skin and underlying tissue, where the pocket is created, for example, by pinching or drawing the skin up and away from underlying tissue.

II. Production of Antagonists

The methods and articles of manufacture of the present invention use, or incorporate, an angiogenesis antagonist. Accordingly, methods for generating such antagonists will be described here.

The angiogenesis antagonist can be a protein antagonist of an angiogenic factor. Preferably the antagonist is a VEGF antagonist. In addition to anti-VEGF antibody, which is a preferred VEGF antagonist for the purpose of this invention, other VEGF antagonists include VEGF variants, soluble VEGF receptor fragments, aptamers capable of blocking VEGF or VEGFR, neutralizing anti-VEGFR antibodies, and low molecule weight inhibitors of VEGFR tyrosine kinases.

A description follows as to exemplary techniques for the production of the antibody antagonists used in accordance with the present invention.

(i) *Polyclonal antibodies*

Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen to a protein that is immunogenic in the species to be immunized, *e.g.*, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, *e.g.*, 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate of the same antigen, but conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

(ii) *Monoclonal antibodies*

Monoclonal antibodies are obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies. For example, the monoclonal antibodies may be made using the hybridoma method first described by Kohler *et al.*, *Nature*, 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Maryland USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur *et al.*, *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson *et al.*, *Anal. Biochem.*, 107:220 (1980).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be

placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra *et al.*, *Curr. Opinion in Immunol.*, 5:256-262 (1993) and Plückerthun, *Immunol. Revs.*, 130:151-188 (1992).

In a further embodiment, antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty *et al.*, *Nature*, 348:552-554 (1990). Clackson *et al.*, *Nature*, 352:624-628 (1991) and Marks *et al.*, *J. Mol. Biol.*, 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks *et al.*, *Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse *et al.*, *Nuc. Acids. Res.*, 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, *et al.*, *Proc. Natl Acad. Sci. USA*, 81:6851 (1984)), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

(iii) *Humanized antibodies*

Methods for humanizing non-human antibodies have been described in the art. Preferably, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones *et al.*, *Nature*, 321:522-525 (1986); Riechmann *et al.*, *Nature*, 332:323-327 (1988); Verhoeven *et al.*, *Science*, 239:1534-1536 (1988)), by substituting hypervariable region sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the

corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some hypervariable region residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework region (FR) for the humanized antibody (Sims *et al.*, *J. Immunol.*, 151:2296 (1993); Chothia *et al.*, *J. Mol. Biol.*, 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter *et al.*, *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); Presta *et al.*, *J. Immunol.*, 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *i.e.*, the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

(iv) *Human antibodies*

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (*e.g.*, mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, *e.g.*, Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:2551 (1993); Jakobovits *et al.*, *Nature*,

362:255-258 (1993); Bruggermann *et al.*, *Year in Immuno.*, 7:33 (1993); and US Patent Nos. 5,591,669, 5,589,369 and 5,545,807.

Alternatively, phage display technology (McCafferty *et al.*, *Nature* 348:552-553 (1990)) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B cell. Phage display can be performed in a variety of formats; for their review see, *e.g.*, Johnson, Kevin S. and Chiswell, David J., *Current Opinion in Structural Biology* 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson *et al.*, *Nature*, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks *et al.*, *J. Mol. Biol.* 222:581-597 (1991), or Griffith *et al.*, *EMBO J.* 12:725-734 (1993). See, also, US Patent Nos. 5,565,332 and 5,573,905.

Human antibodies may also be generated by *in vitro* activated B cells (see US Patents 5,567,610 and 5,229,275).

(v) *Antibody fragments*

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, *e.g.*, Morimoto *et al.*, *Journal of Biochemical and Biophysical Methods* 24:107-117 (1992) and Brennan *et al.*, *Science*, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. For example, the antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter *et al.*, *Bio/Technology* 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; US Patent No. 5,571,894; and US Patent No. 5,587,458. The antibody fragment may also be a "linear antibody", *e.g.*, as described in US Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispecific.

(vi) *Bispecific antibodies*

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein *et al.*, *Nature*, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker *et al.*, *EMBO J.*, 10:3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh *et al.*, *Methods in Enzymology*, 121:210 (1986). According to another approach described in US Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface

comprises at least a part of the C_H3 domain of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (*e.g.* tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (*e.g.* alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (US Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in US Patent No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al.*, *Science*, 229: 81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby *et al.*, *J. Exp. Med.*, 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, *J. Immunol.*, 148(5):1547-1553

(1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber *et al.*, *J. Immunol.*, 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.* *J. Immunol.* 147: 60 (1991).

III. Conjugates and Other Modifications of the Antagonist

The antagonist used in the methods or included in the articles of manufacture herein is optionally conjugated to a cytotoxic agent.

Chemotherapeutic agents useful in the generation of such antagonist-cytotoxic agent conjugates have been described above.

Conjugates of an antagonist and one or more small molecule toxins, such as a calicheamicin, a maytansine (US Patent No. 5,208,020), a trichothene, and CC1065 are also contemplated herein. In one embodiment of the invention, the antagonist is conjugated to one or more maytansine molecules (*e.g.* about 1 to about 10 maytansine molecules per antagonist molecule). Maytansine may, for example, be converted to May-SS-Me which may be reduced to May-SH3 and reacted with modified antagonist (Chari *et al.* *Cancer Research* 52: 127-131 (1992)) to generate a maytansinoid-antagonist conjugate.

Alternatively, the antagonist is conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. Structural analogues of calicheamicin which may be used include, but are not limited to, γ_1^I , α_2^I , α_3^I , N-acetyl- γ_1^I , PSAG and θ^I (Hinman *et al.* *Cancer Research* 53: 3336-3342 (1993) and Lode *et al.* *Cancer Research* 58: 2925-2928 (1998)).

Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and

PAP-S), momordica charantia inhibitor, curcin, crocin, saponaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, WO 93/21232 published October 28, 1993.

The present invention further contemplates antagonist conjugated with a compound with nucleolytic activity (*e.g.* a ribonuclease or a DNA endonuclease such as a deoxyribonuclease; DNase).

A variety of radioactive isotopes are available for the production of radioconjugated antagonists. Examples include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³² and radioactive isotopes of Lu.

Conjugates of the antagonist and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridylthiol) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al. Science* 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antagonist. See WO94/11026. The linker may be a "cleavable linker" facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, dimethyl linker or disulfide-containing linker (Chari *et al. Cancer Research* 52: 127-131 (1992)) may be used. Alternatively, a fusion protein comprising the antagonist and cytotoxic agent may be made, *e.g.* by recombinant techniques or peptide synthesis.

The antagonists of the present invention may also be conjugated with a prodrug-activating enzyme which converts a prodrug (*e.g.* a peptidyl chemotherapeutic agent, see WO81/01145) to an active anti-cancer drug. See, for example, WO 88/07378 and U.S. Patent No. 4,975,278.

The enzyme component of such conjugates includes any enzyme capable of acting on a prodrug in such a way so as to convert it into its more active, cytotoxic form. Enzymes that are useful in the method of this invention include, but are not limited to, alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free

drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as β -galactosidase and neuraminidase useful for converting glycosylated prodrugs into free drugs; β -lactamase useful for converting drugs derivatized with β -lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, *e.g.*, Massey, *Nature* 328: 457-458 (1987)).

The enzymes of this invention can be covalently bound to the antagonist by techniques well known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen binding region of an antagonist of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well known in the art (see, *e.g.*, Neuberger *et al.*, *Nature*, 312: 604-608 (1984)).

Other modifications of the antagonist are contemplated herein. For example, the antagonist may be linked to one of a variety of nonproteinaceous polymers, *e.g.*, polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol.

The antagonists disclosed herein may also be formulated as liposomes. Liposomes containing the antagonist are prepared by methods known in the art, such as described in Epstein *et al.*, *Proc. Natl. Acad. Sci. USA*, 82:3688 (1985); Hwang *et al.*, *Proc. Natl. Acad. Sci. USA*, 77:4030 (1980); U.S. Pat. Nos. 4,485,045 and 4,544,545; and WO97/38731 published October 23, 1997. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of an antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.* *J. Biol. Chem.* 257: 286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon *et al.* *J. National Cancer Inst.* 81(19)1484 (1989).

Amino acid sequence modification(s) of protein or peptide antagonists described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antagonist. Amino acid sequence variants of the antagonist are prepared by introducing appropriate nucleotide changes into the antagonist

nucleic acid, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antagonist. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the antagonist, such as changing the number or position of glycosylation sites.

A useful method for identification of certain residues or regions of the antagonist that are preferred locations for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells *Science*, 244:1081-1085 (1989). Here, a residue or group of target residues are identified (*e.g.*, charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with antigen. Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* need not be predetermined. For example, to analyze the performance of a mutation at a given site, ala scanning or random mutagenesis is conducted at the target codon or region and the expressed antagonist variants are screened for the desired activity.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antagonist with an N-terminal methionyl residue or the antagonist fused to a cytotoxic polypeptide. Other insertional variants of the antagonist molecule include the fusion to the N- or C-terminus of the antagonist of an enzyme, or a polypeptide which increases the serum half-life of the antagonist.

Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the antagonist molecule replaced by different residue. The sites of greatest interest for substitutional mutagenesis of antibody antagonists include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 1, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Table 1

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; asp, lys; arg	gln
Asp (D)	glu; asn	glu
Cys (C)	ser; ala	ser
Gln (Q)	asn; glu	asn
Glu (E)	asp; gln	asp
Gly (G)	ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	tyr
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in the biological properties of the antagonist are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

Any cysteine residue not involved in maintaining the proper conformation of the antagonist also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antagonist to improve its stability (particularly where the antagonist is an antibody fragment such as an Fv fragment).

A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody. Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants is affinity maturation using phage display. Briefly, several hypervariable region sites (*e.g.* 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (*e.g.* binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or in additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Another type of amino acid variant of the antagonist alters the original glycosylation pattern of the antagonist. By altering is meant deleting one or more carbohydrate moieties found in the antagonist, and/or adding one or more glycosylation sites that are not present in the antagonist.

Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the antagonist is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antagonist (for O-linked glycosylation sites).

Nucleic acid molecules encoding amino acid sequence variants of the antagonist are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the antagonist.

It may be desirable to modify the antagonist of the invention with respect to effector function, *e.g.* so as to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the antagonist. This may be achieved by introducing one or more amino acid substitutions in an Fc region of an antibody antagonist. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, *J. Exp Med.* 176:1191-1195 (1992) and Shopes, B. *J. Immunol.* 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al. Cancer Research* 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may

thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al. Anti-Cancer Drug Design* 3:219-230 (1989).

To increase the serum half life of the antagonist, one may incorporate a salvage receptor binding epitope into the antagonist (especially an antibody fragment) as described in US Patent 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (*e.g.*, IgG₁, IgG₂, IgG₃, or IgG₄) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

IV. Pharmaceutical Formulations

Therapeutic formulations of the antagonists used in accordance with the present invention are prepared for storage by mixing an antagonist having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.* Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Lyophilized formulations adapted for subcutaneous administration are described in WO97/04801. Such lyophilized formulations may be reconstituted with a suitable diluent to a high protein concentration and the reconstituted formulation may be administered subcutaneously to the mammal to be treated herein.

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide a cytotoxic agent, chemotherapeutic agent, cytokine or immunosuppressive agent (*e.g.* one which acts on T cells, such as cyclosporin or an antibody that binds T cells, *e.g.* one which binds LFA-1). The effective amount of such other agents depends on the amount of antagonist present in the formulation, the type of disease or disorder or treatment, and other

factors discussed above. These are generally used in the same dosages and with administration routes as used hereinbefore or about from 1 to 99% of the heretofore employed dosages.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antagonist, which matrices are in the form of shaped articles, *e.g.* films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

V. Treatment with the Antagonist

The present invention concerns therapy of a subpopulation of mammals, especially humans, with, or susceptible to, an autoimmune disease, who has failed or experience an inadequate response to previous or current treatment. Generally, the mammal to be treated herein will be identified following therapy with one or more treatments with one or more DMARDs or one or more TNF α -inhibitor(s), as experiencing an inadequate response to previous or current treatment because of toxicity and/or inadequate efficacy. However, the invention is not limited to a prior therapy step with such a treatment; for instance, the patient may be considered to be prone to experience a toxicity, *e.g.* cardiac toxicity, with a DMARD or a TNF α -inhibitor before therapy therewith has begun, or the patient may be determined to be one who is unlikely to respond to such therapy.

The various autoimmune diseases to be treated herein are listed in the definitions section above. The preferred indications herein are rheumatoid arthritis, lupus, psoriatic arthritis, multiple sclerosis or Crohn's disease.

For the prevention or treatment of disease, the appropriate dosage of antagonist will depend on the type of disease to be treated, as defined above, the severity and course of the

disease, whether the antagonist is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antagonist, and the discretion of the attending physician. The antagonist is suitably administered to the patient at one time or over a series of treatments. In a combination therapy regimen, the compositions of the present invention are administered in a therapeutically effective or synergistic amount. As used herein, a therapeutically effective amount is such that co-administration of the antagonist and one or more other therapeutic agents, or administration of a composition of the present invention, results in reduction or inhibition of the targeting disease or condition. A therapeutically synergistic amount is that amount of antagonist and one or more other therapeutic agents necessary to synergistically or significantly reduce or eliminate conditions or symptoms associated with a particular disease.

Depending on the type and severity of the disease, about 1 $\mu\text{g}/\text{kg}$ to 50 mg/kg (*e.g.* 0.1-20 mg/kg) of antagonist is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage might range from about 1 $\mu\text{g}/\text{kg}$ to about 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. In a preferred aspect, the antagonist is administered every two to three weeks, at a dose ranged from about 1.5 mg/kg to about 15 mg/kg . More preferably, such dosing regimen is used in combination with another therapeutic agent for autoimmune diseases. The progress of the therapy of the invention is easily monitored by conventional techniques and assays.

As noted above, however, these suggested amounts of antagonist are subject to a great deal of therapeutic discretion. The key factor in selecting an appropriate dose and scheduling is the result obtained, as indicated above. For example, relatively higher doses may be needed initially for the treatment of ongoing and acute diseases. To obtain the most efficacious results, depending on the disease or disorder, the antagonist is administered as close to the first sign, diagnosis, appearance, or occurrence of the disease or disorder as possible or during remissions of the disease or disorder.

The antagonist is administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In addition, the antagonist may suitably be administered by pulse infusion, *e.g.*, with declining doses of the antagonist. Preferably the dosing is given by injections, most preferably intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic.

One may administer other compounds, such as cytotoxic agents, chemotherapeutic agents, immunosuppressive agents and/or cytokines with the antagonists herein. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. For RA, and other autoimmune diseases, the antagonist (*e.g.* anti-VEGF antibody) may be combined with any one or more of disease-modifying antirheumatic drugs (DMARDs) such as hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, azathioprine, D-penicillamine, Gold (oral), Gold (intramuscular), minocycline, cyclosporine, Staphylococcal protein A immunoadsorption; intravenous immunoglobulin (IVIG); nonsteroidal antiinflammatory drugs (NSAIDs); glucocorticoid (*e.g.* via joint injection); corticosteroid (*e.g.* methylprednisolone and/or prednisone); folate etc. The most preferred DMARD is MTX. Low-dose MTX therapy, administered weekly, inhibits DNA and RNA synthesis, accounting for its antiproliferative effects, and stimulates the release of adenosine, a mediator with anti-inflammatory activity. Adverse effects of MTX include nausea, diarrhea, fatigue, mouth ulcers, and hematologic suppression. Rarely, patients may develop a pneumonia-like reaction or cirrhosis. Methotrexate is usually initiated at a dose of 7.5 to 10 mg per week. The dose is increased as tolerated during the next several months, up to 20 to 25 mg per week. However, lower MTX doses should be prescribed to the elderly and those patients with mild renal dysfunction; MTX should not be given to patients with a serum creatinine level higher than 2.5 mg/dL. The ACR has established guidelines for monitoring patients receiving MTX, recommending that blood cell counts and liver enzymes be assessed at 4- to 8-week intervals.

In another embodiment, the angiogenesis antagonist is used in combination with other antagonist biologics that are effective in treating autoimmune diseases. For example, the angiogenesis antagonist can be used in combination with a TNF α -inhibitor, a B-cell antagonist, or both. A TNF α -inhibitor can be any agent that decreases, inhibits, blocks, abrogates or interferes a biological function of TNF α . Preferably, a TNF α -inhibitor binds to TNF α and neutralizes its activity. Examples of TNF inhibitors specifically contemplated herein are Etanercept (ENBREL®), Infliximab (REMICADE®) and Adalimumab (HUMIRA™). A B-cell antagonist can be an antagonist antibody that binds to a B-cell surface marker such as CD20, CD22, CD19 and CD40. Examples of antibodies which bind the CD20 antigen include: "C2B8" which is now called "rituximab" ("RITUXAN®") (US Patent No. 5,736,137, expressly incorporated herein by reference); the yttrium-[90]-labeled 2B8 murine antibody designated "Y2B8" (US Patent No. 5,736,137, expressly incorporated herein by reference); murine IgG2a "B1" optionally labeled with ¹³¹I to generate the "¹³¹I-B1"

antibody (BEXXAR™) (US Patent No. 5,595,721, expressly incorporated herein by reference); murine monoclonal antibody "1F5" (Press *et al. Blood* 69(2):584-591 (1987)); "chimeric 2H7 antibody" (US Patent No. 5,677,180, expressly incorporated herein by reference); "humanized 2H7 v16" (see below); huMax-CD20 (Genmab, Denmark); AME-133 (Applied Molecular Evolution); and monoclonal antibodies L27, G28-2, 93-1B3, B-C1 or NU-B2 available from the International Leukocyte Typing Workshop (Valentine *et al.*, In: *Leukocyte Typing III* (McMichael, Ed., p. 440, Oxford University Press (1987)). Examples of antibodies which bind the CD19 antigen include the anti-CD19 antibodies in Hekman *et al. Cancer Immunol. Immunother.* 32:364-372 (1991) and Vlasveld *et al. Cancer Immunol. Immunother.* 40:37-47 (1995); and the B4 antibody in Kiesel *et al. Leukemia Research II*, 12: 1119 (1987).

Aside from administration of protein antagonists to the patient the present application contemplates administration of antagonists by gene therapy. Such administration of nucleic acid encoding the antagonist is encompassed by the expression "administering a therapeutically effective amount of an antagonist". See, for example, WO96/07321 published March 14, 1996 concerning the use of gene therapy to generate intracellular antibodies.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells; *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the site where the antagonist is required. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes which are implanted into the patient (see, *e.g.* U.S. Patent Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. A commonly used vector for *ex vivo* delivery of the gene is a retrovirus.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are DOTMA, DOPE and DC-Chol, for example). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, *e.g.* capsid proteins or

fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, *J. Biol. Chem.* 262:4429-4432 (1987); and Wagner *et al.*, *Proc. Natl. Acad. Sci. USA* 87:3410-3414 (1990). For review of the currently known gene marking and gene therapy protocols see Anderson *et al.*, *Science* 256:808-813 (1992). See also WO 93/25673 and the references cited therein.

Further details of the invention are illustrated by the following non-limiting Examples. The disclosures of all citations in the specification are expressly incorporated herein by reference.

Example 1

A patient with active rheumatoid arthritis who has failed prior therapy and currently has an inadequate response to MTX is treated with an anti-hVEGF monoclonal antibody such as Avastin®.

Candidates for therapy according to this example include those who were diagnosed with RA for at least six months, according to the revised 1987 ACR criteria. The patients must have received MTX at a dose of 10-25 mg/week per oral or parenteral for at least twelve weeks, with the last four weeks prior to screening at a stable dose. Also, the patients must have failed treatment (lack of efficacy or tolerability) with no more than five DMARDs or biologics (including MTX).

Patients may have swollen joint count (SJC) no less than 6 (66 joint count), and tender joint count (TJC) no less than 6 (68 joint count) at screening and randomization; either CRP no less than 1.2mg/dl (12 mg/L) or ESR no less than 28 mm/h. Patients are preferably between 18 and 64 (inclusive) years old, with less than 5 years since RA diagnosis. Males of reproductive potential preferably use a reliable means of contraception (e.g., physical barrier), and females are preferably post-menopausal or surgically sterilized. Major exclusion criteria are based on concerns of general safety such as evidence of significant uncontrolled concomitant diseases including but not limited to cardiovascular diseases, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders. Also, patients with history of thromboembolic diseases including PE, DVT or CVA, history of diabetes mellitus, history of uncontrolled hypertension or history of proteinuria should be excluded from the treatment.

The anti-VEGF antibody used for therapy is preferably bevacizumab (Avastin® , commercially available from Genentech, Inc.) or a variant thereof having improved binding affinity, inhibitory efficacy or pharmacokinetic properties.

Patients are treated with a therapeutically effective dose of the antibody, for instance, a single dose of 1-2.5 mg/kg i.v. every two weeks (1.0 mg/kg/wk). Patients can also receive

concomitant MTX (10-25 mg/week per oral (p.o.) or parenteral), together with a corticosteroid regimen consisting of methylprednisolone 100 mg i.v. 30 minutes prior to infusions of the anti-VEGF antibody and prednisone 60 mg p.o. on Days 2-7, 30 mg p.o. Days 8-14, returning to baseline dose by Day 16. Patients may also receive folate (5 mg/week) given as either a single dose or as divided daily doses. Patients optionally continue to receive any background corticosteroid (10 mg/d prednisone or equivalent) throughout the treatment period.

The primary endpoint is the proportion of patients with an ACR20 response at Week 24 using a Cochran-Mantel-Haenszel (CMH) test for comparing group differences, adjusted for rheumatoid factor and region.

Additional secondary endpoints include:

1. Proportion of patients with ACR50 and 70 responses at Week 24. These may be analyzed as specified for the primary endpoint.
2. Change in Disease Activity Score (DAS) from screening to Week 24. These may be assessed using an ANOVA model with baseline DAS, rheumatoid factor, and treatment as terms in the model.
3. Categorical DAS responders (EULAR response) at Week 24. These may be assessed using a CMH test adjusted for rheumatoid factor.
4. Changes from screening in ACR core set (SJC, TJC, patient's and physician's global assessments, HAQ, pain, CRP, and ESR). Descriptive statistics may be reported for these parameters.
5. Changes from screening in SF-36. Descriptive statistics are reported for the 8 domain scores and the mental and physical component scores. In addition, the mental and physical component scores are further categorized and analyzed.
6. Change in modified Sharp radiographic total score, erosion score, and joint space narrowing score. These are analyzed using continuous or categorical methodology, as appropriate.

Exploratory endpoints and analysis may involve:

ACR(20/50/70 and ACR n) and change in DAS responses over Weeks 8, 12, 16, 20, 24 and beyond will be assessed using a binary or continuous repeated measures model, as appropriate. Exploratory radiographic analyses including proportion of patients with no erosive progression may be assessed at weeks 24 and beyond.

Further exploratory endpoints (for example complete clinical response, disease free period) will be analyzed descriptively as part of the extended observation period. Changes from Screen in FACIT-F fatigue will be analyzed with descriptive statistics. Therapy of RA with the anti-VEGF antibody in patients with an inadequate response to DMARD or TNF α inhibitor therapy as described above will result in a beneficial clinical response according to any one or more of the endpoints noted above.

What is claimed is:

1. Use of an angiogenesis antagonist in the preparation of a medicament for the treatment of an autoimmune disease in a mammal who has failed prior therapy.
2. The use of claim 1 wherein the angiogenesis antagonist is a VEGF antagonist.
3. The use of claim 1 wherein the antagonist comprises an antibody.
4. The use of claim 3 wherein the antibody is an anti-VEGF antibody.
5. The use of claim 4 wherein the anti-VEGF antibody is bevacizumab.
6. The use of claim 1 wherein the mammal is human.
7. The use of claim 1 wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, juvenile-onset rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and ankylosing spondylitis.
8. The use of claim 1 wherein the prior therapy comprises administration of at least one DMARD agent.
9. The use of claim 8 wherein the prior therapy comprises administration of MTX.
10. The use of claim 1 wherein the prior therapy comprises administration of at least one TNF α -inhibitor.
11. The use of claim 1 wherein the angiogenesis antagonist is administered in combination with or in series of a DMARD agent.
12. The use of claim 11 wherein the DMARD agent is MTX.
13. The use of claim 1 wherein the angiogenesis antagonist is administered in combination with or in series of a TNF α -inhibitor.

14. The use of claim 13 wherein the TNF α -inhibitor is selected from the group consisting of etanercept, infliximab and adalimumab.

15. The use of claim 1 wherein the angiogenesis antagonist is administered in combination with or in series of a B-cell antagonist which binds to a B cell surface antigen.

16. The use of claim 15 wherein the B cell surface antigen is selected from the group consisting of CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD40, CD53, CD72, CD73, CD74, CDw75, CDw76, CD77, CDw78, CD79a, CD79b, CD80, CD81, CD82, CD83, CDw84, CD85 and CD86.

17. The use of claim 15 wherein the B-cell antagonist comprises an antibody against CD20.

18. The use of claim 17 wherein the antibody against CD20 is rituximab.

19. The use of claim 17 wherein the antibody against CD20 is humanized 2H7 v16.

20. Use of an anti-VEGF antibody in the preparation of a medicament for the treatment of rheumatoid arthritis in a patient who has failed prior DMARD or TNF α -inhibitor therapy and currently has an inadequate response to MTX.

INTERNATIONAL SEARCH REPORT

national application No
T/US2005/045600

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/22 A61K39/395				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07K A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	OLIVER S J ET AL: "SUPPRESSION OF COLLAGEN-INDUCED ARTHRITIS USING AN ANGIOGENESIS INHIBITOR, AGM-1470, AND A MICROTUBULE STABILIZER, TAXOL" CELLULAR IMMUNOLOGY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 157, no. 1, 1 August 1994 (1994-08-01), pages 291-299, XP000612505 ISSN: 0008-8749 abstract page 292 - page 293 ----- -/--	1-20		
<table style="width:100%; border: none;"> <tr> <td style="width:50%; border: none;"><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.</td> <td style="width:50%; border: none;"><input checked="" type="checkbox"/> See patent family annex.</td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.			
* Special categories of cited documents :				
<table style="width:100%; border: none;"> <tr> <td style="width:50%; border: none;"> *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed </td> <td style="width:50%; border: none;"> *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family </td> </tr> </table>			*A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family
A document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family			
Date of the actual completion of the international search <p align="center">27 April 2006</p>		Date of mailing of the international search report <p align="center">18/05/2006</p>		
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <p align="center">van Klompenburg, W</p>		

INTERNATIONAL SEARCH REPORT

national application No
PCT/US2005/045600

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WILSON JENNIFER FISHER: "Angiogenesis therapy moves beyond cancer." ANNALS OF INTERNAL MEDICINE. 20 JUL 2004, vol. 141, no. 2, 20 July 2004 (2004-07-20), pages 165-168, XP002378544 ISSN: 1539-3704 page 165, right-hand column page 166, right-hand column</p>	1-20
X	<p>MANLEY P W ET AL: "Therapies directed at vascular endothelial growth factor" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 11, no. 12, December 2002 (2002-12), pages 1715-1736, XP002256125 ISSN: 1354-3784 paragraph [03.2] paragraph [4.1.1]</p>	1-20
X	<p>US 2004/120950 A1 (ALITALO KARI ET AL) 24 June 2004 (2004-06-24) claims 1-43</p>	1-20

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/045600

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004120950	A1	24-06-2004	NONE

Form PCT/ISA/210 (patent family annex) (April 2005)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 May 2006 (26.05.2006)

PCT

(10) International Publication Number
WO 2006/055809 A2

- (51) International Patent Classification:
C07K 16/28 (2006.01)
- (21) International Application Number:
PCT/US2005/041904
- (22) International Filing Date:
18 November 2005 (18.11.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/628,815 18 November 2004 (18.11.2004) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, 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.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

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

(54) Title: ANTIBODIES AGAINST VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-1

(57) Abstract: Monoclonal antibodies that are specific for vascular endothelial growth factor receptor 1 (VEGFR-1). This invention also provides nucleotide sequences encoding and amino acid sequences comprising variable heavy and light chain immunoglobulin molecules, including sequences corresponding to the complementarity determining regions of CDR1, CDR2, and CDR3. The invention also provides methods for generation and expression of anti-VEGFR-1 antibodies and methods of treating angiogenic-related disorders and reducing tumor growth by administering anti-VEGFR-1 antibodies.



WO 2006/055809 A2

ANTIBODIES AGAINST VASCULAR ENDOTHELIAL GROWTH FACTOR
RECEPTOR-1

FIELD OF INVENTION

The present invention relates to antibodies that are specific for vascular endothelial growth factor receptor-1 (VEGFR-1) and methods of treating angiogenesis-associated diseases and tumors with antibodies to VEGFR-1.

BACKGROUND OF THE INVENTION

Angiogenesis, which refers to the formation of capillaries from pre-existing vessels in the embryo and adult organism, is known to be a key element in tumor growth, survival and metastasis. Growth factors and their receptors, including epidermal growth factor (EGF), transforming growth factor- α (TGF- α), transforming growth factor- β (TGF- β), acidic and basic fibroblast growth factor (aFGF and bFGF), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), are thought to play a role in tumor angiogenesis. *See* Klagsbrun & D'Amore, *Annual Rev. Physiol.*, 53: 217-239 (1991). Binding of these growth factors to their cell surface receptors induces receptor activation, which initiates and modifies signal transduction pathways and leads to cell proliferation and differentiation. VEGF, an endothelial cell-specific mitogen, is distinct among these factors in that it acts as an angiogenesis inducer by specifically promoting the proliferation of endothelial cells.

The biological response of VEGF is mediated through its high affinity receptors, which are selectively expressed on endothelial cells during embryogenesis (Millauer, *Cell*, 72: 835-846 (1993)) and during tumor formation. VEGF receptors (VEGFRs) typically are class III receptor-type tyrosine kinases characterized by having several, typically 5 or 7, immunoglobulin-like loops in their amino-terminal extracellular receptor ligand-binding domains (Kaipainen *et al.*, *J. Exp. Med.*, 178:2077-2088 (1993)). The other two regions include a transmembrane region and a carboxy-terminal intracellular catalytic domain interrupted by an insertion of hydrophilic interkinase sequences of variable lengths, called the kinase insert domain (Terman *et al.*, *Oncogene*, 6:1677-1683 (1991)). VEGFRs include *fms*-like tyrosine kinase receptor (flt-1), or VEGFR-1, sequenced by Shibuya *et al.*, *Oncogene*, 5: 519-524 (1990), kinase insert domain-containing receptor/fetal liver kinase (KDR/flk-1),

or VEGFR-2, described in WO 92/14248, filed February 20, 1992, and Terman *et al.*, *Oncogene*, 6: 1677-1683 (1991) and sequenced by Matthews *et al.*, *Proc. Natl. Acad. Sci. USA*, 88: 9026-9030 (1991), although other receptors, such as neuropilin-1 and -2, can also bind VEGF. Another tyrosine kinase receptor, VEGFR-3 (flt-4), binds the VEGF homologues VEGF-C and VEGF-D and is more important in the development of lymphatic vessels.

The importance of VEGFR-1 in regulation of pathological angiogenesis has been shown in *in vivo* experimental models. Deficiency of VEGFR-1 tyrosine kinase domain results in decreased blood vessel formation in tumors, indicating a significant role of VEGFR-1 tyrosine kinase in pathological angiogenesis (Hiratsuka *et al.*, *Cancer Research*, 61:1207-1213 (2001)). VEGFR-1 tyrosine kinase domain is also required for promotion of tumor pathogenesis and metastasis by induction of matrix metalloprotease-9 (MMP-9) in endothelial cells and macrophages (Hiratsuka *et al.*, *Cancer Cell*, 2:289-300 (2002)). In addition, VEGFR-1 has been shown to mediate mobilization and differentiation of PlGF responsive BM-derived precursors (Hattori *et al.*, *Nature Medicine*, 8:841-849 (2002)). Inhibition of VEGFR-1 by an anti-VEGFR-1 antibody led to reduction of tumor angiogenesis by preventing recruitment of bone marrow-derived endothelial and monocyte progenitor cells from vascularization in tumors (Lyden *et al.*, *Nature Medicine*, 7:1194-1201 (2001)). Treatment with an anti-VEGFR-1 antibody also effectively inhibited pathological angiogenesis in tumors and ischemic retina in animal models (Lutten *et al.*, *Nature Medicine*, 8:831-840 (2002)).

In addition to the role of VEGFR-1 in angiogenesis, co-expression of VEGF and its receptors is also frequently found in hematological malignant cells and certain solid tumor cells (Bellamy, *Cancer Research*, 59:728-733 (1999); Ferrer *et al.*, *Urology*, 54:567-572 (1999); Price *et al.*, *Cell Growth Differ.*, 12:129-135 (2001)). VEGF has been shown to directly induce proliferation, survival, and invasion of VEGF receptor expressing leukemia cells by activation of downstream intracellular signaling pathways through a ligand stimulated autocrine loop (Dias *et al.*, *Proc Natl Acad Sci USA*, 98:10857-10862 (2001); Gerber *et al.*, *J Mol Med.*, 81:20-31 (2003)). VEGF stimulation also results in an increased invasiveness of the VEGFR-1 expressing breast cancer cells by inducing the activation of ERK1/2 and PI 3/Akt-kinase signaling pathways (Price *et al.*, *Cell Growth Differ.*, 12:129-135 (2001)).

VEGFR-1 and its ligands have also been shown to play an important role in inflammatory disorders. VEGF-B deficiency resulted in the reduction of inflammation-associated vessel density and synovial inflammation in models of arthritis (Mould *et al.*, *Arthritis Rheum.*, 48:2660-2669 (2003)). PlGF also plays a critical role in the control of cutaneous inflammation by mediating vascular enlargement, inflammatory cells and monocytes/macrophages, and has been shown to contribute to modulation of atherosclerosis and rheumatoid arthritis in animal models (Luttun *et al.*, *Nature Medicine*, 8:831-840 (2002); Autiero & *Thromb Haemost.*, 1:1356-1370 (2003)). Treatment with a neutralizing anti-VEGFR-1 antibody suppressed inflammatory joint destruction in arthritis, reduced atherosclerotic plaque growth and vulnerability. The anti-inflammatory effects of the anti-VEGFR-1 antibody were attributable to a reduced mobilization of bone marrow-derived myeloid progenitors into the peripheral blood, a defective activation of myeloid cells, and an impaired differentiation and infiltration of VEGFR-1-expressing leukocytes in inflamed tissues. Thus, VEGFR-1 may also be a therapeutic target for treatment of inflammation-related disorders.

There remains a need for agents which inhibit VEGF receptor activity, such as fully human monoclonal antibodies (mAbs) specific for VEGFR-1. The anti-VEGFR-1 antibodies may be a useful, novel therapeutic antagonist for treatment of angiogenesis-associated diseases and cancer.

BRIEF SUMMARY OF THE INVENTION

In an embodiment, the present invention provides a monoclonal antibody or fragment thereof that specifically binds to VEGFR-1 and comprises a light chain complementarity determining region-2 (CDR2) of SEQ ID NO: 2 and a light chain complementarity region-3 (CDR3) of SEQ ID NO: 3.

In another embodiment, the present invention provides a monoclonal antibody or fragment thereof that specifically binds to VEGFR-1 and is at least 70% homologous to the amino acid sequence of an antibody or fragment thereof that comprises a light chain complementarity determining region-2 (CDR2) of SEQ ID NO: 2 and a light chain complementarity region-3 (CDR3) of SEQ ID NO: 3.

In another embodiment, the present invention provides an isolated polynucleotide comprising a nucleotide sequence selected from the group consisting

of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, and SEQ ID NO: 27. The nucleotide sequence encodes an antibody or fragment thereof that specifically binds to VEGFR-1.

In another embodiment, the present invention provides an isolated polynucleotide comprising a nucleotide sequence that encodes an antibody or fragment thereof that specifically binds to VEGFR-1 and that is at least 70% homologous to the nucleotide sequence selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, and SEQ ID NO: 27.

In another embodiment, the present invention provides a method of inhibiting angiogenesis or reducing tumor growth by administering a therapeutically effective amount of an antibody or fragment thereof that specifically bind to VEGFR-1 and comprises a light chain complementarity determining region-2 (CDR2) of SEQ ID NO: 2 and a light chain complementarity region-3 (CDR3) of SEQ ID NO: 3.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is the amino acid sequences of the light chain variable region and the heavy chain variable region of embodiments of anti-VEGFR-1 antibodies of the present invention.

Figure 2 is the nucleotide sequences of the light chain variable region and the heavy chain variable region of embodiments of anti-VEGFR-1 antibodies of the present invention.

Figure 3 is a chart depicting the results of an ELISA-based binding assay measuring *in vitro* binding activity of embodiments of anti-VEGFR-1 antibodies of the present invention to VEGFR-1.

Figure 4 is a chart depicting the results of an ELISA-based blocking assay measuring *in vitro* competition of embodiments of anti-VEGFR-1 antibodies of the present invention with PlGF for VEGFR-1 binding.

Figure 5 is a chart depicting the results of an ELISA-based blocking assay measuring *in vitro* competition of embodiments of anti-VEGFR-1 antibodies of the present invention with VEGF for VEGFR-1 binding.

Figure 6A-D are charts depicting the results of specificity of anti-VEGFR-1 antibody 18F1 of the present invention with binding of human VEGFR-1 (**Figure**

6A), but not mouse VEGFR-1 (**Figure 6B**), human VEGFR-2 (**Figure 6C**), or mouse VEGFR-2 (**Figure 6D**).

Figure 7A-E are results of flow cytometry analysis showing binding reactivity of embodiments of anti-VEGFR-1 antibodies of the present invention with VEGFR-1 expressing porcine aorta endothelial cells.

Figure 8A-B is results of flow cytometry analysis showing binding reactivity of anti-VEGFR-1 antibody 18F1 of the present invention with VEGFR-1 expressing porcine endothelial cells (**Figure 8A**) and DU4475 human breast carcinoma cells (**Figure 8B**).

Figure 9 is a chart depicting results of a cell-based blocking assay measuring *in vitro* competition of anti-VEGFR-1 antibody 18F1 of the present invention with VEGF binding to VEGFR-1 on endothelial cells.

Figure 10 is a Western blot analysis demonstrating the reduction of PIGF-stimulated phosphorylation of VEGFR-1 by treatment with anti-VEGFR-1 antibody 18F1 of the present invention in porcine aorta endothelial VEGFR-1 expressing cells.

Figure 11 is a Western blot analysis demonstrating inhibition of PIGF or VEGF-stimulated phosphorylation of VEGFR-1 by treatment with anti-VEGFR-1 antibody 18F1 of the present invention in BT474 breast cancer cells.

Figure 12 is a Western blot analysis demonstrating inhibition of PIGF induced activation of ERK1/2 downstream signaling by embodiments of anti-VEGFR-1 antibodies of the present invention in porcine aorta endothelial VEGFR-1 expressing cells.

Figure 13 is a Western blot analysis demonstrating the inhibition of VEGF induced activation of ERK1/2 downstream signaling by embodiments of anti-VEGFR-1 antibodies of the present invention in porcine aorta endothelial VEGFR-1 expressing cells.

Figures 14A-B is a Western blot analysis demonstrating the inhibition of PIGF(**Figure 14A**) or VEGF (**Figure 14B**)-induced activation of ERK 1/2 downstream signaling by anti-VEGFR-1 antibody 18F1 of the present invention in VEGFR-1 expressing porcine aorta endothelial cells.

Figure 15 is a Western blot analysis demonstrating that the anti-VEGFR-1 antibody 18F1 of the present invention blocked PIGF or VEGF-stimulated phosphorylation of Akt in BT474 breast cancer cells.

Figure 16 is a dose response curve showing the inhibition of VEGF stimulated cell proliferation in DU4475 breast carcinoma cells treated with embodiments of anti-VEGFR-1 antibodies of the present invention in a dose response manner.

Figure 17 is a dose response curve showing the inhibition of PlGF stimulated cell proliferation in DU4475 breast carcinoma cells treated with embodiments of anti-VEGFR-1 antibodies of the present invention in a dose response manner.

Figure 18 A-B is a dose response curve showing the inhibition of PlGF (**Figure 18A**) or VEGF (**Figure 18B**)-stimulated cell proliferation in DU4475 breast carcinoma cells treated with anti-VEGFR-1 antibody 18F1 of the present invention in a dose response manner.

Figure 19 A and 19B are charts plotting tumor growth of DU4475 breast tumors versus days after treatment with embodiments of anti-VEGFR-1 antibodies of the present invention.

Figure 20 A-C is a chart plotting tumor growth of DU4475 (**Figure 20A**), MDA-MB-231 (**Figure 20B**) and MDA-MB-435 (**Figure 20C**) breast tumors versus days after treatment with anti-VEGFR-1 antibody 18F1 of the present invention.

Figure 21A-B is a chart plotting tumor growth of DU4475 (**Figure 21A**) and MDA-MB-231 (**Figure 21B**) breast tumors versus days after treatment with anti-human VEGFR-1 antibody 18F1 of the present invention and anti-mouse VEGFR-1 antibody MF1.

Figure 22 is a chart of the number of colon cancer cell colonies present after treatment with anti-human VEGFR-1 antibody 18F1 in the presence of VEGF-A and VEGF-B.

Figure 23A is a chart of the number of migrated tumor cells after treatment with anti-human VEGFR-1 antibody 18F1 in the presence of VEGF-A and VEGF-B.

Figure 23B are photomicrographs of stained migrated cells after treatment with anti-human VEGFR-1 antibody 18F1 in the presence of VEGF-A and VEGF-B.

Figure 24A is a chart of the number of tumor cells that migrated across a layer of MATRIGEL™ after treatment with anti-human VEGFR-1 antibody 18F1 in the presence of VEGF-A or VEGF-B.

Figure 24B are photomicrographs of stained migrated cells after treatment with anti-human VEGFR-1 antibody 18F1 in the presence of VEGF-A and VEGF-B.

Figure 25 is a chart plotting tumor growth of DU4475 (**Figure 25A**) and MDA-MB-435 (**Figure 25B**) breast tumors versus days after treatment with anti-VEGFR-1 antibodies 18F1, 6F9 and 15F11.

Figure 26 is a chart plotting growth of HT-29 (**Figure 26A**), DLD-1 (**Figure 26B**) and GEO (**Figure 26C**) colon cancer cells versus days after treatment with particular doses of anti-human VEGFR-1 antibody 18F1.

Figure 27 are photomicrographs of MDS-MB-231 xenograft tumors after treatment with anti-human VEGFR-1 antibody 18F1.

Figure 28 is a chart plotting tumor growth versus days after treatment with particular doses of anti-human anti-VEGFR-1 antibody 18F1, anti-mouse anti-VEGFR-1 antibody MF1, or both in MDA-MB-231 (**Figure 28A**) and DU4475 (**Figure 28B**) xenografts.

Figure 29 is a chart plotting tumor growth versus days after treatment with anti-human anti-VEGFR-1 antibody 18F1 and anti-mouse anti-VEGFR-1 antibody MF1 in combination with cyclophosphamide in MDS-MB-231 xenografts.

Figures 30A and B are charts plotting tumor growth versus days after treatment with 5-FU/LV or doxorubicin in combination with anti-human anti-VEGFR-1 antibody 18F1 and anti-mouse anti-VEGFR-1 antibody MF1 in MDA-MB-231 xenografts.

Figure 31 is a chart of total tumor cell count versus antibody concentration of various amounts of 18F1 in the presence of VEGF-A (**Figure 31A**) or PIGF (**figure 31B**) following treatment with desferrioxamine.

Figure 32A, B, and C are charts depicting the specificity of anti-human anti-VEGFR-1 antibody 18F1 and anti-mouse anti-VEGFR-1 antibody MF1.

DETAILED DESCRIPTION OF THE INVENTION

In an embodiment, the present invention provides a monoclonal antibodies and fragments thereof that specifically bind to VEGFR-1 (such antibodies and fragments thereof referred to herein as “anti-VEGFR-1 antibodies” unless otherwise indicated). Anti-VEGFR-1 antibodies of the present invention comprise a light chain complementarity determining region-2 (CDR2) of SEQ ID NO: 2 and a light chain complementarity region-3 (CDR3) of SEQ ID NO: 3. Alternatively and preferably, anti-VEGFR-1 antibodies of the present invention comprise a light chain

complementarity region-1 (CDR1) having the following sequence:

RASQ₁SSSYLA, where X₁ is V or G (SEQ ID NO: 1 or 4). Alternatively and preferably, anti-VEGFR-1 antibodies of the present invention comprise a heavy chain CDR1 having the following sequence: GFX₂FSSYGMH, where X₂ is T or A (SEQ ID NO: 5 or 11). Alternatively and preferably, anti-VEGFR-1 antibodies of the present invention comprise a heavy chain CDR2 having the following sequence:

VIWX₃DGSNKYYADSVX₄G, where X₃ is Y or F and X₄ is K or R (SEQ ID NO: 6, 9, or 12). Alternatively and also preferably, anti-VEGFR-1 antibodies of the present invention comprise a heavy chain CDR3 having the following sequence:

DHX₅GSGX₆HX₇YX₈YYGX₉DV, where X₅ is F or Y; X₆ is A or V; X₇ is Y, S, or H; X₈ is Y or F; and X₉ is M or L (SEQ ID NO: 7, 8, 10, 13). The amino acid sequences of the CDRs of preferred anti-VEGFR-1 antibodies (designated as clones "6F9," "13G12," "15F11," and "18F1" (or "IMC-18F1")) are set forth below in Table 1.

Table 1 - CDR sequence of anti-VEGFR-1 antibodies			
Clone	CDR1	CDR2	CDR3
Light Chain			
6F9	RASQSGSSSYLA (SEQ ID NO:1)	GASSRAT (SEQ ID NO:2)	QQYGSSPLT (SEQ ID NO:3)
13G12	RASQSGSSSYLA (SEQ ID NO:1)	GASSRAT (SEQ ID NO:2)	QQYGSSPLT (SEQ ID NO:3)
15F11	RASQSVSSSYLA (SEQ ID NO:4)	GASSRAT (SEQ ID NO:2)	QQYGSSPLT (SEQ ID NO:3)
18F1	RASQSVSSSYLA (SEQ ID NO:4)	GASSRAT (SEQ ID NO:2)	QQYGSSPLT (SEQ ID NO:3)
Heavy Chain			
6F9	GFTFSSYGMH (SEQ ID NO:5)	VIWYDGSNKYYADSVKG (SEQ ID NO:6)	DHFGSGAHYYYYYGMDV (SEQ ID NO:7)
13G12	GFTFSSYGMH (SEQ ID NO:5)	VIWYDGSNKYYADSVKG (SEQ ID NO:6)	DHYGSGAHYYYYYGMDV (SEQ ID NO:8)
15F11	GFTFSSYGMH (SEQ ID NO:5)	VIWFDGSNKYYADSVKG (SEQ ID NO:9)	DHYGSGAHSYYYYGLDV (SEQ ID NO:10)

13G12	<u>QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVI</u> <u>WYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDHY</u> <u>GSGAHYYYYYGMDVWGQGT TTVTVSS</u> SEQ ID NO:18
15F11	<u>QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVI</u> <u>WFDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDHY</u> <u>SGAHSYYYYGLDVWGQGT S TTVTVSS</u> SEQ ID NO:19
18F1	<u>QAQVVESGGGVVQSGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAVI</u> <u>WYDGSNKYYADSVRGRFTISRDN SENTLYLQMNSLRAEDTAVYYCARDHYG</u> <u>SGVHHYFYYGLDVWGQGT TTVTVSS</u> SEQ ID NO:20

In a preferred embodiment, the anti-VEGFR-1 antibodies of the present invention are human antibodies.

Anti-VEGFR-1 antibodies of the present invention include whole antibodies and antibody fragments that specifically bind to VEGFR-1. Non-limiting examples of types of antibodies according to the present invention include naturally occurring antibodies; single chain antibodies; multivalent single chain antibodies such as diabodies and tribodies; monovalent fragments such as Fab (Fragment, antigen binding), bivalent fragments such as (Fab')₂; Fv (fragment variable) fragments or derivatives thereof such as single chain Fv (scFv) fragments; and single domain antibodies that bind specifically to VEGFR-1.

Naturally occurring antibodies typically have two identical heavy chains and two identical light chains, with each light chain covalently linked to a heavy chain by an interchain disulfide bond and multiple disulfide bonds further linking the two heavy chains to one another. Individual chains can fold into domains having similar sizes (110-125 amino acids) and structures, but different functions. The light chain can comprise one V_L and one constant domain (C_L). The heavy chain can also comprise one V_H and/or depending on the class or isotope of antibody, three or four constant domains (C_{H1}, C_{H2}, C_{H3}, and C_{H4}). In humans, the isotypes are IgA, IgD, IgE, IgG, and IgM, with IgA and IgG further subdivided into subclasses or subtypes (IgA₁₋₂ and IgG₁₋₄).

Single chain antibodies lack some or all of the constant domains of the whole antibody from which they are derived. The peptide linkers used to produce the single

chain antibodies may be flexible peptides selected to assure that the proper three-dimensional folding of the V_L and V_H domains occurs. Generally, the carboxyl terminus of the V_L or V_H sequence may be covalently linked by such a peptide linker to the amino acid terminus of a complementary V_H or V_L sequence. The linker is generally 10 to 50 amino acid residues, preferably 10 to 30 amino acid residues, more preferably 12 to 30 amino acid residues, and most preferably 15 to 25 amino acid residues. An example of such linker peptides include (Gly-Gly-Gly-Gly-Ser)₃ (SEQ ID NO: 28).

Multiple single chain antibodies, each single chain having one V_H and one V_L domain covalently linked by a first peptide linker, can be covalently linked by at least one or more peptide linkers to form a multivalent single chain antibody, which can be monospecific or multispecific. Each chain of a multivalent single chain antibody includes a variable light chain fragment and a variable heavy chain fragment, and is linked by a peptide linker to at least one other chain.

Two single chain antibodies can be combined to form a diabody, also known as a trivalent dimer. Diabodies have two chains and two binding sites and can be monospecific or bispecific. Each chain of the diabody includes a V_H domain connected to a V_L domain. The domains are connected with linkers that are short enough to prevent pairing between domains on the same chain, thus driving the pairing between complementary domains on different chains to recreate the two antigen-binding sites.

Three single chain antibodies can be combined to form triabodies, also known as trivalent trimers. Triabodies are constructed with the amino acid terminus of a V_L or V_H domain directly fused to the carboxyl terminus of a V_L or V_H domain, i.e., without any linker sequence. The triabody has three Fv heads with the polypeptides arranged in a cyclic, head-to-tail fashion. A possible conformation of the triabody is planar with the three binding sites located in a plane at an angle of 120 degrees from one another. Triabodies can be monospecific, bispecific or trispecific.

Fab fragments refer to fragments of the antibody consisting of $V_L C_L V_H C_H1$ domains. Those generated by papain digestion are referred to as "Fab" and do not retain the heavy chain hinge region. Those generated by pepsin digestion are referred to either as "(Fab')₂," in which case the interchain disulfide bonds are intact, or as

Fab', in which case the disulfide bonds are not retained. Bivalent (Fab')₂ fragments have higher avidity for antigen than that of monovalent Fab fragments.

Fv fragments are the portion of an antibody consisting of the V_L and V_H domains and constitute the antigen-binding site. scFv is an antibody fragment containing a V_L domain and V_H domain on one polypeptide chain, wherein the N terminus of one domain and the C terminus of the other domain are joined by a flexible linker to allow the two fragments to associate to form a functional antigen binding site (*see*, for example U.S. Pat. No. 4,946,778 (Ladner *et al.*), WO 88/09344, (Huston *et al.*), both of which are incorporated by reference herein). WO 92/01047 (McCafferty *et al.*), which is incorporated by reference herein, describes the display of scFv fragments on the surface of soluble recombinant genetic display packages, such as bacteriophage.

Single domain antibodies have a single variable domain that is capable of efficiently binding antigen. Examples of antibodies wherein binding affinity and specificity are contributed primarily by one or the other variable domain are known in the art. *See, e.g.*, Jeffrey, P.D. *et al.*, *Proc. Natl. Acad. Sci. U S A* 90:10310-4 (1993), which is incorporated by reference herein and which discloses an anti-digoxin antibody which binds to digoxin primarily by the antibody heavy chain. Accordingly, single antibody domains can be identified that bind well to VEGF receptors. It is understood that, to make a single domain antibody from an antibody comprising a V_H and a V_L domain, certain amino acid substitutions outside the CDR regions may be desired to enhance binding, expression or solubility. For example, it may be desirable to modify amino acid residues that would otherwise be buried in the V_H-V_L interface.

Each domain of anti-VEGFR-1 antibodies of the present invention may be a complete antibody heavy or light chain variable domain, or it may be a functional equivalent or a mutant or derivative of a naturally occurring domain, or a synthetic domain constructed, for example, *in vitro* using a technique such as one described in WO 93/11236 (Griffiths *et al.*). For instance, it is possible to join together domains corresponding to antibody variable domains which are missing at least one amino acid. The important characterizing feature is the ability of each domain to associate with a complementary domain to form an antigen binding site. Accordingly, the terms "variable heavy/light chain fragment" should not be construed to exclude variants which do not have a material effect on VEGFR-1 binding specificity.

As used herein, an “anti-VEGFR-1 antibody” include modifications of an anti-VEGFR-1 antibody of the present invention that retain specificity for VEGFR-1. Such modifications include, but are not limited to, conjugation to an effector molecule such as a chemotherapeutic agent (e.g., cisplatin, taxol, doxorubicin) or cytotoxin (e.g., a protein, or a non-protein organic chemotherapeutic agent). Modifications further include, but are not limited to conjugation to detectable reporter moieties. Modifications that extend antibody half-life (e.g., pegylation) are also included.

Proteins and non-protein agents may be conjugated to the antibodies by methods that are known in the art. Conjugation methods include direct linkage, linkage via covalently attached linkers, and specific binding pair members (e.g., avidin-biotin). Such methods include, for example, that described by Greenfield et al., *Cancer Research* 50, 6600-6607 (1990), which is incorporated by reference herein, for the conjugation of doxorubicin and those described by Arnon et al., *Adv. Exp. Med. Biol.* 303, 79-90 (1991) and by Kiseleva et al., *Mol. Biol. (USSR)*25, 508-514 (1991), both of which are incorporated by reference herein, for the conjugation of platinum compounds.

Anti-VEGFR-1 antibodies of the present invention also include those for which binding characteristics have been improved by direct mutation, methods of affinity maturation, phage display, or chain shuffling. Affinity and specificity may be modified or improved by mutating any of the CDRs of the antibodies of the present invention and screening for antigen binding sites having the desired characteristics (see, e.g., Yang et al., *J. Mol. Biol.*, 254: 392-403 (1995), which is incorporated by reference herein). The CDRs may be mutated in a variety of ways that are known to one of skill in the art. For example, one way is to randomize individual residues or combinations of residues so that in a population of otherwise identical antigen binding sites, all twenty amino acids are found at particular positions. Alternatively, mutations are induced over a range of CDR residues by error prone PCR methods (see, e.g., Hawkins et al., *J. Mol. Biol.*, 226: 889-896 (1992), which is incorporated by reference herein). For example, phage display vectors containing heavy and light chain variable region genes may be propagated in mutator strains of *E. coli* (see, e.g., Low et al., *J. Mol. Biol.*, 250: 359-368 (1996), which is incorporated by reference herein).

Anti-VEGFR-1 antibodies also include functional equivalents that include polypeptides with amino acid sequences substantially the same as the amino acid sequence of the variable or hypervariable regions of the antibodies of the present invention. "Substantially the same" amino acid sequence includes an amino acid sequence with at least 70%, preferably at least 80%, and more preferably at least 90% identity to another amino acid sequence when the amino acids of the two sequences are optimally aligned and compared to determine exact matches of amino acids between the two sequences. "Substantially the same" amino acid sequence also includes an amino acid sequence with at least 70%, preferably at least 80%, and more preferably at least 90% homology to another amino acid sequence, as determined by the FASTA search method in accordance with Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85, 2444-8 (1988).

As stated earlier, anti-VEGFR-1 antibodies of the present invention specifically bind to VEGFR-1. Such antibodies can be monospecific or bispecific so long as one antigen-binding site is specific for VEGFR-1. Antibody specificity, which refers to selective recognition of an antibody for a particular epitope of an antigen, of antibodies for VEGFR-1 can be determined based on affinity and/or avidity. Affinity, represented by the equilibrium constant for the dissociation of an antigen with an antibody (K_d), measures the binding strength between an antigenic determinant (epitope) and an antibody binding site. Avidity is the measure of the strength of binding between an antibody with its antigen. Antibodies typically bind with a K_d of 10^{-5} to 10^{-11} liters/mole. Any K_d less than 10^{-4} liters/mole is generally considered to indicate non-specific binding. The lesser the value of the K_d , the stronger the binding strength between an antigenic determinant and the antibody binding site.

Anti-VEGFR-1 antibodies of the present invention specifically bind to the extracellular region of VEGFR-1 and preferably neutralize activation of VEGFR-1 by preventing binding of a ligand of VEGFR-1 to the receptor. In such preferable embodiments, the antibody binds VEGFR-1 at least as strongly as the natural ligands of VEGFR-1 (including VEGF(A), VEGF-B and PlGF).

Neutralizing activation of VEGFR-1 includes diminishing, inhibiting, inactivating, and/or disrupting one or more of the activities associated with signal transduction. Such activities include receptor dimerization, autophosphorylation of

VEGFR-1, activation of VEGFR-1's internal cytoplasmic tyrosine kinase domain, and initiation of multiple signal transduction and transactivation pathways involved in regulation of DNA synthesis (gene activation) and cell cycle progression or division. One measure of VEGFR-1 neutralization is inhibition of the tyrosine kinase activity VEGFR-1. Tyrosine kinase inhibition can be determined using well-known methods such as phosphorylation assays which measuring the autophosphorylation level of recombinant kinase receptor, and/or phosphorylation of natural or synthetic substrates. Phosphorylation can be detected, for example, using an antibody specific for phosphotyrosine in an ELISA assay or on a western blot. Some assays for tyrosine kinase activity are described in Panek *et al.*, *J. Pharmacol. Exp. Ther.*, 283: 1433-44 (1997) and Batley *et al.*, *Life Sci.*, 62: 143-50 (1998), both of which are incorporated by reference.

In addition, methods for detection of protein expression can be utilized to determine whether an antibody neutralizes activation of VEGFR-1, wherein the proteins being measured are regulated by VEGFR-1 tyrosine kinase activity. These methods include immunohistochemistry (IHC) for detection of protein expression, fluorescence *in situ* hybridization (FISH) for detection of gene amplification, competitive radioligand binding assays, solid matrix blotting techniques, such as Northern and Southern blots, reverse transcriptase polymerase chain reaction (RT-PCR) and ELISA. *See, e.g.*, Grandis *et al.*, *Cancer*, 78:1284-92. (1996); Shimizu *et al.*, *Japan J. Cancer Res.*, 85:567-71 (1994); Sauter *et al.*, *Am. J. Path.*, 148:1047-53 (1996); Collins, *Glia*, 15:289-96 (1995); Radinsky *et al.*, *Clin. Cancer Res.*, 1:19-31 (1995); Petrides *et al.*, *Cancer Res.*, 50:3934-39 (1990); Hoffmann *et al.*, *Anticancer Res.*, 17:4419-26 (1997); Wikstrand *et al.*, *Cancer Res.*, 55:3140-48 (1995), all of which are incorporated by reference.

In vivo assays can also be utilized to detect VEGFR-1 neutralization. For example, receptor tyrosine kinase inhibition can be observed by mitogenic assays using cell lines stimulated with receptor ligand in the presence and absence of inhibitor. For example, HUVEC cells (ATCC) stimulated with VEGF(A) or VEGF-B can be used to assay VEGFR-1 inhibition. Another method involves testing for inhibition of growth of VEGF-expressing tumor cells, using for example, human tumor cells injected into a mouse. *See e.g.*, U.S. Patent No. 6,365,157 (Rockwell *et al.*), which is incorporated by reference herein.

Of course, the present invention is not limited by any particular mechanism of VEGFR-1 neutralization. Anti-VEGFR-1 antibodies of the present invention can, for example, bind externally to VEGFR-1, block binding of ligand to VEGFR-1 and subsequent signal transduction mediated via receptor-associated tyrosine kinase, and prevent phosphorylation of VEGFR-1 and other downstream proteins in the signal transduction cascade. The receptor-antibody complex can also be internalized and degraded, resulting in receptor cell surface down-regulation. Matrix metalloproteinases, which function is tumor cell invasion and metastasis, can also be down-regulated by anti- VEGFR-1 antibodies of the present invention.

Human anti-VEGFR-1 antibodies can be obtained from naturally occurring antibodies, or Fab or scFv phage display libraries constructed, for example, from human heavy chain and light chain variable region genes and the CDR sequences of the anti-VEGFR-1 antibodies of the present invention can be inserted into such human anti-VEGFR-1 antibodies.

Human anti-VEGFR-1 antibodies can be produced by methods well known to one of skill in the art. Such methods include the hybridoma method using transgenic mice described by Kohler and Milstein, *Nature*, 256: 495-497 (1975) and Campbell, *Monoclonal Antibody Technology, The Production and Characterization of Rodent and Human Hybridomas*, Burdon *et al.*, Eds., *Laboratory Techniques in Biochemistry and Molecular Biology*, Volume 13, Elsevier Science Publishers, Amsterdam (1985), all of which are incorporated by reference herein; as well as by the recombinant DNA method described by Huse *et al.*, *Science*, 246, 1275-1281 (1989), which is incorporated by reference herein.

Antibody fragments can be produced by cleaving a whole antibody, or by expressing DNA that encodes the fragment. Fragments of antibodies may be prepared by methods described by Lamoyi *et al.*, *J. Immunol. Methods*, 56: 235-243 (1983) and by Parham, *J. Immunol.* 131: 2895-2902 (1983), both of which are incorporated by reference herein. Such fragments may contain one or both Fab fragments or the F(ab')₂ fragment. Such fragments may also contain single-chain fragment variable region antibodies, *i.e.* scFv, diabodies, or other antibody fragments. Methods of producing such antibodies are disclosed in PCT Application WO 93/21319, European Patent Application No. 239,400; PCT Application WO 89/09622; European Patent

Application 338,745; and European Patent Application EP 332,424, all of which are incorporated by reference herein.

In another embodiment, the present invention provides polynucleotides encoding the anti-VEGFR-1 antibodies of the present invention. Such polynucleotides encode the light chain CDR2 of SEQ ID NO.: 2, the light chain CDR3 of SEQ ID NO: 3, and, preferably, one or more of the other CDRs listed in Table 1. Table 3 sets forth the nucleic acid sequences of preferred anti-VEGFR-1 antibodies.

Table 3 – Nucleotide sequence of anti-VEGFR-1 antibodies	
Clone	Light Chain
6F9	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCCTTGTCTCCAGGGGAA AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGGTAGCAGCAGCTACTT AGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTT GCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCGCTCACTTTCGGCGGA GGGACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCAT CTTCCCG SEQ ID NO:21
13G12	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCCTTGTCTCCAGGGGAA AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGGTAGCAGCAGCTACTT AGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTT GCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCGCTCACTTTCGGCGGA GGGACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCAT CTTCCCG SEQ ID NO:21
15F11	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCCTTGTCTCCAGGGGAA AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGGTAGCAGCAGCTACTT AGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTT GCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCTCTCACCTTCGGCCAA GGGACACGACTGGAGATTAACGAACTGTGGCTGCACCATCTGTCTTCAT CTTCCCG SEQ ID NO:22

<p>18F1</p>	<p>GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAA AGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTT AGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTT GCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCGCTCACTTTCGGCGGA GGGACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCAT CTTTCCG SEQ ID NO:23</p>
<p>Clone</p>	<p>Heavy Chain</p>
<p>6F9</p>	<p>CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGTTATGGCAT GCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTA TATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGA TTCACCATCTCCAGAGACAATTCCAAGAACACGGTGTATCTGCAAATGAA CAGCCTGAGAGCCGAGGACACGGCTGTGTATCACTGTACGAGAGATCACT TTGGTTCGGGGGCTCACTACTACTACTACTACGGTATGGACGTCTGGGGCC AAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO:24</p>
<p>13G12</p>	<p>CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCAT GCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTA TATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGA TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAA CAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCACT ATGGTTCGGGGGCTCACTACTACTACTACTACGGTATGGACGTCTGGGGC CAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO:25</p>
<p>15F11</p>	<p>CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCAT GCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTA TATGGTTTGTATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGA TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAA CAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCACT ATGGTTCGGGGGCTCACTCCTACTACTACTACTACGGTTTGGACGTTTGGGGCC AAGGGACCTCGGTCACCGTCTCCTCA SEQ ID NO:26</p>

18F1	CAGGCCGCAGGTGGTGGAGTCTGGGGGAGGCGTGGTCCAGTCTGGGAGGTC CCTGAGACTCTCCTGTGCAGCGTCTGGATTCGCCTTCAGTAGCTACGGCAT GCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTA TATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAGGGGCCGA TTCACCATCTCCAGAGACAATTCCGAGAACACGCTGTATCTGCAAATGAA CAGCCTGAGAGCCGAGGACACCGCTGTGTATTACTGTGCCAGAGATCACT ATGGTTCGGGGGTGCACCACTATTTCTACTACGGTCTGGACGTCTGGGGCC AAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO:27
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DNA encoding human antibodies can be prepared by recombining DNA encoding human constant regions and variable regions, other than the CDRs, derived substantially or exclusively from the corresponding human antibody regions and DNA encoding CDRs derived from a human (SEQ ID NOs: 1-4 for the light chain variable domain CDRs and SEQ ID Nos: 5-13 for the heavy chain variable domain CDRs).

Polynucleotides encoding anti-VEGFR-1 antibodies of the present invention include polynucleotides with nucleic acid sequences that are substantially the same as the nucleic acid sequences of the polynucleotides of the present invention.

“Substantially the same” nucleic acid sequence is defined herein as a sequence with at least 70%, preferably at least 80%, and more preferably at least 90% identity to another nucleic acid sequence when the two sequences are optimally aligned (with appropriate nucleotide insertions or deletions) and compared to determine exact matches of nucleotides between the two sequences.

Suitable sources of DNAs that encode fragments of antibodies include any cell, such as hybridomas and spleen cells, that express the full-length antibody. The fragments may be used by themselves as antibody equivalents, or may be recombined into equivalents, as described above. The DNA deletions and recombinations described in this section may be carried out by known methods, such as those described in the published patent applications listed above in the section entitled “Functional Equivalents of Antibodies” and/or other standard recombinant DNA techniques, such as those described below. Another source of DNAs are single chain antibodies produced from a phage display library, as is known in the art.

Additionally, the present invention provides expression vectors containing the polynucleotide sequences previously described operably linked to an expression sequence, a promoter and an enhancer sequence. A variety of expression vectors for the efficient synthesis of antibody polypeptide in prokaryotic, such as bacteria and

eukaryotic systems, including but not limited to yeast and mammalian cell culture systems have been developed. The vectors of the present invention can comprise segments of chromosomal, non-chromosomal and synthetic DNA sequences.

Any suitable expression vector can be used. For example, prokaryotic cloning vectors include plasmids from *E. coli*, such as *colE1*, *pCR1*, *pBR322*, *pMB9*, *pUC*, *pKSM*, and *RP4*. Prokaryotic vectors also include derivatives of phage DNA such as *M13* and other filamentous single-stranded DNA phages. An example of a vector useful in yeast is the 2μ plasmid. Suitable vectors for expression in mammalian cells include well-known derivatives of SV-40, adenovirus, retrovirus-derived DNA sequences and shuttle vectors derived from combination of functional mammalian vectors, such as those described above, and functional plasmids and phage DNA.

Additional eukaryotic expression vectors are known in the art (e.g., P.J. Southern & P. Berg, *J. Mol. Appl. Genet.*, 1:327-341 (1982); Subramani *et al.*, *Mol. Cell. Biol.*, 1: 854-864 (1981); Kaufmann & Sharp, "Amplification And Expression of Sequences Cotransfected with a Modular Dihydrofolate Reductase Complementary DNA Gene," *J. Mol. Biol.*, 159:601-621 (1982); Kaufmann & Sharp, *Mol. Cell. Biol.*, 159:601-664 (1982); Scahill *et al.*, "Expression And Characterization Of The Product Of A Human Immune Interferon DNA Gene In Chinese Hamster Ovary Cells," *Proc. Nat'l Acad. Sci. USA*, 80:4654-4659 (1983); Urlaub & Chasin, *Proc. Nat'l Acad. Sci. USA*, 77:4216-4220, (1980), all of which are incorporated by reference herein).

The expression vectors useful in the present invention contain at least one expression control sequence that is operatively linked to the DNA sequence or fragment to be expressed. The control sequence is inserted in the vector in order to control and to regulate the expression of the cloned DNA sequence. Examples of useful expression control sequences are the *lac* system, the *trp* system, the *tac* system, the *trc* system, major operator and promoter regions of phage lambda, the control region of fd coat protein, the glycolytic promoters of yeast, e.g., the promoter for 3-phosphoglycerate kinase, the promoters of yeast acid phosphatase, e.g., Pho5, the promoters of the yeast alpha-mating factors, and promoters derived from polyoma, adenovirus, retrovirus, and simian virus, e.g., the early and late promoters or SV40, and other sequences known to control the expression of genes of prokaryotic or eukaryotic cells and their viruses or combinations thereof.

The present invention also provides recombinant host cells containing the expression vectors previously described. Anti-VEGFR-1 antibodies of the present invention can be expressed in cell lines other than in hybridomas. Nucleic acids, which comprise a sequence encoding a polypeptide according to the invention, can be used for transformation of a suitable mammalian host cell.

Cell lines of particular preference are selected based on high level of expression, constitutive expression of protein of interest and minimal contamination from host proteins. Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines, such as but not limited to, Chinese Hamster Ovary (CHO) cells, Baby Hamster Kidney (BHK) cells and many others. Suitable additional eukaryotic cells include yeast and other fungi. Useful prokaryotic hosts include, for example, *E. coli*, such as *E. coli* SG-936, *E. coli* HB 101, *E. coli* W3110, *E. coli* X1776, *E. coli* X2282, *E. coli* DHI, and *E. coli* MRCl, *Pseudomonas*, *Bacillus*, such as *Bacillus subtilis*, and *Streptomyces*.

These present recombinant host cells can be used to produce an antibody by culturing the cells under conditions permitting expression of the antibody and purifying the antibody from the host cell or medium surrounding the host cell. Targeting of the expressed antibody for secretion in the recombinant host cells can be facilitated by inserting a signal or secretory leader peptide-encoding sequence (*See, Shokri et al.*, (2003) *Appl Microbiol Biotechnol.* 60(6):654-664, *Nielsen et al.*, *Prot. Eng.*, 10:1-6 (1997); *von Heinje et al.*, *Nucl. Acids Res.*, 14:4683-4690 (1986), all of which are incorporated by reference herein) at the 5' end of the antibody-encoding gene of interest. These secretory leader peptide elements can be derived from either prokaryotic or eukaryotic sequences. Accordingly suitably, secretory leader peptides are used, being amino acids joined to the N-terminal end of a polypeptide to direct movement of the polypeptide out of the host cell cytosol and secretion into the medium.

The anti-VEGFR-1 antibodies of the present invention can be fused to additional amino acid residues. Such amino acid residues can be a peptide tag to facilitate isolation, for example. Other amino acid residues for homing of the antibodies to specific organs or tissues are also contemplated.

In another embodiment, the present invention provides methods of treating a medical condition by administering a therapeutically effective amount of an anti-

VEGFR-1 antibody according to the present invention to a mammal in need thereof. Therapeutically effective means an amount effective to produce the desired therapeutic effect, such as inhibiting tyrosine kinase activity.

In a preferred embodiment, the present invention provides a method of reducing tumor growth or inhibiting angiogenesis by administering a therapeutically effective amount of an anti-VEGFR-1 antibody of the present invention to a mammal in need thereof. While not intended to be bound to a particular mechanism, the conditions that may be treated by the present methods include, for example, those in which tumor growth or pathogenic angiogenesis is stimulated through a VEGFR paracrine and/or autocrine loop.

With respect to reducing tumor growth, such tumors include primary tumors and metastatic tumors, as well as refractory tumors. Refractory tumors include tumors that fail to respond or are resistant to other forms of treatment such as treatment with chemotherapeutic agents alone, antibodies alone, radiation alone or combinations thereof. Refractory tumors also encompass tumors that appear to be inhibited by treatment with such agents, but recur up to five years, sometimes up to ten years or longer after treatment is discontinued.

Anti-VEGFR-1 antibodies of the present invention are useful for treating tumors that express VEGFR-1. Such tumors are characteristically sensitive to VEGF present in their environment, and may further produce and be stimulated by VEGF in an autocrine stimulatory loop. The method is therefore effective for treating a solid or non-solid tumor that is not vascularized, or is not yet substantially vascularized.

Examples of solid tumors which may be accordingly treated include breast carcinoma, lung carcinoma, colorectal carcinoma, pancreatic carcinoma, glioma and lymphoma. Some examples of such tumors include epidermoid tumors, squamous tumors, such as head and neck tumors, colorectal tumors, prostate tumors, breast tumors, lung tumors, including small cell and non-small cell lung tumors, pancreatic tumors, thyroid tumors, ovarian tumors, and liver tumors. Other examples include Kaposi's sarcoma, CNS neoplasms, neuroblastomas, capillary hemangioblastomas, meningiomas and cerebral metastases, melanoma, gastrointestinal and renal carcinomas and sarcomas, rhabdomyosarcoma, glioblastoma, preferably glioblastoma multiforme, and leiomyosarcoma. Examples of vascularized skin cancers for which anti-VEGFR-1 antibodies of the present invention are effective include squamous cell

carcinoma, basal cell carcinoma and skin cancers that can be treated by suppressing the growth of malignant keratinocytes, such as human malignant keratinocytes.

Examples of non-solid tumors include leukemia, multiple myeloma and lymphoma. Some examples of leukemias include acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), erythrocytic leukemia or monocytic leukemia. Some examples of lymphomas include Hodgkin's and non-Hodgkin's lymphoma.

With respect to inhibiting angiogenesis, anti-VEGFR-1 antibodies of the present invention are effective for treating subjects with vascularized tumors or neoplasms, or angiogenic diseases characterized by excessive angiogenesis. Such tumors and neoplasms include, for example, malignant tumors and neoplasms, such as blastomas, carcinomas or sarcomas, and highly vascular tumors and neoplasms. Cancers that may be treated by the methods of the present invention include, for example, cancers of the brain, genitourinary tract, lymphatic system, stomach, renal, colon, larynx and lung and bone. Non-limiting examples further include epidermoid tumors, squamous tumors, such as head and neck tumors, colorectal tumors, prostate tumors, breast tumors, lung tumors, including lung adenocarcinoma and small cell and non-small cell lung tumors, pancreatic tumors, thyroid tumors, ovarian tumors, and liver tumors. The method is also used for treatment of vascularized skin cancers, including squamous cell carcinoma, basal cell carcinoma, and skin cancers that can be treated by suppressing the growth of malignant keratinocytes, such as human malignant keratinocytes. Other cancers that can be treated include Kaposi's sarcoma, CNS neoplasms (neuroblastomas, capillary hemangioblastomas, meningiomas and cerebral metastases), melanoma, gastrointestinal and renal carcinomas and sarcomas, rhabdomyosarcoma, glioblastoma, including glioblastoma multiforme, and leiomyosarcoma.

Non-limiting examples of pathological angiogenic conditions characterized by excessive angiogenesis involving, for example inflammation and/or vascularization include atherosclerosis, rheumatoid arthritis (RA), neovascular glaucoma, proliferative retinopathy including proliferative diabetic retinopathy, macular degeneration, hemangiomas, angiofibromas, and psoriasis. Other non-limiting examples of non-neoplastic angiogenic disease are retinopathy of prematurity (retrolental fibroplastic), corneal graft rejection, insulin-dependent diabetes mellitus,

multiple sclerosis, myasthenia gravis, Crohn's disease, autoimmune nephritis, primary biliary cirrhosis, psoriasis, acute pancreatitis, allograft rejection, allergic inflammation, contact dermatitis and delayed hypersensitivity reactions, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, cognition defects induced by neuronal inflammation, Osler-Weber syndrome, restinosis, and fungal, parasitic and viral infections, including cytomegaloviral infections.

The identification of medical conditions treatable by anti-VEGFR-1 antibodies of the present invention is well within the ability and knowledge of one skilled in the art. For example, human individuals who are either suffering from a clinically significant neoplastic or angiogenic disease or who are at risk of developing clinically significant symptoms are suitable for administration of the present VEGF receptor antibodies. A clinician skilled in the art can readily determine, for example, by the use of clinical tests, physical examination and medical/family history, if an individual is a candidate for such treatment.

Anti-VEGFR-1 antibodies of the present invention can be administered for therapeutic treatments to a patient suffering from a tumor or angiogenesis associated pathologic condition in an amount sufficient to prevent, inhibit, or reduce the progression of the tumor or pathologic condition. Progression includes, *e.g.*, the growth, invasiveness, metastases and/or recurrence of the tumor or pathologic condition. Amounts effective for this use will depend upon the severity of the disease and the general state of the patient's own immune system. Dosing schedules will also vary with the disease state and status of the patient, and will typically range from a single bolus dosage or continuous infusion to multiple administrations per day (*e.g.*, every 4-6 hours), or as indicated by the treating physician and the patient's condition. It should be noted, however, that the present invention is not limited to any particular dose.

In another embodiment, the present invention provides a method of treating a medical condition by administering an anti-VEGFR-1 antibody of the present invention in combination with one or more other agents. For example, an embodiment of the present invention provides a method of treating a medical condition by administering an anti-VEGFR-1 antibody of the present invention with an antineoplastic or antiangiogenic agent. The anti-VEGFR-1 antibody can be

chemically or biosynthetically linked to one or more of the antineoplastic or antiangiogenic agents.

Any suitable antineoplastic agent can be used, such as a chemotherapeutic agent or radiation. Examples of chemotherapeutic agents include, but are not limited to, cisplatin, doxorubicin, cyclophosphamide, paclitaxel, irinotecan (CPT-11), topotecan or a combination thereof. When the antineoplastic agent is radiation, the source of the radiation can be either external (external beam radiation therapy – EBRT) or internal (brachytherapy – BT) to the patient being treated.

Further, anti-VEGFR-1 antibodies of the present invention may be administered with antibodies that neutralize other receptors involved in tumor growth or angiogenesis. One example of such a receptor is VEGFR-2/KDR. In an embodiment, an anti-VEGR-1 antibody of the present invention is used in combination with a receptor antagonist that binds specifically to VEGFR-2. Particularly preferred are antigen-binding proteins that bind to the extracellular domain of VEGFR-2 and block binding by any one of its ligands, such as VEGF(A), VEGF-C, VEGF-D, or VEGF-E.

Another example of such a receptor is EGFR. In an embodiment of the present invention, an anti-VEGFR-1 antibody is used in combination with an EGFR antagonist. An EGFR antagonist can be an antibody that binds to EGFR or a ligand of EGFR and inhibits binding of EGFR to its ligand. Ligands for EGFR include, for example, EGF, TGF- α amphiregulin, heparin-binding EGF (HB-EGF) and betarecullulin. EGF and TGF- α are thought to be the main endogenous ligands that result in EGFR-mediated stimulation, although TGF- α has been shown to be more potent in promoting angiogenesis. It should be appreciated that the EGFR antagonist can bind externally to the extracellular portion of EGFR, which may or may not inhibit binding of the ligand, or internally to the tyrosine kinase domain. Examples of EGFR antagonists that bind EGFR include, without limitation, biological molecules, such as antibodies (and functional equivalents thereof) specific for EGFR, and small molecules, such as synthetic kinase inhibitors that act directly on the cytoplasmic domain of EGFR.

Other examples of growth factor receptors involved in tumorigenesis are the receptors for platelet-derived growth factor (PDGFR), insulin-like growth factor (IGFR), nerve growth factor (NGFR), and fibroblast growth factor (FGFR).

In an additional alternative embodiment, the present invention provides a method of treating a medical condition by administering an anti-VEGFR-1 antibody of the present invention in combination with one or more suitable adjuvants, such as, for example, cytokines (IL-10 and IL-13, for example) or other immune stimulators. *See, e.g., Larrivée et al., supra.*

In a combination therapy, the anti-VEGFR-1 antibody can be administered before, during, or after commencing therapy with another agent, as well as any combination thereof, *i.e.*, before and during, before and after, during and after, or before, during and after commencing the antineoplastic agent therapy. For example, an anti-VEGFR-1 antibody of the present invention may be administered between 1 and 30 days, preferably 3 and 20 days, more preferably between 5 and 12 days before commencing radiation therapy. The present invention, however is not limited to any particular administration schedule. The dose of the other agent administered depends on numerous factors, including, for example, the type of agent, the type and severity of the medical condition being treated and the route of administration of the agent. The present invention, however, is not limited to any particular dose.

Any suitable method or route can be used to administer an anti-VEGFR-1 antibody of the present invention, and optionally, to coadminister antineoplastic agents and/or antagonists of other receptors. Routes of administration include, for example, oral, intravenous, intraperitoneal, subcutaneous, or intramuscular administration. It should be emphasized, however, that the present invention is not limited to any particular method or route of administration.

It is noted that an anti-VEGFR-1 antibody of the present invention can be administered as a conjugate, which binds specifically to the receptor and delivers a toxic, lethal payload following ligand-toxin internalization.

It is understood that anti-VEGFR-1 antibodies of the invention, where used in a mammal for the purpose of prophylaxis or treatment, will be administered in the form of a composition additionally comprising a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers include, for example, one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the

binding proteins. The compositions of the injection may, as is well known in the art, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the mammal.

Although human antibodies of the invention are particularly useful for administration to humans, they may be administered to other mammals as well. The term "mammal" as used herein is intended to include, but is not limited to, humans, laboratory animals, domestic pets and farm animals.

The present invention also includes kits for inhibiting tumor growth and/or angiogenesis comprising a therapeutically effective amount of an anti-VEGFR-1 antibody of the present invention. The kits can further contain any suitable antagonist of, for example, another growth factor receptor involved in tumorigenesis or angiogenesis (e.g., VEGFR-2/FKDR, EGFR, PDGFR, IGFR, NGFR, FGFR, etc, as described above). Alternatively, or in addition, the kits of the present invention can further comprise an antineoplastic agent. Examples of suitable antineoplastic agents in the context of the present invention have been described herein. The kits of the present invention can further comprise an adjuvant, examples of which have also been described above.

In another embodiment, the present invention provides investigative or diagnostic methods using anti-VEGFR-1 antibodies of the present invention *in vivo* or *in vitro*. In such methods, anti-VEGFR-1 antibodies can be linked to target or reporter moieties.

EXAMPLES

The following examples do not include detailed descriptions of conventional methods, such as those employed in the construction of vectors and plasmids, the insertion of genes encoding polypeptides into such vectors and plasmids, or the introduction of plasmids into host cells. Such methods are well known to those of ordinary skill in the art and are described in numerous publications including Sambrook, J., Fritsch, E.F. and Maniatis, T. (1989), *Molecular Cloning: A Laboratory Manual*, 2nd edition, Cold Spring Harbor Laboratory Press, which is incorporated by reference herein.

Materials

All reagents and chemicals were purchased from Sigma (St. Louis, MO) unless otherwise noted. Human VEGF165 and soluble recombinant human VEGFR-1 alkaline phosphatase (rhVEGFR-1 AP) proteins were expressed in stably transfected cells and purified from cell culture supernatant following the procedures known to one skilled in the art (Tessler, *J. Biol. Chem.*, 269:12456-12461 (1994), which is incorporated by reference herein). PlGF and soluble recombinant VEGFR-1 Fc (rhVEGFR-1 Fc) proteins were purchased from (R&D Systems Inc. Minneapolis, MN). Cell cultureware and assay plates were purchased from (BD Biosciences, Bedford, MA).

Cell Lines

The human breast cancer cell lines DU4475, MDA-MB-231, MDA-MB-435, and mouse myeloma cell lines P3-X63-Ag8.653 and NS0 were obtained from American Type Tissue Culture Collection (Manassas, VA). P3-X63-Ag8.653 Bcl/2 transfectant cell line was created in house as previously described (Ray S, Diamond B. *Proc Natl Acad Sci USA*. 91:5548-51, 1994). The tumor cells were maintained in RPMI1640 medium (Invitrogen/Life Technologies, Inc., Rockville, MD) containing 10% FCS (Hyclone, Logan, UT). Porcine aorta endothelial VEGFR-1 expressing cell line was provided by Dr. L. Claesson-Welsh, Uppsala University, and cultured in F12 medium (Invitrogen/Life Technologies, Inc., Rockville, MD) containing 10% FCS (Hyclone, Logan, UT). All cells were maintained at 37°C in a humidified, 5% CO₂ atmosphere.

Example 1: Generation of anti-VEGFR 1 antibodies

Human anti-VEGFR-1 monoclonal antibodies (referred to herein as “anti-VEGFR-1 antibodies”) were generated by a standard hybridoma technology (Harlow & Lane, ed., *Antibodies: A Laboratory Manual*, Cold Spring Harbor, 211-213 (1998), which is incorporated by reference herein) using KM transgenic mice (Medarex, San Jose, Calif.), which produce human immunoglobulin gamma heavy and kappa light chains. KM mice were immunized subcutaneously (s.c.) with VEGFR-1 fragment crystallization (Fc) in complete Freund's adjuvant. Animals were intraperitoneally (i.p.) boosted three times with the same VEGFR-1 protein in incomplete Freund's adjuvant before fusion. The animals were rested for a month before they received the final i.p. boost of 25 micrograms of VEGFR-1 protein in phosphate buffer solution

(PBS). Four days later, splenocytes were harvested from the immunized mouse and fused with P3-X63-Ag8.653 Bcl-2 transfectant plasmacytoma cells using polyethylene glycol (PEG, MW: 1450 KD). After fusion, the cells were resuspended in HAT (hypoxanthine, aminopterin, thymidine) medium supplemented with 10% fetal bovine serum (FBS) and distributed to 96 well plates at a density of 200 microliters per well for establishment of hybridoma cells. At day 6 post-fusion, 100 microliters of medium was aspirated and replaced with 100 microliters of fresh medium.

Example 2A: Anti-VEGFR-1 Antibodies From Example 1 Bind to VEGFR-1 and Inhibit VEGFR-1 Binding to Its Ligands

a. VEGFR-1 Binding and Blocking Assays

At day 10-12 post-fusion, the hybridomas were screened for antibody production and specific binding activity of culture supernatant with rhuVEGFR-1 protein in ELISA-based binding and blocking assays. The positive hybridomas were subcloned three times by a limiting dilution culture for establishment of monoclonal hybridomas.

Specifically, hybridoma supernatants or purified antibodies were diluted in PBS with 5% FBS and 0.05% Tween 20 (ELISA buffer) and incubated in rhuVEGFR-1 AP or AP coated 96-well microtiter plates for 30 minutes. Plates were washed with the ELISA buffer and incubated with goat anti-mouse IgG-horseradish peroxidase (HRP) conjugate (BioSource International, Camarillo, CA) for 30 minutes. TMB (3,3', 5,5'-tetra-methylbenzidine) substrate (Kierkegaard and Perry Lab, Inc., Gaithersburg, MD) was used for color development following the manufacturer's instruction. The absorbance at 450 nanometers (nm) was read for quantification of binding activity of antibodies. For identification of the hybridomas producing anti-VEGFR-1 antibodies, hybridoma supernatants were preincubated with VEGFR-1 AP for 1 hour. The mixtures were incubated with the ELISA buffer in VEGF or PlGF coated 96-well microtiter plates for 1 hour. PNPP (p-nitrophenyl phosphate) substrate for AP was used for color development following the manufacturer's instruction. The absorbance at 405 nm was read for quantification of VEGFR-1 binding to VEGF or PlGF. Optical density (OD) values were read on a microtiter plate reader (Molecular

Devices Corp., Sunnyvale, CA). ED50 and IC50 of the antibodies were analyzed using GraphPad Prism 3 software (GraphPad Software, Inc., San Diego, CA).

Figure 3 shows the binding activity of purified antibodies produced from hybridomas designated “6F9,” “13G12,” “15F11,” and “18F1.” These antibodies exhibited a binding activity with ED50 of 0.1-0.3 nM in ELISA-based binding assay. **Figures 4 and 5** show respectively that clones 6F9, 13G12, 15F11, 18F1 effectively blocked PlGF binding to VEGFR-1 with IC50 of 0.4-0.8 nM and VEGF binding to VEGFR-1 with IC50 of 0.7-0.8 nM. The binding and blocking characteristics of the antibodies are summarized in Table 4.

Clone	Binding Activity (ED50)	Blocking Activity (IC50)
6F9	0.1 nM	0.86 nM: PlGF 0.82 nM: VEGF
13G12	0.3 nM	0.82 nM: PlGF 0.70 nM: VEGF
15F11	0.3 nM	0.49 nM: PlGF 0.73 nM: VEGF
18F1	0.1 nM	0.55 nM: PlGF 0.84 nM: VEGF

b. Measurement of Affinity of Anti-VEGFR-1 Antibodies

Affinities of anti-VEGFR-1 antibody clones 6F9, 13G12, 15F11, 18F1 were determined by plasmon resonance technology using BIAcore 2000 (Pharmacia, Piscataway, NJ) according to the procedures provided by the manufacturer. Kinetic analyses of the antibodies were performed by immobilization of recombinant extracellular domain of VEGFR-1 onto a sensor surface at a low density. The (k_{on})

and dissociation (k_{off}) rates were determined using the BIAevaluation 2.1 software provided by the manufacturer.

Anti-VEGFR-1 antibody clones 6F9, 13G12, F11, and 18F1 exhibited a high affinity with a K_D value of 69, 121, 70, and 54 pM, respectively. The kinetics of the antibodies are summarized in Table 5.

Table 5 – Kinetics of human anti-VEGFR-1 antibodies			
Clone	K_{on}	K_{off}	K_D
6F9	1.01e6 M	7.38e-5 M	69 pM
13G12	0.95e6 M	10.9e-5 M	121 pM
15F11	1.02e6 M	7.16e-5 M	70 pM
18F1	0.81e6 M	4.27e-5 M	54 pM

c. Evaluation of Specificity of Anti-VEGFR-1 Antibody

To determine the specificity of an anti-VEGFR-1 monoclonal antibody to human VEGFR-1, purified antibodies 18F1 were tested in an ELISA-based assay. One $\mu\text{g/ml}$ of recombinant human VEGFR-1 Fc, mouse VEGFR-1 Fc, mouse VEGFR-2 Fc, or human VEGFR-2 alkaline phosphatase was coated with PBS in a 96-well microtiter plates at 4 °C over night. After wash, the receptor coated plates were blocked with PBS containing 5% Dry Milk and 0.05% Tween 20. Serial dilutions of primary antibody 18F1 to human VEGFR-1, MF1 to mouse VEGFR-1, 1C11 to human VEGFR-2, or DC101 to mouse VEGFR-2 were incubated in the receptor-coated plates for 30 minutes. After wash secondary anti-primary HRP conjugate antibodies was incubated in the plates for 30 minutes. Plates were washed and incubated with the substrate TMB (3,3', 5,5'-tetra-methylbenzidine) for color development. The absorbance at 450 nm was read as OD values for quantification of binding activity of antibodies. Data were analyzed using a GraphPad Prism Software.

Figures 6 A-D show the specificity of monoclonal antibody 18F1 to human VEGFR-1 (**Figure 6A**), and that the antibody has no cross reactivity with mouse

VEGFR-1 (**Figure 6B**), human VEGFR-2 (**Figure 6C**) and mouse VEGFR-2 (**Figure 6D**). The results indicate that the anti-human VEGFR-1 antibody 18F1 has a strict binding specificity with its respective receptor.

d. Western Blot

Confluent porcine aorta endothelial VEGFR-1 expressing (PAE-VEGFR-1) cells and BT474 human breast carcinoma cells were cultured in serum-depleted F12 medium for 48 hours. The cells were then preincubated with anti-VEGFR-1 antibody clone 18F1 at concentrations ranging from 0.1 to 30 $\mu\text{g/ml}$ for 1 hour followed by stimulating with VEGF or PlGF for 5 minutes at 37°C. The cells were then rinsed with ice-cold PBS and lysed in lysis buffer (50 mM HEPES, 150 mM NaCl, 1% Triton X-100, and 10% glycerol containing 1 mM phenylmethylsulfonyl fluoride, 10 $\mu\text{g/ml}$ aprotinin, 10 $\mu\text{g/ml}$ leupeptin, and 1 mM sodium vanadate). Cell lysates were subjected to SDS-PAGE and transferred onto Immobilon membranes (Millipore Corp. Billerica, MA). After transfer, blots were incubated with the blocking solution and probed with antiphosphotyrosine antibody (PY20, Santa Cruz Biotechnology, Santa Cruz, CA) followed by washing. The protein contents were visualized using horseradish peroxidase-conjugated secondary antibodies followed by enhanced chemiluminescence (Amersham Pharmacia Biotech, Piscataway, NJ). An anti-VEGFR-1 specific antibody (Oncogene Research Products, San Diego, CA) was used for re-blot of VEGFR-1.

All anti-VEGFR-1 antibodies recognized a 180 KD molecule of VEGFR-1 recombinant protein.

Example 2B: Anti-Human Anti-VEGFR-1 Antibody is Specific for Human VEGFR-1

HuVEGFR-1-Fc, mouse VEGFR-1-AP (ImClone Systems) or huVEGFR-2-AP (ImClone Systems) (100 ng/well) was coated on 96 strip-well plates and blocked with 5% milk/PBS. The binding of 18F1 and other anti-human VEGFR-1 antibodies or a rat anti-mouse VEGFR-1 antibody, MF1 (ImClone Systems, ref. 18), to plate bound VEGFR-1 or VEGFR-2 was evaluated as described for the hybridoma supernatant screening above, except that bound antibody was detected with a goat anti-human kappa-HRP antibody (BioSource International, Camarillo, CA) for 18F1

and anti-human VEGFR-2 antibody 1C11, or a goat anti-rat IgG-HRP antibody (BioSource International) for MF1.

8F1 showed a specific reactivity with human VEGFR-1 (**Figure 32A**) but no cross reactivity with mouse VEGFR-1 (**Figure 32B**) and human VEGFR-2 (**Figure 32C**). The anti-mouse VEGFR-1 blocking antibody MF1 was also demonstrated to be species specific, binding mouse (**Figure 32B**), but not human VEGFR-1 (**Figure 32A**).

Example 3: Anti-VEGFR-1 Antibodies Bind to Native VEGFR-1 on VEGFR-1 Expressing Cells

a. Flow Cytometry Analysis

Aliquots of 10^6 PAE-VEGFR-1 cells were harvested from subconfluent cultures and incubated with anti-VEGFR-1 antibody clones 6F9, 13G12, F11, and 18F1 in PBS with 1% bovine serum albumin (BSA) and 0.02% sodium azide (staining buffer) for one hour on ice. Aliquots of 10^6 DU4475 human breast carcinoma cells were harvested from subconfluent cultures and incubated with anti-VEGFR-1 antibody clone 18F1 in PBS with 1% bovine serum albumin (BSA) and 0.02% sodium azide (staining buffer) for one hour on ice. A matched IgG isotype (Jackson ImmunoResearch, West Grove, PA) was used as a negative control. Cells were washed twice with flow buffer and then incubated with a fluorescein isothiocyanate (FITC)-labeled goat anti-human IgG antibody (BioSource International, Camarillo, CA) in staining buffer for 30 minutes on ice. Cells were washed as above and analyzed on an Epics XL flow cytometer (Beckman-Coulter, Hialeah, FL). Dead cells and debris were eliminated from the analysis on the basis of forward and sideways light scatter. The mean fluorescent intensity units (MFIU) were calculated as the mean log fluorescence multiplied by the percentage of positive population.

Figure 7 shows binding reactivity of clones 6F9, 13G12, 15F11 and 18F1 with the PAE-VEGFR-1 expressing cells. **Figures 8A** and **8B** show binding reactivity of clone 18F1 with PAE-VEGFR-1 expressing cells and DU4475 human breast carcinoma, respectively. These results indicate that the human anti-VEGFR-1 antibodies bind to native VEGFR-1 expressed in cell surface.

b. Surface VEGFR-1 blocking assay

The binding of ^{125}I -VEGF to VEGFR-1 on cell surface was performed using PAE-VEGFR-1 expressing cells. Cells were grown on non-coated plastic cell culture plates, which were found to decrease nonspecific binding without affecting the specific binding of ^{125}I -VEGF. Confluent cells were incubated in serum- and growth supplement-free Dulbecco's Modified Eagle Medium (DMEM)/F-12 medium (Invitrogen, Carlsbad, CA) for 24 hours. Cells were rinsed once with ice-cold DMEM/F-12 medium containing 0.025 M HEPES and 1 mg/ml bovine serum albumin (BSA). A serial dilution of anti-VEGFR-1 antibody 18F1 or cold VEGF at the concentration of a 200-fold molar excess of labeled VEGF was added to each well in the plate and incubated at 4 °C for 1 hour. After wash, ^{125}I -VEGF was added at the concentration of 2 ng/ml and was incubated at 4 °C for 2 hours on a platform shaker. The cells were washed three times with PBS containing 1 mg/ml BSA and 0.25 mM CaCl_2 , and were incubated for 5 minutes in the presence of 1% Triton X-100, 1 mg/ml BSA, and 0.16% NaN_3 to remove bound VEGF. The soluble content of each well was counted in a gamma counter. The assays were performed in triplicate in at least three independent experiments and the data were analyzed using Prism GraphPad software 3.03.

Figure 9 shows the strong blocking activity of the anti-VEGFR-1 antibody 18F1 that dramatically prevents the native VEGFR-1 from binding to the ^{125}I -VEGF on the porcine aorta endothelial cells.

Example 4: Anti-VEGFR-1 Antibodies Inhibit Autophosphorylation of VEGFR-1 and Activation of MAPK and Akt in Response to VEGF and PlGF

a. VEGFR-1 Phosphorylation Assay

Autophosphorylation of the VEGFR-1 induced by its ligands and resulting activation of a classical MAPK, extracellular signal-regulated protein kinases 1/2 (ERK1/2) and the PI3K/Akt downstream signaling pathways mediate cellular biological responses such as proliferation, motility, survival, and differentiation. The ability of an anti-VEGFR-1 antibody to inhibit phosphorylation of VEGFR-1 and activation of ERK1/2 and the Akt kinases downstream signaling were determined by using the PAE-VEGFR-1 transfectant and BT474 breast carcinoma cells.

PAE-VEGFR-1 and BT474 cells were seeded at a density of 5×10^5 /well in 100 or 150 mm² plates and cultured in serum-free medium for 18-48 hours. After

replacing the culture medium, the cells were treated at 37 °C with anti-VEGFR-1 antibody clones 6F9, 15F11, and 18F1 or isotype control for 1 hour and then incubated with 50 ng/ml of VEGF or 100 ng/ml of PlGF for 10 minutes. After treatments, total cell protein extracts were isolated with lysis buffer [20 mM HEPES (pH 7.4), 10 mM MgCl₂, 2 mM, MnCl₂, 0.05% Triton X-100, and 1 mM DTT], and immunoprecipitated with anti-VEGFR-1 antibody (C-17, Santa Cruz Biotechnology, Santa Cruz, CA). Western blot of phosphorylated VEGFR-1 was detected using anti-phospho-kinase antibody (PY-20, Santa Cruz Biotechnology, Santa Cruz, CA). Proteins were detected using an electrogenerated chemiluminescence system (ECL)(Amersham Pharmacia Biotech, Piscataway, NJ), and quantified by densitometry using NIH Image (National Institute of Mental Health, Bethesda, MD).

b. In vitro Kinase Assay

For evaluation of MAPK and Akt phosphorylation, BT474 cells were seeded at a density of 5×10^5 /well in 12 well plates in serum-free conditions for 18 hours. Cells were treated at 37 °C with anti-VEGFR-1 antibody clone 18F1 or isotype control for 1 hour and then incubated with 50 ng/ml of VEGF or 100 ng/ml of PlGF for 5-10 minutes. Cell lysis, protein isolation and electroblotting were performed. Membranes were incubated with antibodies against phosphorylated p44/p42 MAP kinases (Thr202/Tyr204, Santa Cruz Biotechnology, Santa Cruz, CA) or phosphorylated Akt (Ser473, Cell Signaling Technology, Beverly, MA), at a concentration of 1 µg/ml, followed by incubation with a secondary IgG-HRP (1:5000). To ensure equal loading of samples, membranes were stripped and reprobed with anti-p44/p42 (Santa Cruz Biotechnology, Santa Cruz, CA) or anti-Akt antibodies (Cell Signaling Technology, Beverly, MA).

c. Results

As shown in **Figures 10-14** a significant phosphorylation of VEGFR-1 and activation of ERK1/2 and Akt signaling in the PAE-VEGFR-1 transfectant and BT474 breast cancer cells was induced by VEGF and PlGF stimulation, suggesting the intrinsic activity of the VEGFR-1 and the receptor-associated downstream kinase signaling pathways in both breast cancer and endothelial cells. As shown in **Figures 10 and 11**, respectively, treatment with anti-VEGFR-1 antibody 18F1 significantly

reduced PIGF or VEGF-stimulated phosphorylation of VEGFR-1 compared to untreated control in PAE-VEGFR-1 transfectant and BT474 breast cancer cells. As shown in **Figures 12 and 13** respectively, treatment with anti-VEGFR-1 antibodies 15F11 and 6F9 also dramatically inhibited PIGF and VEGF induced activation of ERK1/2 downstream signaling induced by PIGF and VEGF in PAE-VEGFR-1 transfectant cells. Activation of Akt protein kinase is an important intracellular signaling event mediating cell survival in breast cancer. As shown in **Figure 14A and B**, respectively, treatment with anti-VEGFR-1 antibody 18F1 dramatically inhibited PIGF or VEGF-induced activation of ERK ½ downstream signaling induced by PIGF and VEGF in PAE-VEGFR-1 transfectant cells.

As shown in **Figure 15**, the anti-VEGFR-1 antibody 18F1 significantly blocked PIGF-stimulated phosphorylation of Akt in BT474 breast cancer cells. These results demonstrated that treatment with the anti-VEGFR-1 antibodies is effective to inhibit activation of the VEGFR-1 and downstream signaling kinase pathways in both breast cancer and endothelial cells.

Example 5: Anti-VEGFR-1 Antibodies Blocks *In Vitro* Growth of Breast Tumor Cells

Tumor hypoxia is associated with enhancement of malignant progression, increase of aggressiveness and chemotherapeutic drug resistance. Hypoxic tumor cells undergo biological responses that activate signaling pathways for survival and proliferation by upregulation of a variety of gene expression including the VEGFR-1 (Harris AL. Nat Rev Cancer. 2:38-47, 2002).

Cell Growth Assay

DU4475 carcinoma cells were seeded at a density of 5×10^3 /well into 96-well plates in serum-free conditions for 18 hours, and in some case followed by treatment with 100 nM of desferrioxamine for additional 5 hours. Inhibitory effect of anti-VEGFR-1 antibody on tumor cell growth was determined by incubation of cells with anti-VEGFR-1 antibody clones 6F9, 13G12, 15F11, and 18F1 at doses of 3, 10, and 30 $\mu\text{g/ml}$ in the presence of 50 ng/ml of VEGF or 200 ng/ml of PIGF for 48 hours. Viable cells were then counted in triplicate using a Coulter cytometer (Coulter Electronics Ltd. Luton, Beds, England). Each experiment was done in triplicate.

The growth rate of the hypoxia-mimic agent desferrioxamine pre-treated DU4475 tumor cells was increased by approximately 2 fold in response to either VEGF or PIGF stimulation. As shown in **Figures 16** and **17**, respectively, treatment with the anti-VEGFR-1 antibodies effectively reduced VEGF and PIGF stimulated proliferation of DU4475 breast carcinoma cells in a dose response manner. **Figure 18A** and **B** separately plots the antibody concentration of antibody clone 18F1 versus cell count of VEGF and PIGF stimulated proliferation of DU4475 breast carcinoma cells. The inhibition of PIGF-induced DU4475 cell growth *in vitro* by the anti-VEGFR-1 antibodies as represented in IC50 values is summarized in Table 6.

Clone	<i>in vitro</i> cell growth
6F9	IC50: 43nM
13G12	IC50: 66nM
15F11	IC50: 44nM
18F1	IC50: 24Nm

Example 6A: Anti-VEGFR-1 Antibodies Suppress Growth of Breast Tumor Xenografts

Treatment of Human Breast Carcinoma Xenografts

Antitumor efficacy of the human anti-VEGFR-1 antibodies was tested in the human xenograft breast tumor models.

Athymic nude mice (Charles River Laboratories, Wilmington, MA) were injected subcutaneously in the left flank area with 2×10^6 of DU4475 cells or 5×10^6 of MDA-MB-231 and MDA-MB-435 cells mixed in Matrigel (Collaborative Research Biochemicals, Bedford, MA). In the DU4475 and MDA-MB-231 models, tumors were allowed to reach approximately 200 mm³ in size and then mice were randomized into groups of 12-16 animals per group. Animals received i.p. administration of the anti-VEGFR-1 antibody clones 6F9, 15F11, or 18F1 at a dose of 0.5 mg (MDA-MB-

231) or 1 mg (DU4475) three times each week. In the MDA-MB-435 model, the tumor cells were implanted subcutaneously into mammary fat pad area in the mouse. After tumors grew to reach approximately 200 mm³ in size, mice were randomized into groups of 15 animals per group and intraperitoneally administered with 0.5 mg per dose of 18F1 antibody three times each week. Mice in control groups received an equal volume of saline solution. Treatment of animals was continued for the duration of the experiment. Tumors were measured twice each week with calipers. Tumor volumes were calculated using the formula [$\pi/6$ (w1 X w2 X w2)], where “w1” represents the largest tumor diameter and “w2” represents the smallest tumor diameter.

As shown in **Figure 19A** and **19B**, systemic administration of anti-VEGFR-1 antibodies 6F9, 15F11, 13G12 and 18F1 at a dose of 1 mg per dose three times each week led to a statistically significant suppression of tumor growth of the DU4475 xenograft ($p < 0.05$). As shown in **Figures 20 A, B, and C** respectively, systemic administration of anti-VEGFR-1 antibody 18F1 at a dose of 0.5 or 1 mg per dose three times each week led to a statistically significant suppression of tumor growth of the DU4475, MDA-MB-231, MDA-MB-435 xenografts (ANOVA $p < 0.05$). As shown in **Figures 21A** and **B**, treatment with antibody clone 18F1 against human VEGFR-1 for inhibiting cancer cell growth and clone MF1 against mouse VEGFR-1 for inhibiting tumor angiogenesis at a dose of 20 or 40 mg/kg twice each week resulted in a stronger inhibition of tumor growth in the DU4475 and MDA-MB-231 xenograft models ($P < 0.05$) when compared to either antibody alone. These results demonstrate that blockade of the *in vivo* function of VEGFR-1 in directly promoting cancer cell growth and modulating tumor vascularization by the anti-VEGFR-1 antibody is effective to suppress growth of VEGFR-1 positive breast tumors in xenograft models.

Example 6B: Anti-Human Anti-VEGFR-1 Antibody Blocks *In Vitro* Growth of Breast Cancer Cells

DU4475 carcinoma cells (2×10^4 per well) were seeded into 24-well plates in serum-free conditions for 18 hours and then treated with hypoxia-mimic agent desferrioxamine (Sigma) for an additional 6 hours. A serial dilution of anti-human VEGFR-1 antibody 18F1 was added to the plates in triplicate and incubated in the

presence of 50 ng/mL of VEGF-A (R&D Systems) or 200 ng/mL of PlGF for 48 hours. Total cell number (bound and in suspension) was determined for each well using a Coulter cell counter (Coulter Electronics Ltd., England).

Treatment of IMC-18F1 significantly blocked VEGF-A and PlGF stimulated proliferation of DU4475 breast carcinoma cells (**Figure 31A and 31B**, respectively; estimated IC₅₀:30-50 nM). The isotype control antibody had no effect on cell proliferation. Thus, 18F1 inhibited VEGFR-1 ligand induced promotion of tumor cell proliferation/survival.

Example 7: Anti-VEGFR-1 Antibody Inhibits VEGF-A and VEGF-B Stimulated Colony Formation of Colon Cancer Cells

One mL DMEM medium containing 10% FBS and 1% agarose (Cambrex Corporation, East Rutherford, NJ) was plated in each well of six well plates. HT-29 human colon carcinoma cells in serum free medium were treated with 66 nM 18F1 or control IgG for 1 hour and followed by treatment with 10 ng/mL VEGF-A or 50 ng/mL VEGF-B for additional 4 hours. The treated cells were mixed with 1 mL 10% FBS DMEM containing 0.5 % agarose and the appropriate antibodies and/or ligands. One mL of this suspension, containing 250 cells, was plated in each well on top of the 1% agarose base layer. After 2 days, additional medium containing antibodies and/or ligands was added to the wells to keep the agarose hydrated. Cells were allowed to grow for 14 days at 37°C. Afterwards, colonies larger than 50 µm in diameter were counted using a dissecting microscope. Statistical analysis was performed using InStat Statistical Software (V2.03, GraphPad Software, San Diego, CA)

The number and size of colonies were significantly increased in the wells where cells were treated with VEGF-A or VEGF-B compared to untreated cells in complete medium only. As shown in **Figure 22**, treatment with 18F1 completely suppressed ligand-induced colony formation compared to basal activity in the absence of stimulation with ligands ($p < 0.03$) (Figure 22). Thus, for both adherent and non-adherent cells, 18F1 has the capability of suppressing the survival and growth of tumor cells.

Example 8: Anti-VEGFR-1 Antibody Inhibits VEGF-A and VEGF-B Induced Migration and Invasion of Colon Cancer Cells

HT-29 cells (2.5×10^4) or SW480 cells (1.5×10^4) were incubated in medium containing 1% FBS with the anti-VEGFR-1 antibody 18F1 (66 nM) in the upper surface of a 24 well MATRIGEL™ coated (HT-29) or uncoated (SW480) 8.0- μ m pore size membrane insert (Becton Dickinson Labware, Bedford, MA). The inserts were placed into lower chambers containing 10 ng/mL VEGF-A (R&D Systems) or 50 ng/mL VEGF-B (R&D Systems) for 48 hours. Cells remaining in the top chamber of the inserts were removed with a cotton swab. Cells migrating to the underside of the inserts were stained with Diff-Quik (Harleco, Gibbstown, NJ) and counted in ten random fields at 100X magnification. Statistical analysis was performed using InStat Statistical Software (V2.03, GraphPad Software, San Diego, CA).

As shown in **Figure 23A** and **23B**, VEGF-A or VEGF-B induced migration of HT-29 cells towards ligand through an uncoated membrane. As shown in **Figure 24A** and **24B**, these ligands also induced invasion of SW480 cells through a MATRIGEL™ coated membrane. 18F1 completely blocked VEGFR-1 ligand induced migration and invasion compared to basal activity in the absence of stimulation with ligands ($p < 0.05$, **Figures 23 and 24**). Thus, in addition to negative effects on tumor cell proliferation and survival, 18F1 may provide a means to inhibit the invasion and subsequent metastasis of tumor cells.

Example 9: Treatment with Anti-VEGFR-1 Specific Antibody Suppresses *In Vivo* Growth of VEGFR-1 Expressing Human Xenograft Tumors

Female athymic nu/nu mice, 6-8 weeks of age, were injected subcutaneously on the lateral dorsal surface with 0.4 mL volume of a suspension containing a human tumor cell line in media, diluted 1:1 with MATRIGEL™ (BD Biosciences). The cell lines used in xenograft models, with the cell doses indicated in parenthesis (10^6 cells/mouse), were: human colon carcinoma cell lines DLD-1 (5), GEO (5) and HT-29 (5); human breast carcinoma cell lines DU4475 (2), MDA-MB-231 (5), MDA-MB-435 (5), and BT474 (5). When tumors reached approximately 200-300 mm³, mice were randomized by tumor size and divided into treatment groups. Tumor growth was evaluated approximately twice weekly, with tumor volume calculated as $\pi/6 * (\text{Length} * \text{Width}^2)$, where Length = longest diameter and Width = diameter perpendicular to Length. Tumor dimensions were measured with calipers. T/C% was

calculated as $100 * (\text{Final Treatment Tumor Volume} / \text{Initial Treatment Tumor Volume}) / (\text{Final Control Tumor Volume} / \text{Initial Control Tumor Volume})$.

18F1 was diluted in 0.9% USP saline (Braun) or phosphate buffered saline (PBS) and administered intraperitoneally in a volume of 0.5 mL per mouse. The effect of treatment on tumor growth was analyzed using repeated measures analysis of variance (RM ANOVA), $p < 0.05$ was considered significant.

As shown in **Figure 25**, administration of intraperitoneal 18F1 significantly ($p < 0.05$) suppressed the growth of DU4475 (**Figure 25A**), MDA-MB-231, and MDA-MB-435 (**Figure 25B**) xenograft tumors. As shown in **Figure 26**, a significant antitumor effect of 18F1 monotherapy was also observed against HT-29 (**Figure 26A**), DLD-1 (**Figure 26B**), and GEO (**Figure 26C**) colon cancer xenografts. These results demonstrate that blockade of human VEGFR-1 effectively suppresses the growth of xenograft tumors established with VEGFR-1 expressing human tumor cell lines.

Example 10: Anti-Human VEGFR-1 Treatment Inhibits *In Vivo* Signaling of Proliferation and Survival Pathways and Induced Tumor Cell Apoptosis

Paraffin-embedded MDA-MB-231 xenografts were evaluated immunohistochemically for markers of tumor cell proliferation, survival, and apoptosis. Markers of proliferation and survival included Ki-67 (rabbit pAb; Lab Vision Corporation, Fremont, CA), phospho-specific p44/42 MAPK (Thr202/Tyr204) (rabbit pAb; Cell Signaling Technology) and phospho-specific Akt (Ser473) (rabbit pAb; Cell Signaling Technology). The EnVision+ System for rabbit antibodies (DAKO Cytomation, Carpinteria, CA) was used with 3,3' diaminobenzidine (DAB) as the chromagen, per kit instructions. After brief counterstaining in Mayer's hematoxylin all sections were dehydrated, cleared and coverslipped using a permanent mounting medium. Tumor apoptosis was assessed by TUNEL assay using ApopTag® Peroxidase In Situ Apoptosis Detection Kit (Chemicon, Temecula, CA) per kit instructions. Stained sections were coverslipped with Gelmount (Biomedica, Foster City, CA). Positive immunostaining and TUNEL positive immunofluorescence were analyzed and imaged using an Axioskop light microscope with an Axiocam digital camera (Carl Zeiss, Germany).

As shown in **Figure 27**, a marker for proliferating cells (Ki-67) was significantly reduced after 14 days of treatment with 18F1 at 20 mg/kg (about 0.5 mg/dose with female nu/nu athymic mice), 2x/week (Study Number 3067-04). In addition, 18F1 treatment resulted in a marked decrease in the activation of MAPK at this time point (**Figure 27**). An increase in apoptosis (**Figure 27**) as measured by TUNEL positive events and a significant decrease in Akt phosphorylation were also detected in MDA-MB-231 xenograft tumors after 1 week of treatment with 18F1 (0.5 mg/dose, M-W-F).

Example 11: *In Vivo* Blockage of Both Human and Murine VEGFR-1 Leads to Greater Antitumor Activity Against Human Breast Carcinoma Xenografts

18F1 was used in combination with an antibody to mouse VEGFR-1, MF1. 18F1 was diluted in 0.9% USP saline (Braun) or phosphate buffered saline (PBS) and administered intraperitoneally in a volume of 0.5 mL per mouse. The effect of treatment on tumor growth was analyzed using repeated measures analysis of variance (RM ANOVA), $p < 0.05$ was considered significant. As shown in **Figure 28**, in both the MDA-MB-231 (**Figure 28A**) and DU4475 (**Figure 28B**) xenograft models, inhibition of tumor expressed human VEGFR-1 with 18F1 and endogenous mouse VEGFR-1 with MF1, resulted in significant tumor growth inhibition ($p < 0.05$). MF1 has previously been shown to inhibit tumor growth through a reduction in tumor angiogenesis. The combination of 18F1 and MF1 resulted in significantly more tumor growth inhibition than the monotherapies ($p < 0.05$). 18F1 + MF1 combination therapy was not associated with body weight loss. These data support dual inhibition of tumor vascularization and tumor cell proliferation and survival with 18F1 treatment in patients.

Example 12: *Anti-VEGFR-1* Antibody in Combination with Chemotherapeutics

18F1 + MF1 was combined with cytotoxic therapies, 5-fluorouracil, leucovorin, and paclitaxel in the MDA-MB-231 model. 18F1 was diluted in 0.9% USP saline (Braun) or phosphate buffered saline (PBS). Antibody treatments administered at a constant dose per mouse were administered in a volume of 0.5 mL per mouse. Antibody and cytotoxic treatments administered at a dose proportional to body weight were given in a volume of 10 μ L per gram body weight. 5-Fluorouracil

and leucovorin (5-FU/LV) were diluted separately in USP saline and dosed separately. Paclitaxel was either made in 5% benzyl alcohol (Sigma), 5% Cremophor EL (Sigma), and 90% USP saline or in 5% ethyl alcohol (Sigma), 5% Cremophor EL, and 90% USP saline. Cyclophosphamide and Doxorubicin were dissolved in USP saline for dosing. All treatments were administered i.p. The effect of treatments on tumor growth were analyzed using repeated measures analysis of variance (RM ANOVA), $p < 0.05$ was considered significant.

As shown in **Figure 29**, in the MDA-MB-231 model, adding 18F1 + MF1 to an active dose of cyclophosphamide therapy significantly increased the antitumor effect. As shown in **Figure 30**, when 5-FU/LV and doxorubicin chemotherapy were administered at certain dose levels, 18F1 + MF1 increased the antitumor effects of these two chemotherapies.

In the DU4475 xenograft model, there was a trend for increased activity (lower T/C%) when IMC-18F1 + MF1 was combined with 5-FU/LV, doxorubicin and paclitaxel, although the effect did not reach statistical significance compared to the IMC-18F1 + MF1 alone, or cytotoxic agent monotherapy. In MDA-MB-231 this was again the case for doxorubicin, although for 5-FU/LV and paclitaxel there was no trend for increased activity with the combination. The lack of additivity may be due to the minimal effects of 5-FU/LV and paclitaxel as monotherapies at the selected dose levels. The combination with cyclophosphamide also had increased activity in the MDA-MB-435 model (T/C% = 51) compared to IMC-18F1 + MF1 alone (T/C% = 60) or cyclophosphamide monotherapy (T/C% = 65), although these differences did not reach statistical significance. This was also the case for doxorubicin and paclitaxel in the same study. Similar to the MDA-MB-231 and MDA-MB-435 data above, a combination of IMC-18F1, MF1, and cyclophosphamide exhibited increased antitumor activity compared to antibody or cytotoxic therapy alone in a DU4475 xenograft model, although the trend did not reach statistical significance.

Statistical analysis

Tumor volumes and analysis of *in vitro* tumor cell growth were analyzed using Student's *t* test using the SigmaStat statistical package (v. 2.03; Jandel Scientific, San Rafael, CA). Differences of $p < 0.05$ were considered statistically significant.

Example 13: Cloning and sequencing of VH/VL regions of anti-VEGFR-1 antibodies

Poly (A+) mRNA was isolated from hybridoma cells producing clones 6F9, 13G12, 15F11, and 18F1 derived from VEGFR-1 immunized KM mice using a Fast-Track kit (Invitrogen, Carlsbad, CA). The generation of random primed cDNA was followed by polymerase chain reaction (PCR) using a Clontech kit. Primers (forward: 5'-ATGGAGTTTGGGCTGAGCTG and reverse: 3'-TGCCAGGGGGAAGACCGATGG) and (forward: 5'-ATG GAA ACC CCA GCG CAG CTT CTC and reverse: 3'-CGGGAAGATGAAGACAGATG) were used for binding to variable regions of heavy and kappa light chains, respectively. Sequences of human immunoglobulin-derived heavy and kappa chain transcripts from hybridomas were obtained by direct sequencing of PCR products generated from poly (A+) RNA using the primers described above. PCR products were also cloned into pCR2.1 using a TA cloning kit (Invitrogen, Carlsbad, CA) and both strands were sequenced using Prism dye-terminator sequencing kits and an ABI 3730 Sequencer (GENEWIZ, North Brunswick, NJ). All sequences were analyzed by alignments to the Kataman antibody sequence program using the DNASTAR software.

Table 2, above, shows amino acid sequences of the light and heavy chain variable regions of anti-VEGFR-1 antibody clones 6F9, 13G12, 15F11, and 18F1. The sequences of CDR1, CDR2, and CDR3 domains are indicated by underlining. Table 3, above, shows nucleotide sequences of the cDNA encoding the heavy and light chain variable regions of clones 6F9, 13G12, 15F11, and 18F1

Example 14: Engineering and expression of human IgG1 anti-VEGFR-1 antibodies

The DNA sequences encoding the heavy and light chain variable regions of the anti-VEGFR-1 antibody clones 6F9, 13G12, 15F11, and 18F1 were amplified by PCR for cloning into expression vectors. The heavy chain variable regions were fused in frame to the human immunoglobulin heavy chain gamma1 constant region in vector pEE6.1 (Lonza Biologics plc, Slough, Berkshire, UK). The entire human light chain cDNA was cloned directly into vector pEE12.1 (Lonza Biologics PLC, Slough, Berkshire, UK). Engineered immunoglobulin expression vectors were stably transfected in NS0 myeloma cells by electroporation and selected in glutamine synthetase selection medium. Stable clones were screened for antibody expression by anti-Fc and VEGFR-1 specific binding ELISA. Positive clones were expanded into

serum-free medium culture for antibody production in spinner flasks or bioreactors for a period of up to two weeks. Full length IgG1 antibody was purified by protein A affinity chromatography (Poros A, PerSeptive Biosystems Inc., Foster City, CA) and eluted into a neutral buffered saline solution.

The foregoing description and examples have been set forth merely to illustrate the invention and are not intended as being limiting. Each of the disclosed aspects and embodiments of the present invention may be considered individually or in combination with other aspects, embodiments, and variations of the invention. In addition, unless otherwise specified, none of the steps of the methods of the present invention are confined to any particular order of performance. Modifications of the disclosed embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art and such modifications are within the scope of the present invention. Furthermore, all references cited herein are incorporated by reference in their entirety.

What is claimed is:

1. An isolated human monoclonal antibody or fragment thereof that binds specifically to VEGFR-1 comprising a light chain complementarity determining region-2 (CDR2) of SEQ ID NO:2 and a light chain CDR3 of SEQ ID NO:3.
2. The antibody or fragment thereof of claim 1, further comprising a light chain CDR1 region having the following sequence:

RASQSX₁SSSYLA,

wherein X₁ is V or G.

3. The antibody or fragment thereof of claim 1, further comprising a heavy chain CDR1 having the following sequence:

GFX₂FSSYGMH,

wherein X₂ is T or A.

4. The antibody or fragment thereof of claim 1, further comprising a heavy chain CDR2 having the following sequence:

VIWX₃DGSNKYYADSVX₄G,

wherein X₃ is Y or F and X₄ is K or R.

5. The antibody or fragment thereof of claim 1, further comprising a heavy chain CDR3 having the following sequence:

DHX₅GSGX₆HX₇YX₈YYGX₉DV

wherein X₅ is F or Y; X₆ is A or V; X₇ is Y, S, or H; X₈ is Y or F; and X₉ is M or L.

6. An antibody or fragment thereof comprising (i) a light chain variable region selected from the group consisting of SEQ ID NO:14, 15, and 16 or (ii) a heavy chain variable region selected from the group consisting of SEQ ID NO:17, 18, 19, and 20.

7. An isolated polynucleotide comprising a nucleotide sequence encoding the antibody or fragment thereof of claim 1.
8. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, and SEQ ID NO: 27, the nucleotide sequence encoding an antibody or fragment thereof that specifically binds to VEGFR-1.
9. An expression vector comprising the polynucleotide sequence of claim 7 linked to an expression sequence.
10. A recombinant host cell comprising the expression vector of claim 9.
11. The recombinant host cell of claim 10, or a progeny thereof, wherein the cell expresses the antibody or fragment thereof of claim 7 .
12. A method of producing an antibody or fragment thereof comprising culturing the cell of claim 10 under conditions permitting expression of the antibody or fragment thereof of claim 7.
13. A method of modulating activity of VEGFR-1 in a mammal comprising administering to the mammal an effective amount of an antibody or fragment thereof of claim 1.
14. A method of inhibiting angiogenesis in a mammal comprising administering to the mammal an effective amount of an antibody or fragment thereof of claim 1.
15. A method of reducing tumor growth in a mammal comprising administering to the mammal an effective amount of an antibody or fragment thereof of claim 1.

16. The method of claim 15, wherein the method further comprises administering an anti-neoplastic agent or treatment.

17. The method of claim 15, wherein the tumor is a breast tumor.

Figure 1. Amino acid sequence of the human anti-VEGFR-1 antibodies

6F9-Light chain

METPAQLLFLLLLWLPSTGEIVLTQSPGTLSPGERATLSCRASQSGSSSYLAWYQQKPGQAPRLLI
Y

GASSRATGIPDRFSGSGSGTDFLTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIKRTVAAPSVFIFP
CDR2 CDR1 CDR3

6F9-Heavy chain

MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEW
CDR1

VAVIWDGSNKYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAVYHCTRDHFGSGAHYYYYYGMD
V

CDR2 CDR3
WGQGTTVTVSS

13G12-Light chain

METPAQLLFLLLLWLPSTGEIVLTQSPGTLSPGERATLSCRASQSGSSSYLAWYQQKPGQAPRLLI
Y

GASSRATGIPDRFSGSGSGTDFLTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIKRTVAAPSVFIFP
CDR2 CDR1 CDR3

13G12-Heavy chain

MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEW
CDR1

VAVIWDGSNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDDHYGSGAHYYYYYGMD
V

CDR2 CDR3
WGQGTTVTVSS

15F11-Light chain

MEAPAQLLFLLLLWLPDTTGEIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI
Y CDR1

GASSRATGIPDRFSGSGSGTDFLTISRLEPEDFAVYYCQQYGSSPLTFGQTRLEIKRTVAAPSVFIFP
CDR2 CDR3

15F11-Heavy chain

MEFGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEW
CDR1

VAVIWFDGSNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDDHYGSGAHSYYYYGLDV
CDR2 CDR3

WGQGTSVTVSS

18F1-Light chain

METPAQLLFLLLLWLPDTTGEIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI
Y CDR1

GASSRATGIPDRFSGSGSGTDFLTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIKRTVAAPSVFIFP
CDR2 CDR3

18F1-Heavy chain

MEFGLSWVFLVALLRGVQCQAVVESGGGVVQSGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLE
W CDR1

VAVIWDGSNKYYADSVRGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDDHYGSGVHHYFYGLDV
CDR2 CDR3

WGQGTTVTVSS

Figure 2. Nucleotide sequence of the human anti-VEGFR-1 antibodies

6F9-Light chain

ATGGAACCCAGCGCAGCTTCTCTTCTCCTCTGCTACTCTGGCTCCCAGAAAGCACCCGGAGAAATTGTGTTGACGC
 AGTCTCCAGGCACCCCTGTCTTGTCTCCAGGGGAAAGAGCCACCCCTCTCCTGCAGGGCCAGTCAGAGTGGTAGCAG
 CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGATCCAGCAGGGCC
 ACTGGCATCCCAGACAGGTTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTG
 AAGATTTTGCAGTGTATTACTGTGTCAGCAGTATGGTAGCTCACCGCTCACTTTTCGGCGGAGGGACCAAGGTGGAGAT
 CAAACGAACTGTGGCTGCACCATCTGTCTTTCATCTTCCC

6F9-Heavy chain

ATGGAGTTTGGGCTGAGCTGGGTTTTCTCGTTGCTCTTTTAAAGAGGTGTCCAGTGTCCAGGTGCAGCTGGTGGAGT
 CTGGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACTTCACTAGTTA
 TGGCATGCAGTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAAT
 AAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACCGTGTATCTGCAA
 TGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATCACTGTACGAGAGATCACTTTGGTTTCGGGGGCTCACTACTA
 CTACTACTACGGTATGGACGTCTGGGGCCAAGGGACACGGTCACCGTCTCCTCA

13G12-Light chain

ATGGAACCCAGCGCAGCTTCTCTTCTCCTCTGCTACTCTGGCTCCCAGAAAGCACCCGGAGAAATTGTGTTGACGC
 AGTCTCCAGGCACCCCTGTCTTGTCTCCAGGGGAAAGAGCCACCCCTCTCCTGCAGGGCCAGTCAGAGTGGTAGCAG
 CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGATCCAGCAGGGCC
 ACTGGCATCCCAGACAGGTTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTG
 AAGATTTTGCAGTGTATTACTGTGTCAGCAGTATGGTAGCTCACCGCTCACTTTTCGGCGGAGGGACCAAGGTGGAGAT
 CAAACGAACTGTGGCTGCACCATCTGTCTTTCATCTTCCC

13G12-Heavy chain

ATGGAGTTTGGGCTGAGCTGGGTTTTCTCGTTGCTCTTTTAAAGAGGTGTCCAGTGTCCAGGTGCAGCTGGTGGAGT
 CTGGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACTTCACTAGCTA
 TGGCATGCAGTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAAT
 AAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACCGTGTATCTGCAA
 TGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCACTATGGTTTCGGGGGCTCACTACTA
 CTACTACTACGGTATGGACGTCTGGGGCCAAGGGACACGGTCACCGTCTCCTCA

15F11-Light chain

ATGGAAGCCCCAGCGCAGCTTCTCTTCTCCTCTGCTACTCTGGCTCCCAGATAACCACCCGGAGAAATTGTGTTGACGC
 AGTCTCCAGGCACCCCTGTCTTGTCTCCAGGGGAAAGAGCCACCCCTCTCCTGCAGGGCCAGTCAGAGTGGTAGCAG
 CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGATCCAGCAGGGCC
 ACTGGCATCCCAGACAGGTTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTG
 AAGATTTTGCAGTGTATTACTGTGTCAGCAGTATGGTAGCTCACCTCTCACCTTCGGCCAAGGGACACGACTGGAGAT
 TAAACGAACTGTGGCTGCACCATCTGTCTTTCATCTTCCC

15F11-Heavy chain

ATGGAGTTTGGGCTGAGCTGGGTTTTCTCGTTGCTCTTTTAAAGAGGTGTCCAGTGTCCAGGTGCAGCTGGTGGAGT
 CTGGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACTTCACTAGCTA
 TGGCATGCAGTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTTTATGGAAGTAAT
 AAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACCGTGTATCTGCAA
 TGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCACTATGGTTTCGGGGGCTCACTCCTA
 CTACTACTACGGTTTGGACGTTCGGGGCCAAGGGACCTCGGTACCGTCTCCTCA

18F1-Light chain

ATGGAACCCAGCGCAGCTTCTCTTCTCCTCTGCTACTCTGGCTCCCAGATAACCACCCGGAGAAATTGTGTTGACGC
 AGTCTCCAGGCACCCCTGTCTTGTCTCCAGGGGAAAGAGCCACCCCTCTCCTGCAGGGCCAGTCAGAGTGGTAGCAG
 CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGATCCAGCAGGGCC
 ACTGGCATCCCAGACAGGTTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTG
 AAGATTTTGCAGTGTATTACTGTGTCAGCAGTATGGTAGCTCACCGCTCACTTTTCGGCGGAGGGACCAAGGTGGAGAT
 CAAACGAACTGTGGCTGCACCATCTGTCTTTCATCTTCCC

18F1-Heavy chain

ATGGAGTTTGGGCTGAGCTGGGTTTTCTCGTTGCTCTTTTAAAGAGGTGTCCAGTGTCCAGGCGCAGGTGGTGGAGT
 CTGGGGGAGGCCTGGTCCAGTCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTTCGCTTCACTAGCTA
 CGGCATGCAGTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAAT
 AAATACTATGCAGACTCCGTGAGGGCCGATTACCATCTCCAGAGACAATTCCGAGAACACCGTGTATCTGCAA
 TGAACAGCCTGAGAGCCGAGGACACCGCTGTATATTACTGTGCCAGAGATCACTATGGTTTCGGGGGCTGCACCCTA
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Figure 3

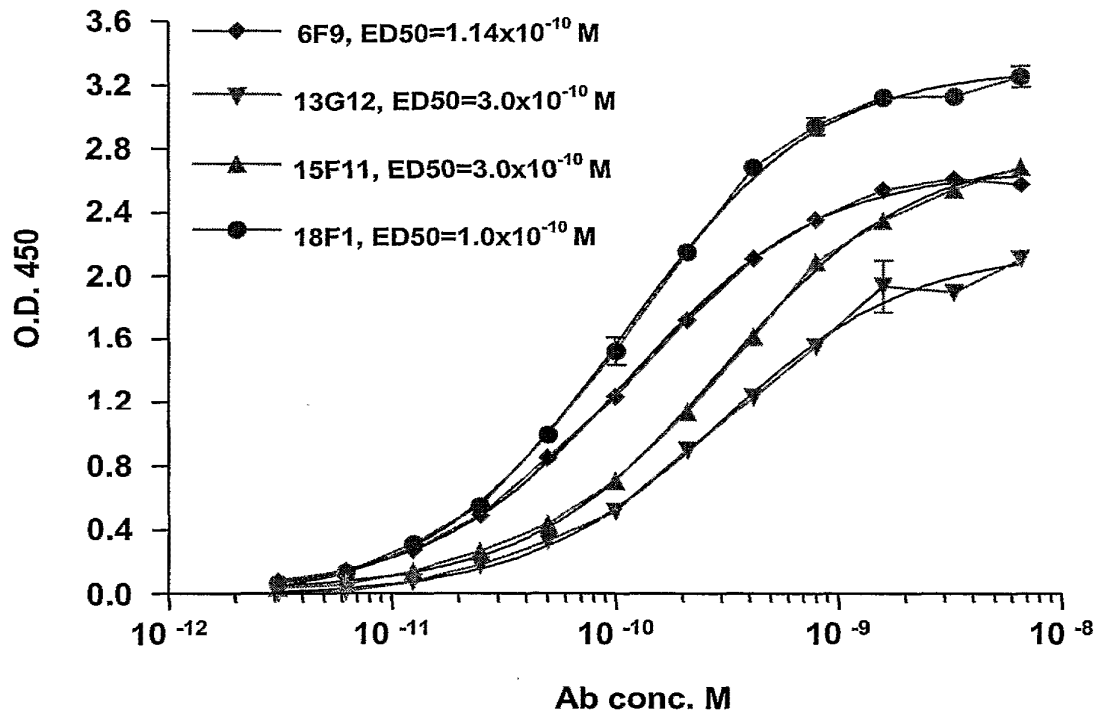


Figure 4

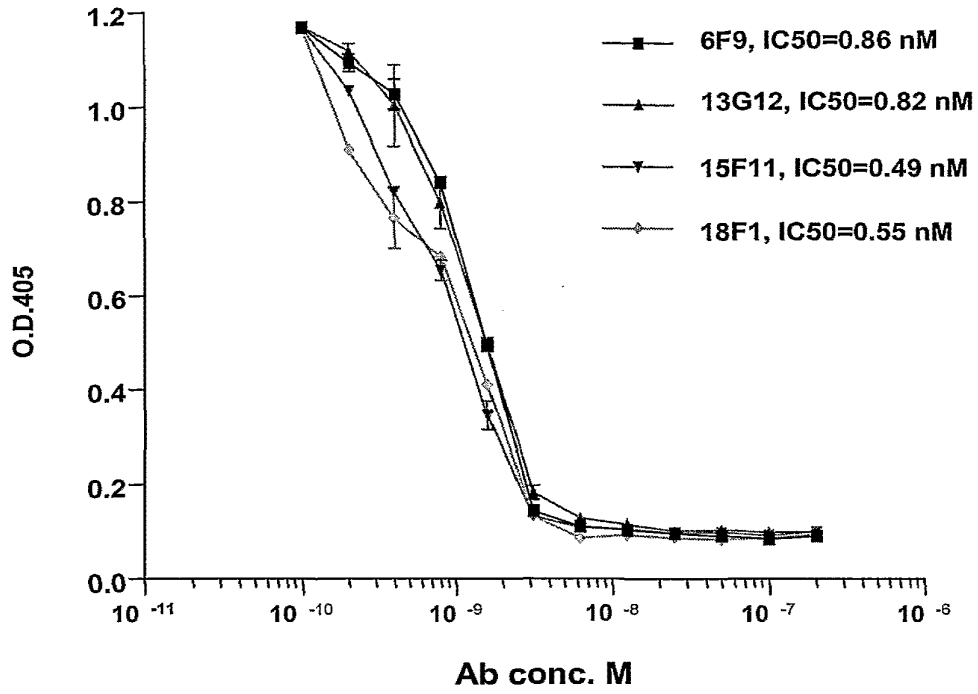


Figure 5

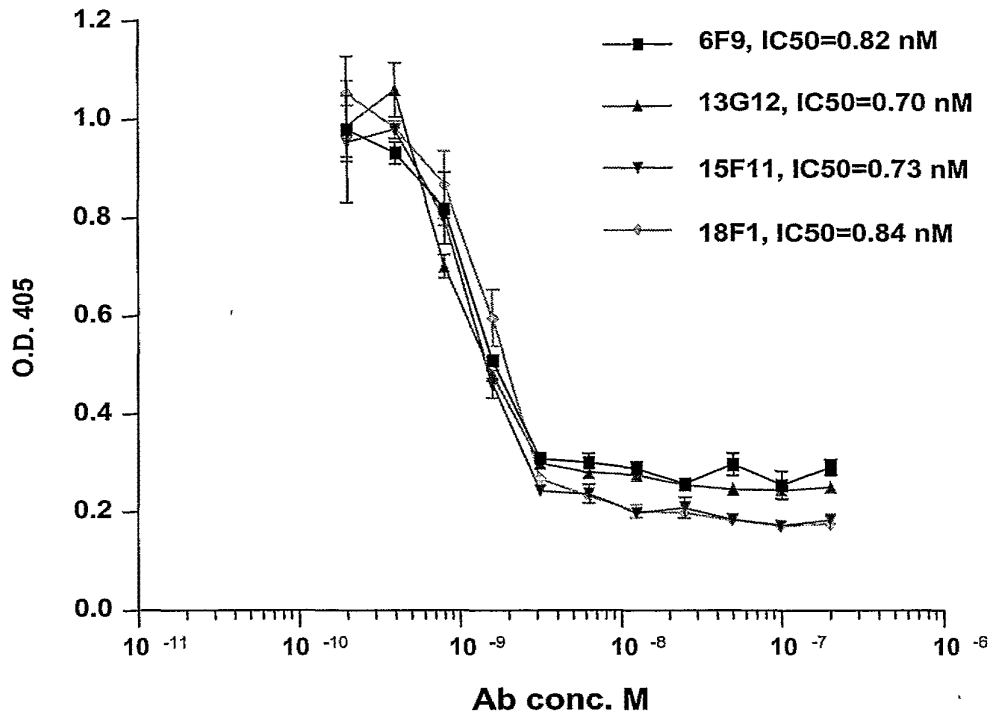


Figure 6

Figure 6A

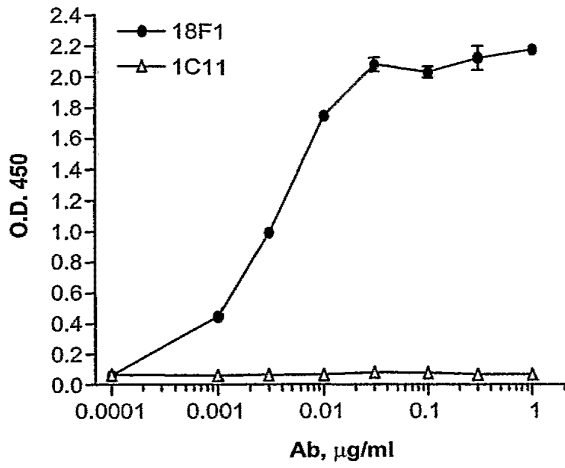


Figure 6B

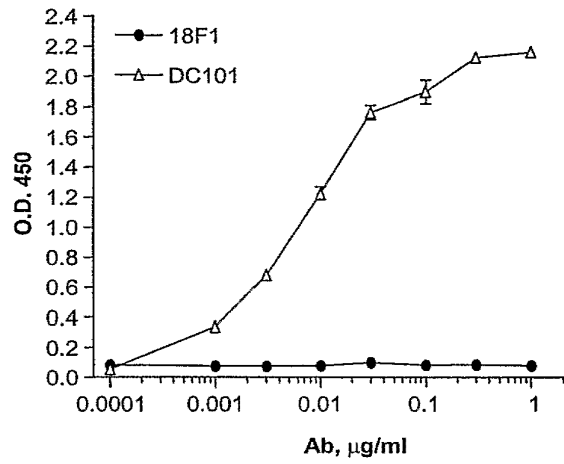
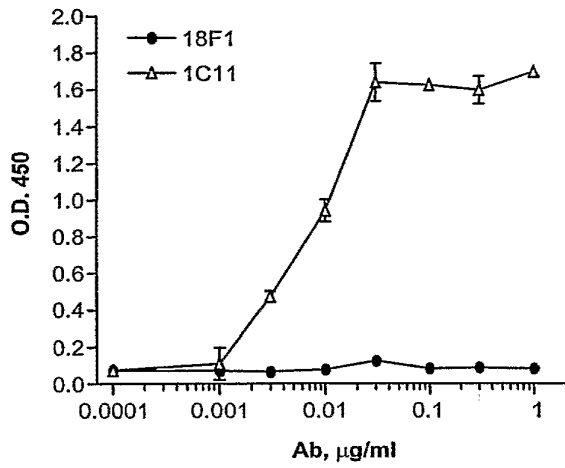
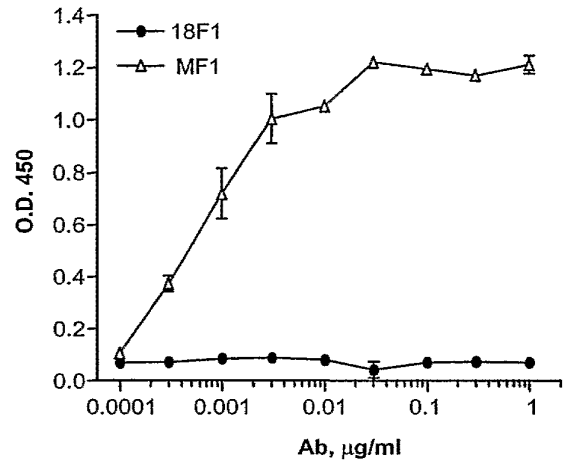


Figure 6C

Figure 6D

Figure 7

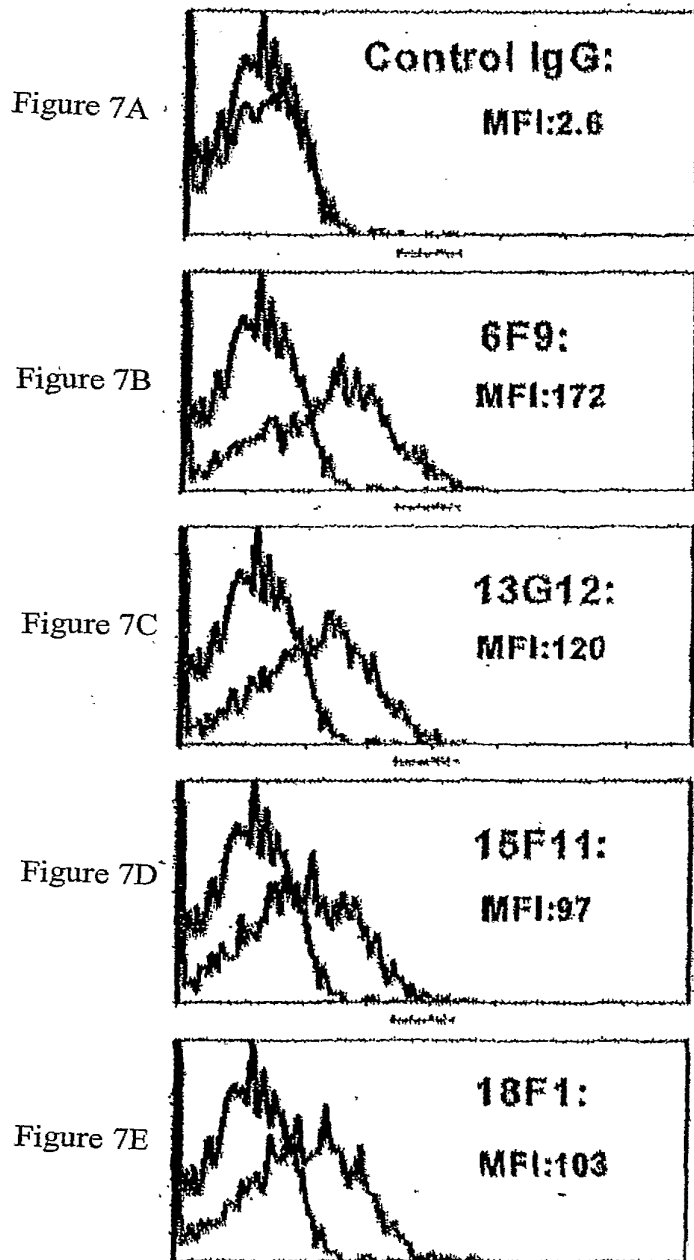
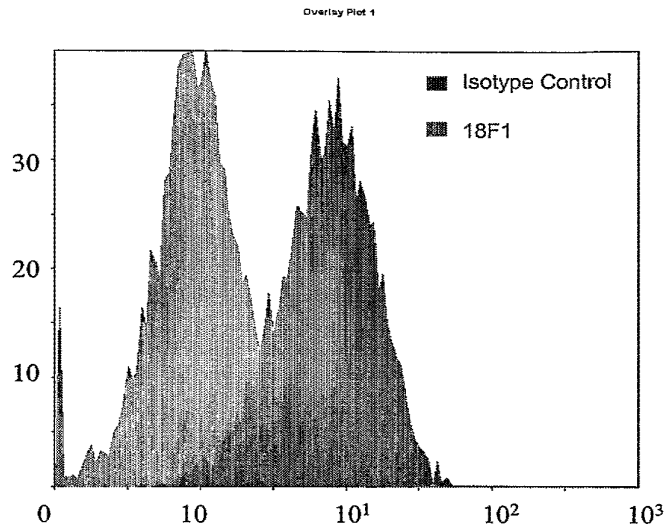


Figure 8

PAE-VEGFR-1 Cells

Figure 8A



DU4475 Tumor Cells

Figure 8B

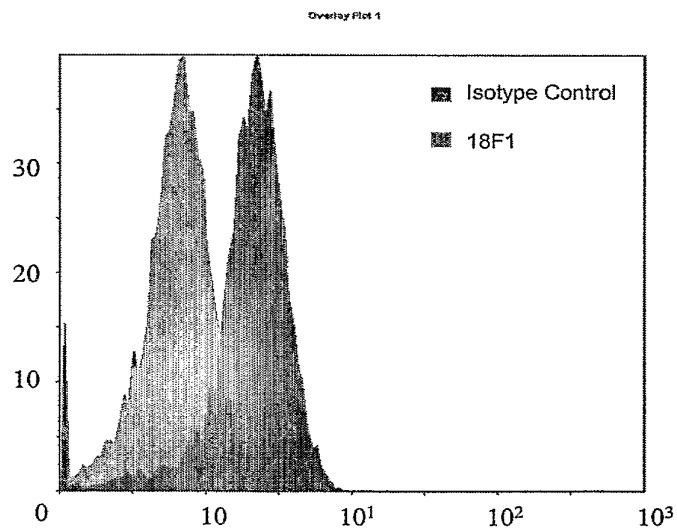


Figure 9

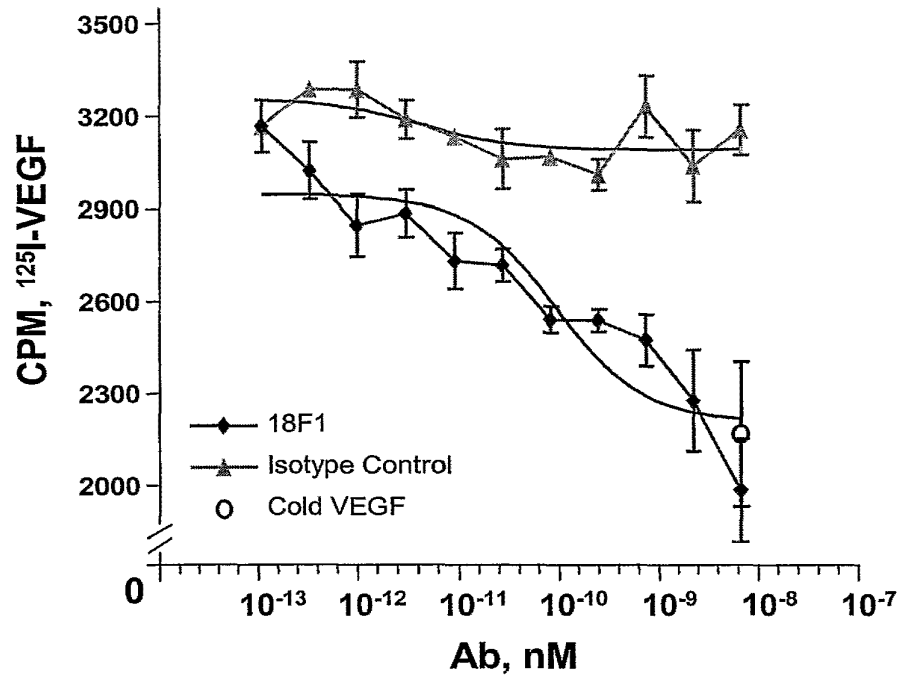


Figure 10

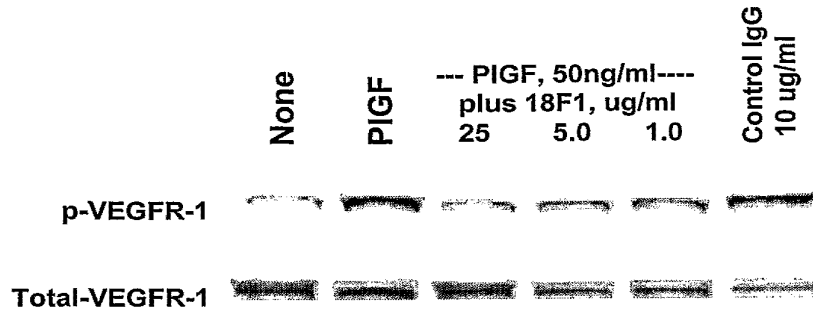


Figure 11

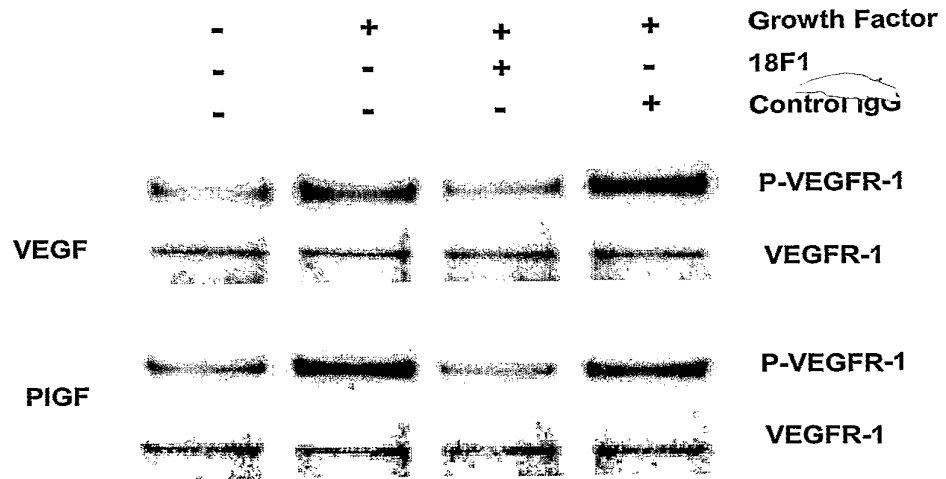


Figure 12

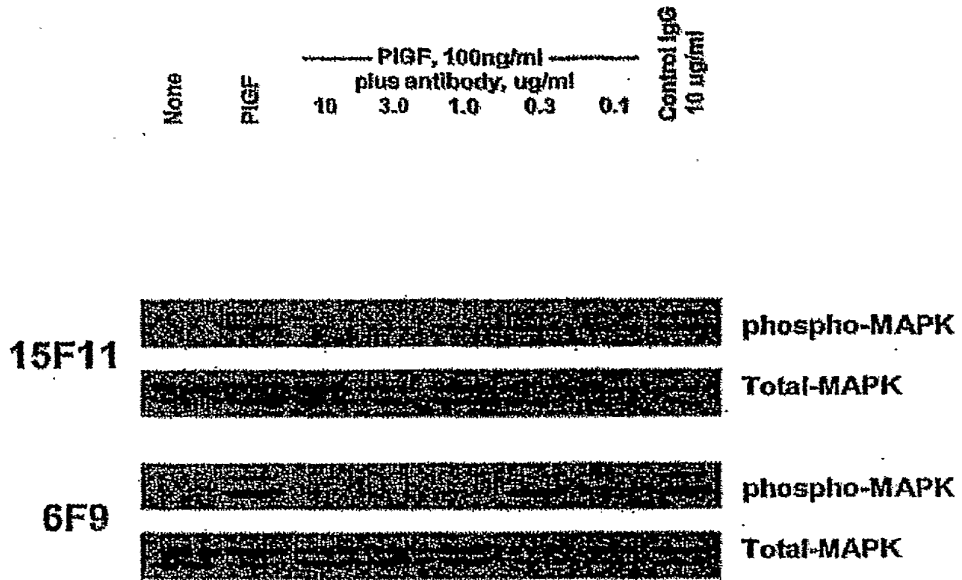


Figure 13

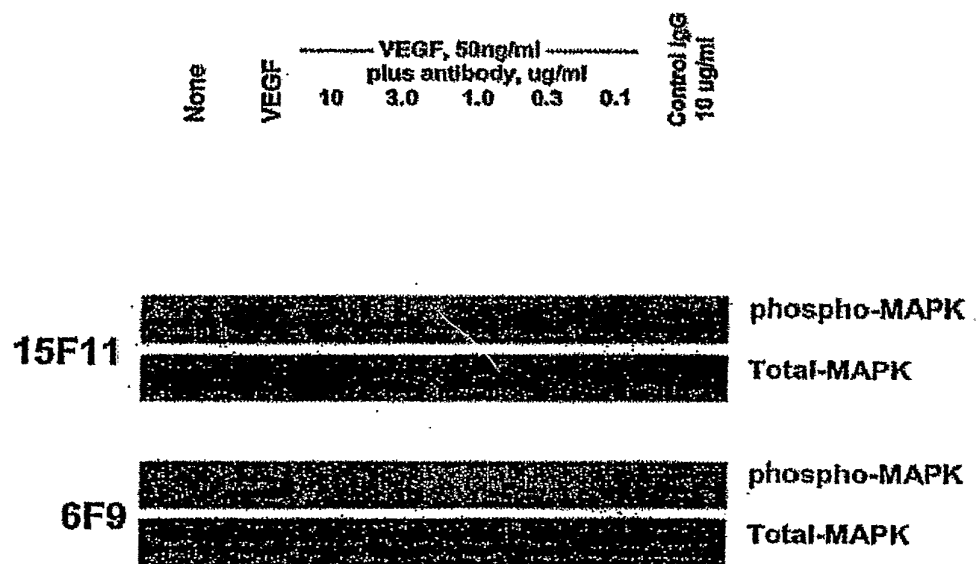


Figure 14

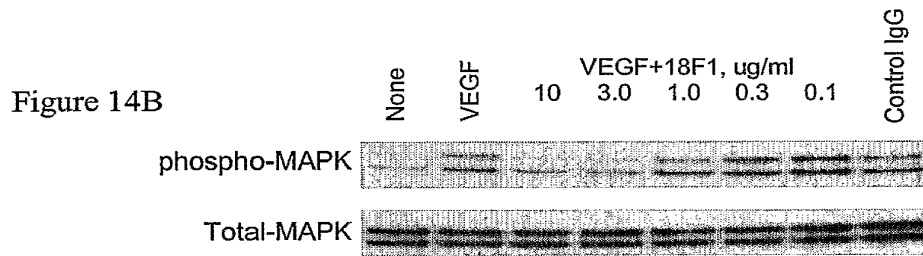
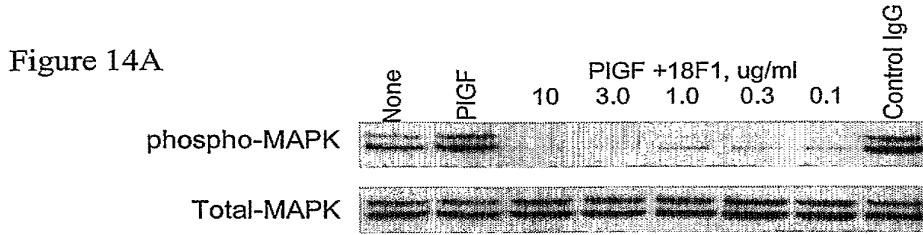


Figure 15

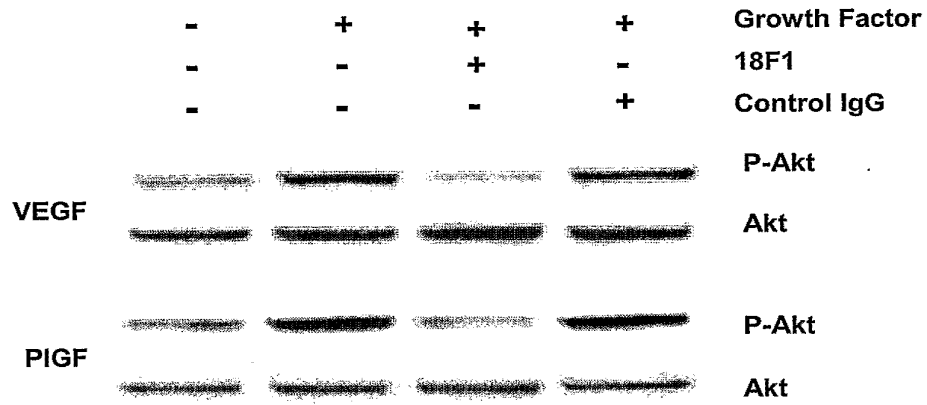


Figure 16

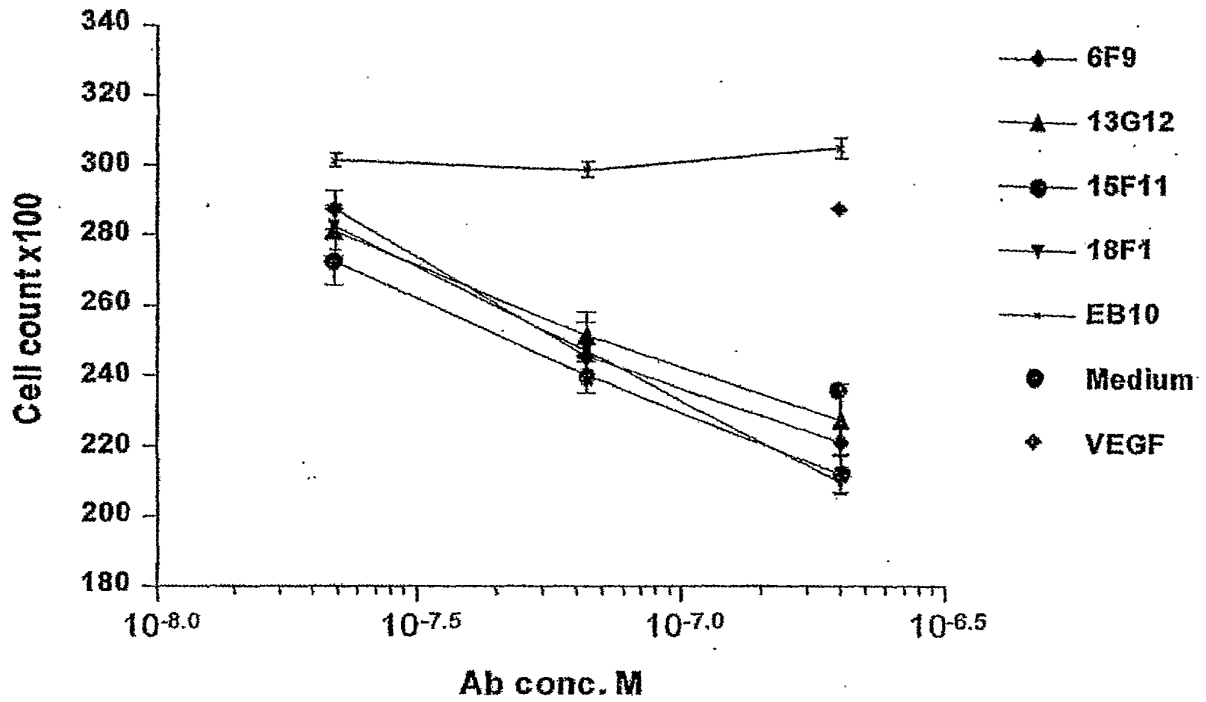


Figure 17

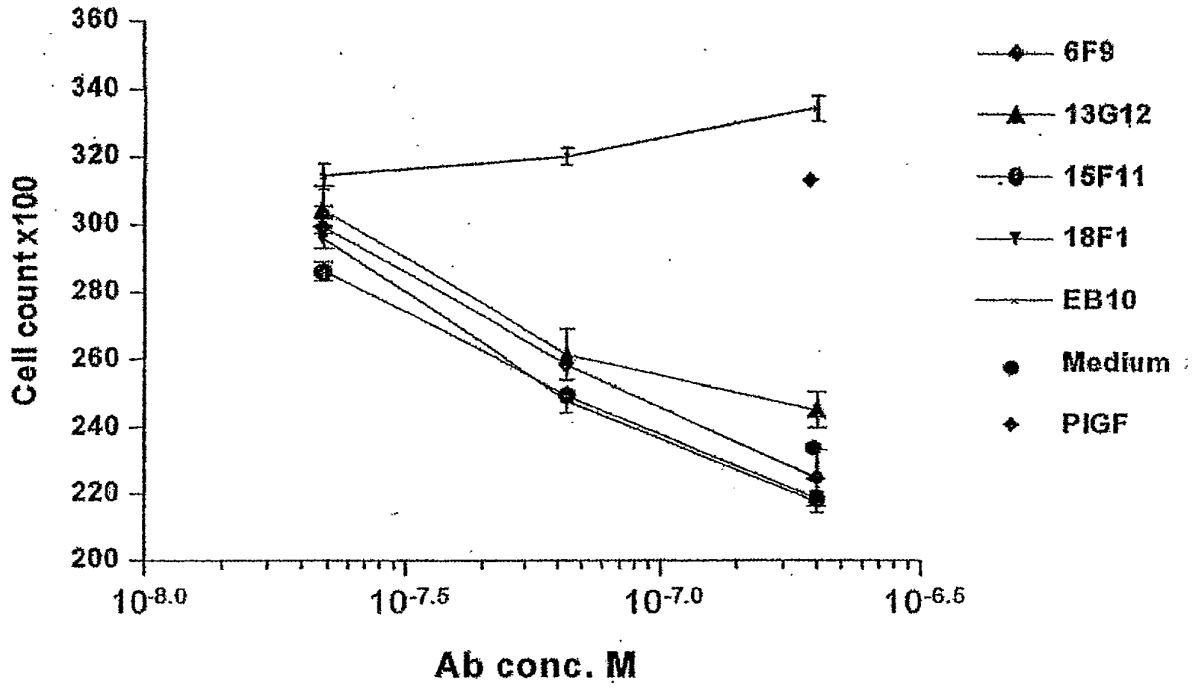


Figure 18

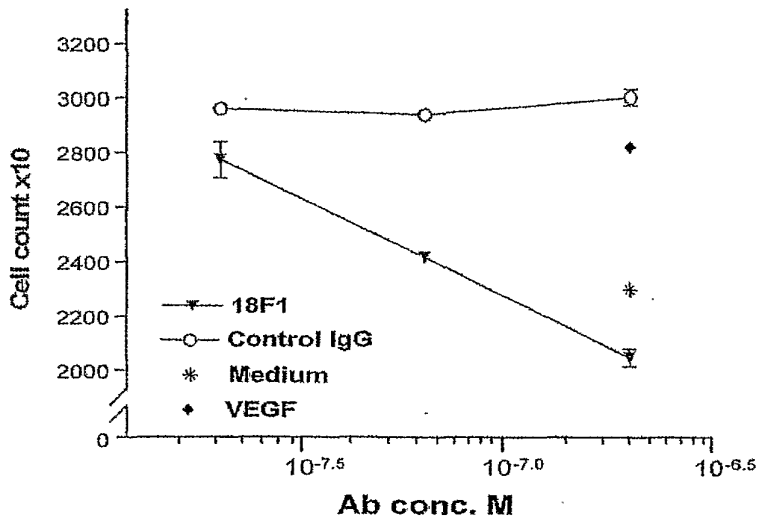
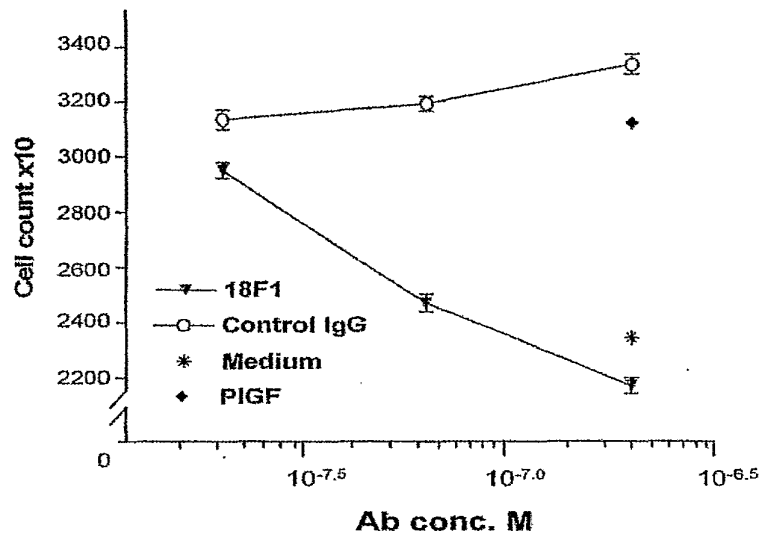


Figure 19A

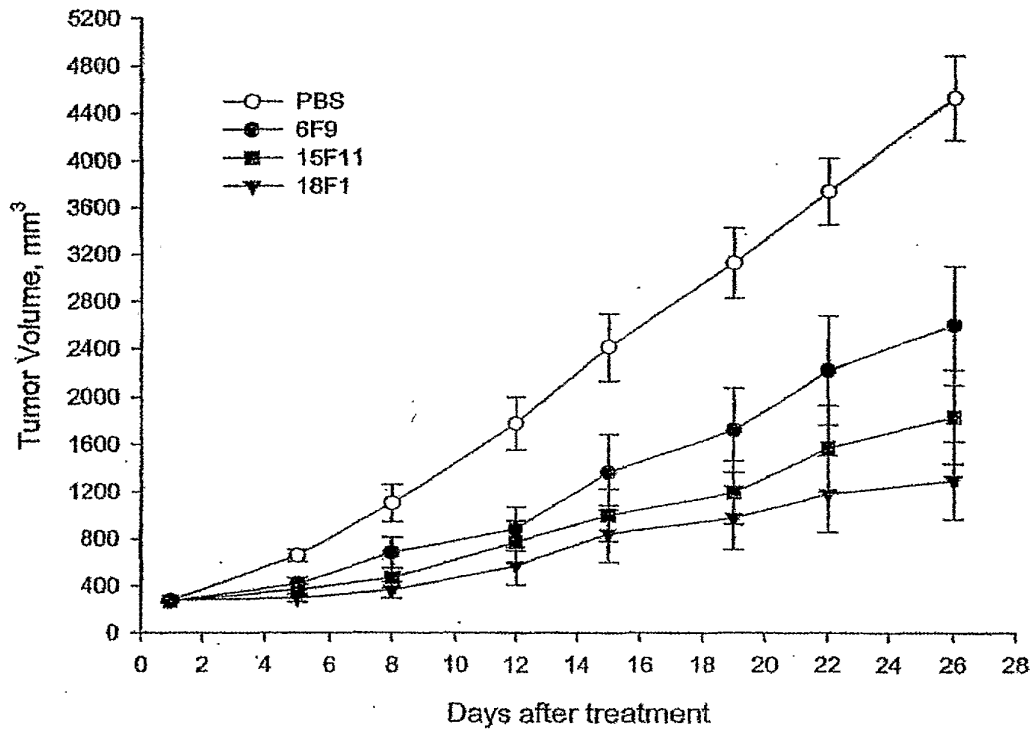


Figure 19B

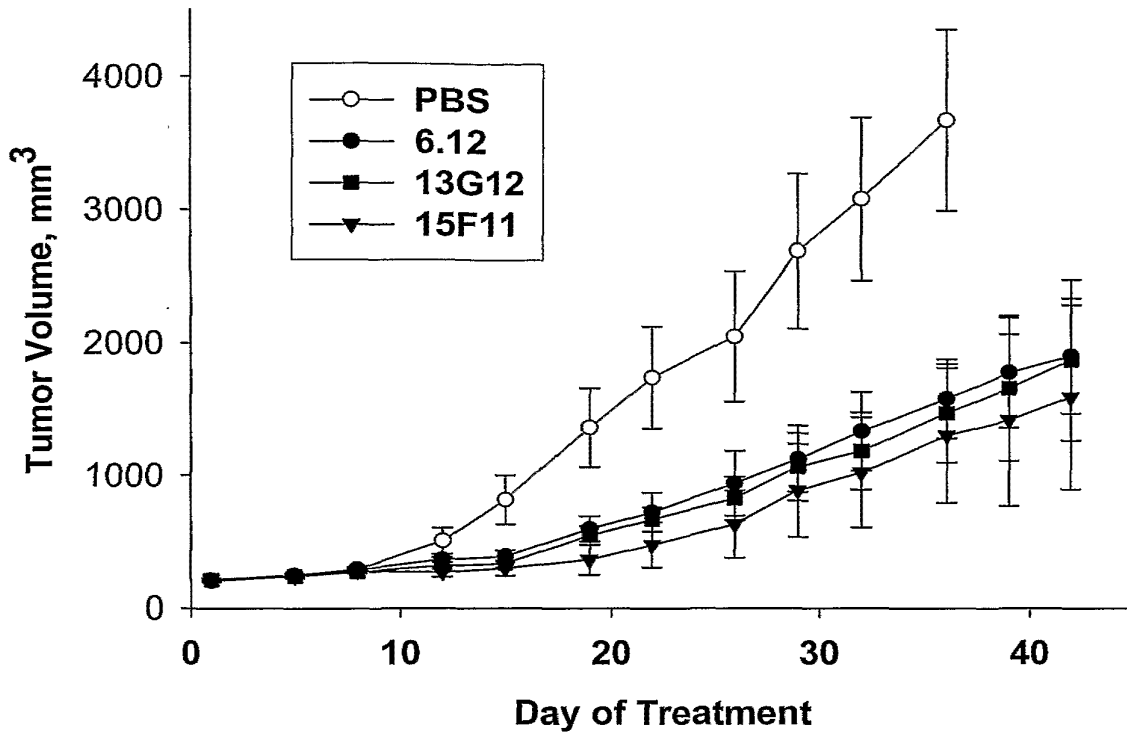


Figure 20.

Figure 20A

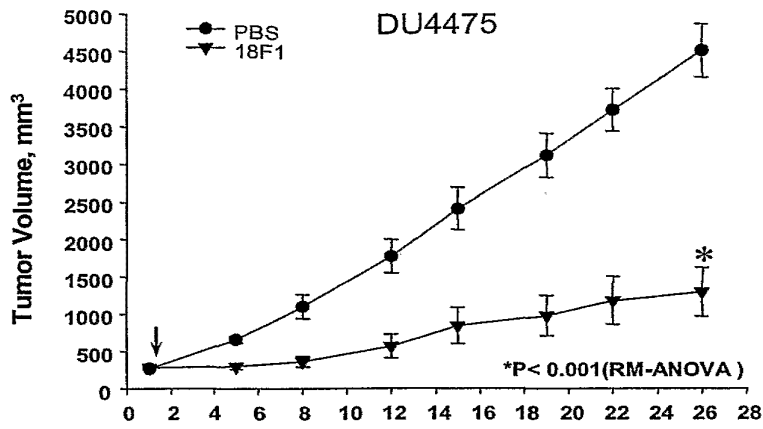


Figure 20B

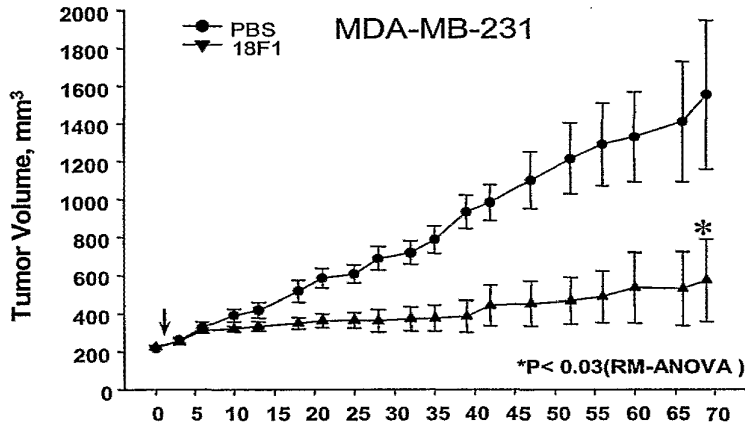


Figure 20C

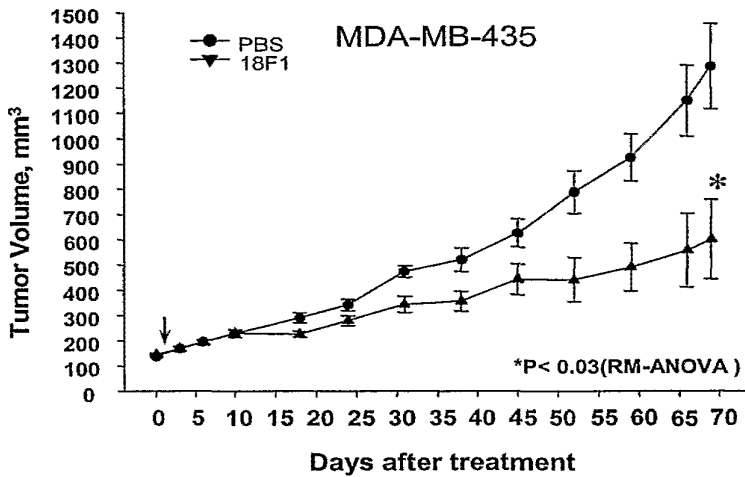


Figure 21

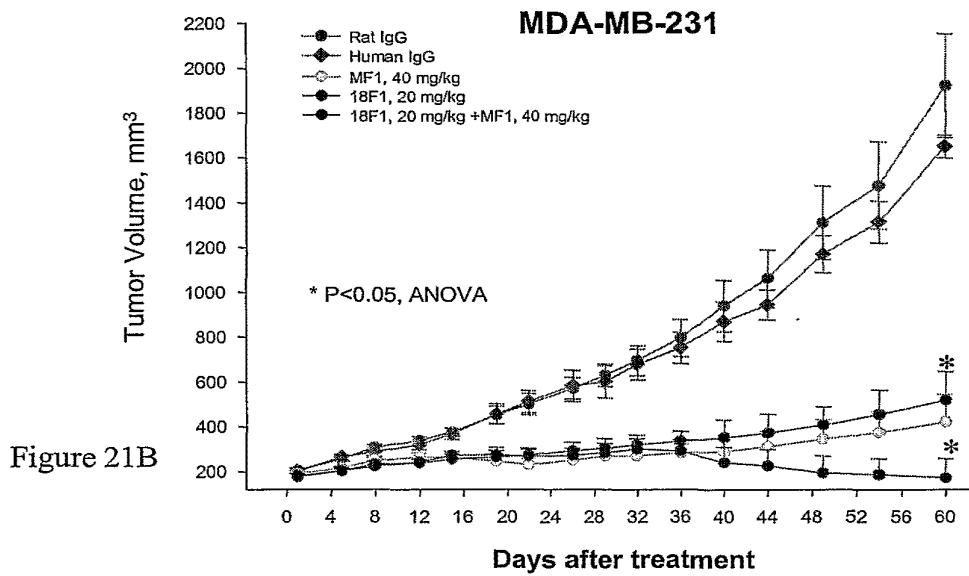
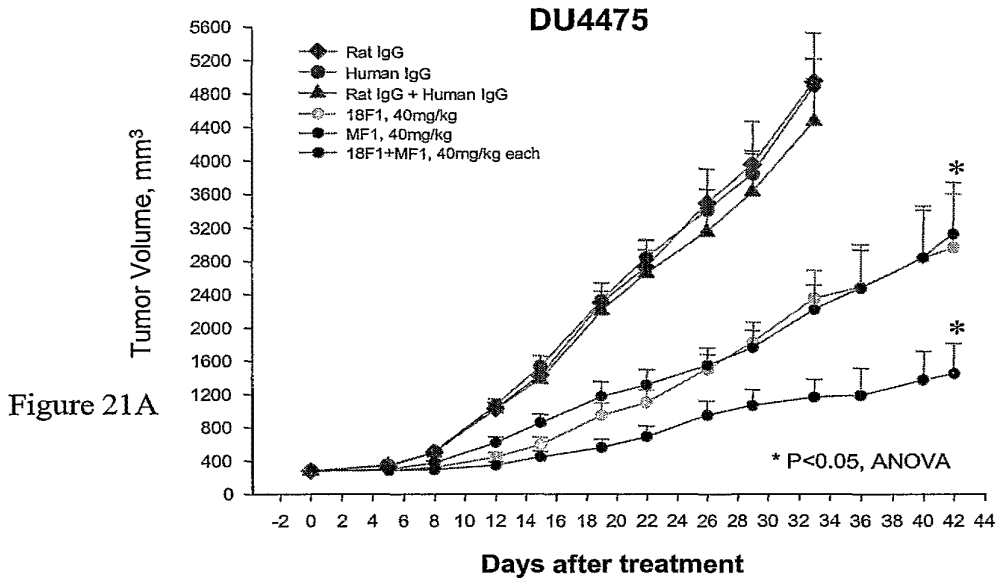


Figure 22

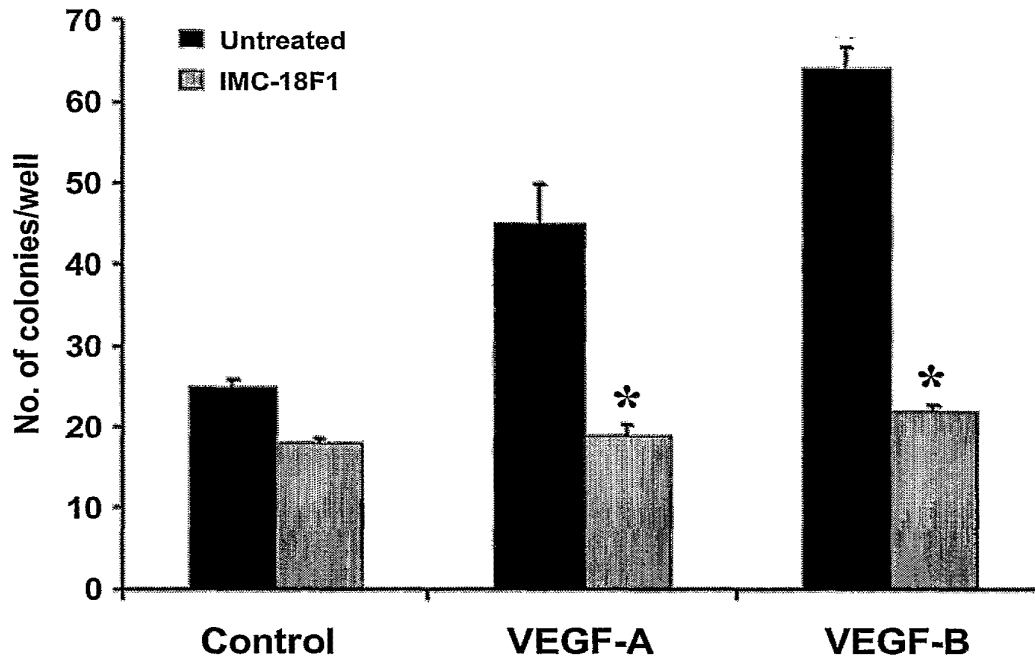


Figure 22: Inhibition of Tumor Cell Colony Formation. HT29 tumor cells were seeded in medium containing soft agar with or without ^{18}F in the presence of VEGF-A or VEGF-B and incubated for 14 days. Colonies were counted under microscope. Treatment with ^{18}F decreased colony formation induced by the VEGF ligands ($*P < 0.03$). Bars indicate SEM. Data from Pavco *et al*; Clin. Cancer Res. 2000; 6:2094-103.

Figure 23

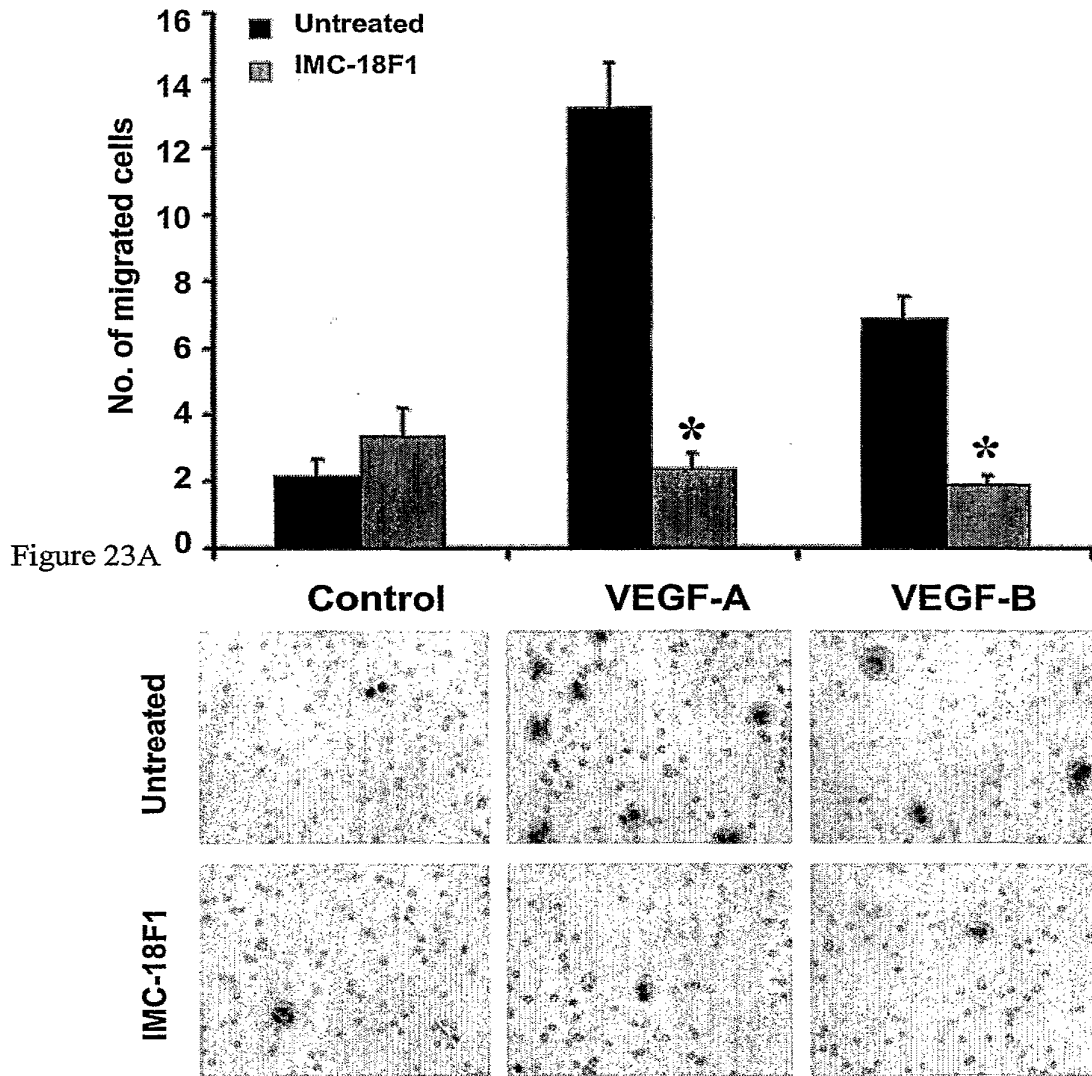


Figure 23B

Figure 23A and B: Inhibition of Tumor Cell Migration. (A) HT-29 tumor cells were treated with 18F1 in the presence of VEGF-A or VEGF-B for 48 hours. Cell migration across a layer of Matrigel is plotted as Mean \pm SEM (* $P < 0.0001$). (B) Photomicrographs of migrated cells stained with Diff-Quik. Data from Pavco *et al*; Clin. Cancer Res. 2000; 6:2094-103.

Figure 24

Figure 24A

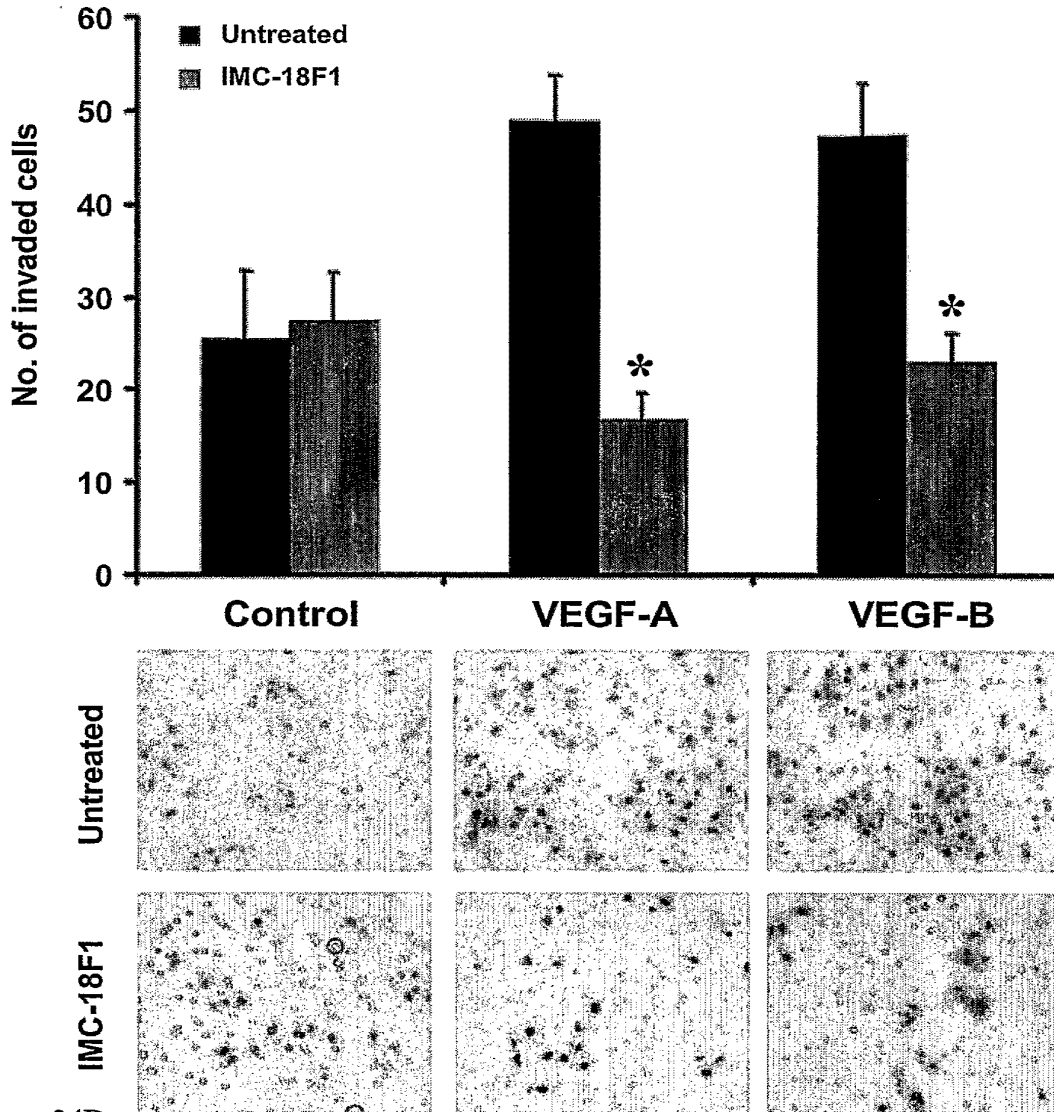


Figure 24B

Figure 24A and B: Inhibition of Tumor Cell Invasion. (A) SW480 tumor cells were treated with 18F1 in the presence of VEGF-A or VEGF-B for 48 hours. Cell migration across a layer of Matrigel is plotted as Mean \pm SEM (* $P < 0.0001$). (B) Photomicrographs of migrated cells stained with Diff-Quik. Data from Pavco *et al*; Clin. Cancer Res. 2000; 6:2094-103.

Figure 25

Figure 25A

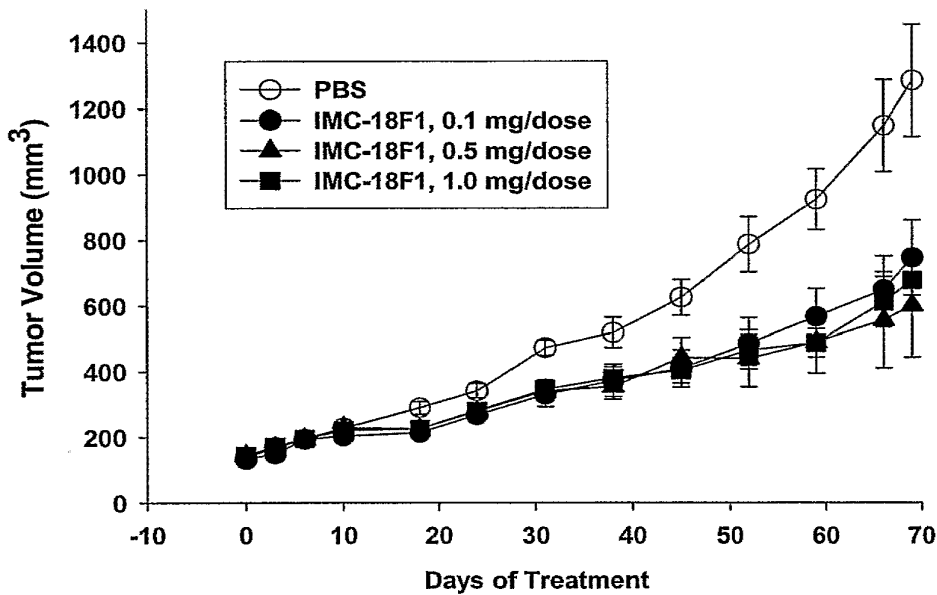
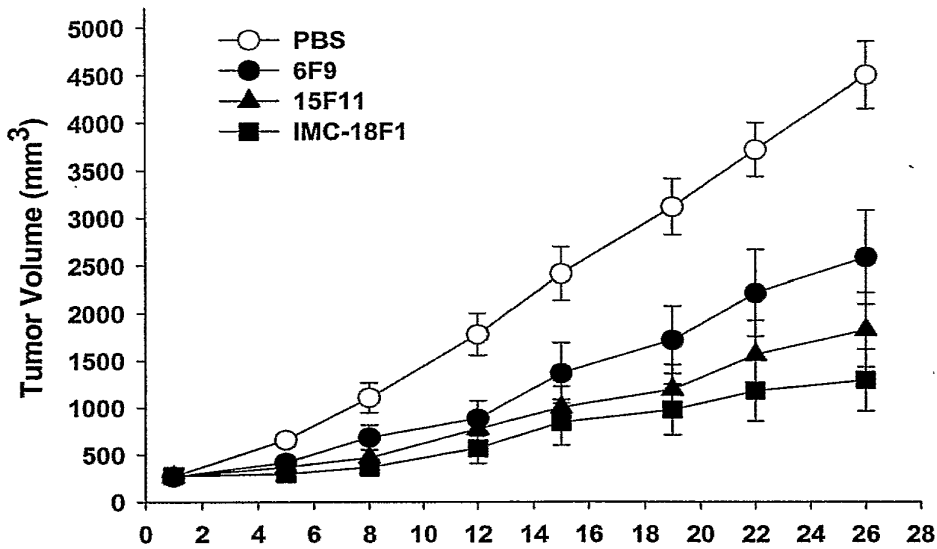


Figure 25B

Figure 25A and B: Effect of 18F1 Monotherapy on Breast Cancer Xenografts. (A) Mice with DU4475 xenografts were treated with 18F1, 6F9, or 15F11 antibodies to VEGFR-1, at 1.0 mg/dose, M-W-F. (B) Mice with MDA-MB-435 xenografts were treated with 18F1 at the indicated dosages or PBS at 0.5 mL/dose, M-W-F. Mean tumor volume \pm SEM is plotted for n=12 per group.

Figure 26

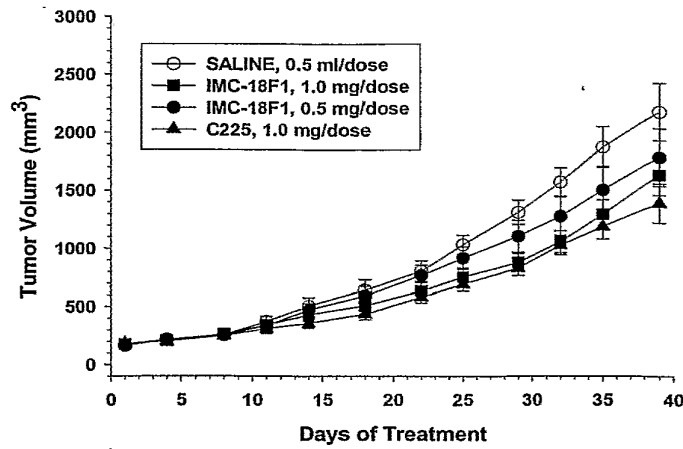


Figure 26A

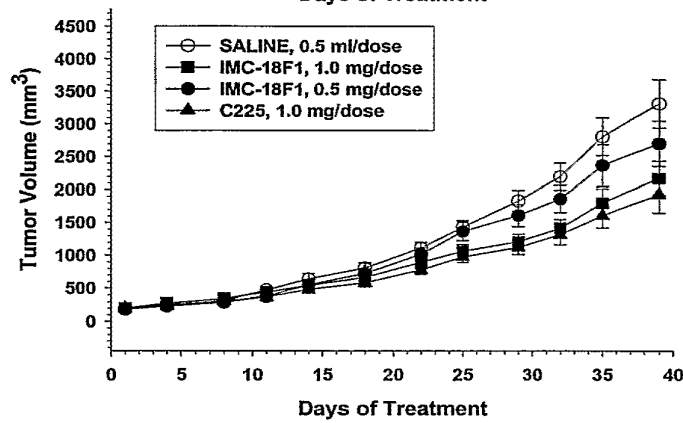


Figure 26B

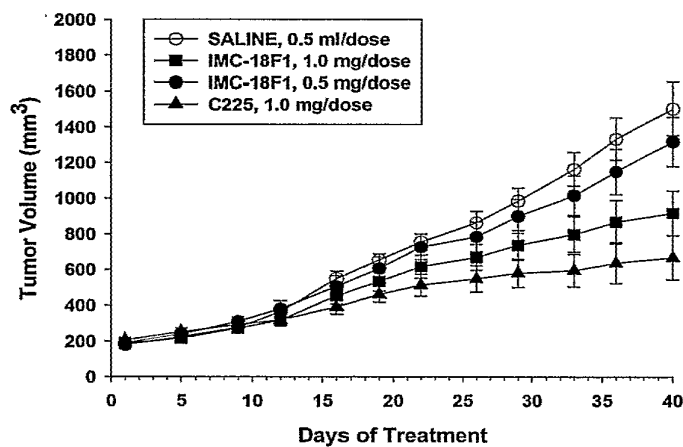


Figure 26C

Figure 26A, B, and C: Effect of 18F1 Monotherapy on Colon Cancer Xenografts. Mice with HT-29 (A), DLD-1 (B), and GEO (C) xenografts were treated with 18F1 at the indicated dosages, M-W-F. Mean tumor volume \pm SEM is plotted for n=10 per group.

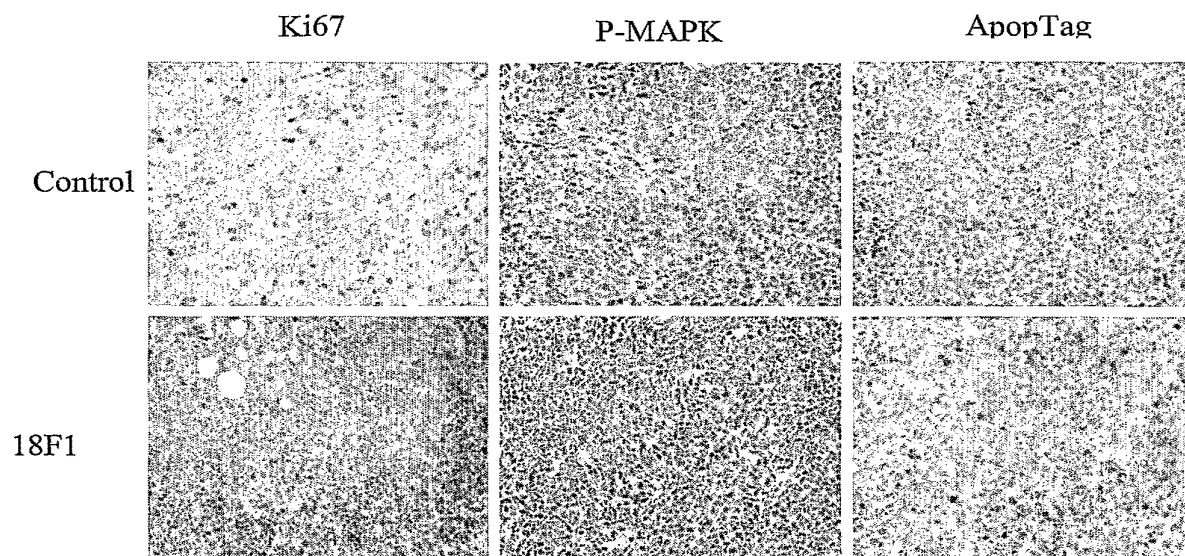
Figure 27

Figure 27: Ki-67, phosphorylated MAPK (P-MAPK) and TUNEL (ApopTag) Staining in MDA-MB-231 Xenograft Tumors. Tumor sections were stained for Ki67, P-MAPK (14 days of 18F1 treatment at 20 mg/kg, 2x/week); or ApopTag (7 days of 18F1 treatment at 0.5 mg/dose, 3x/week) Representative tumor sections are shown. Control indicates the matching dose of Human IgG.

Figure 28

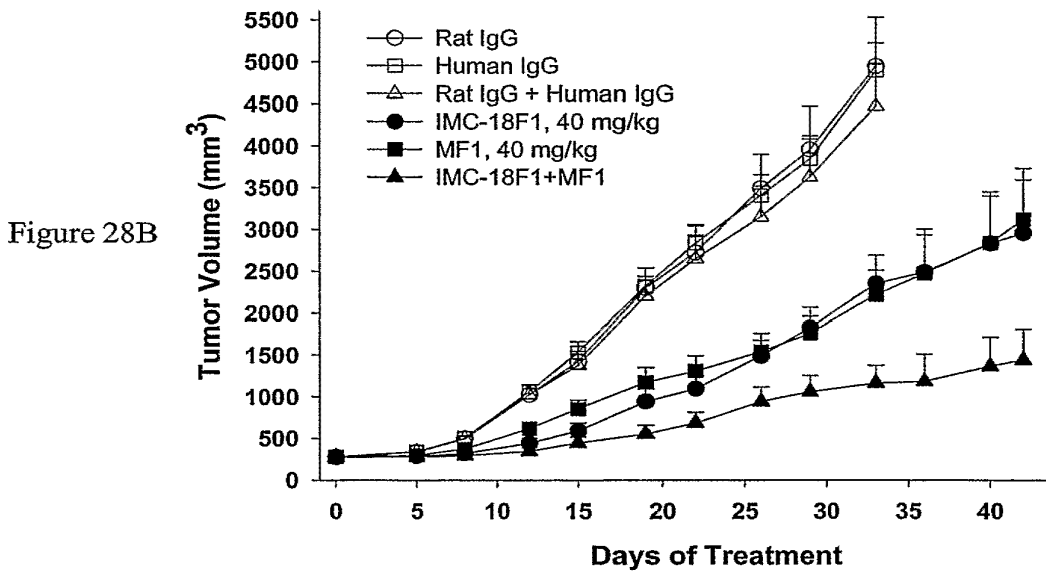
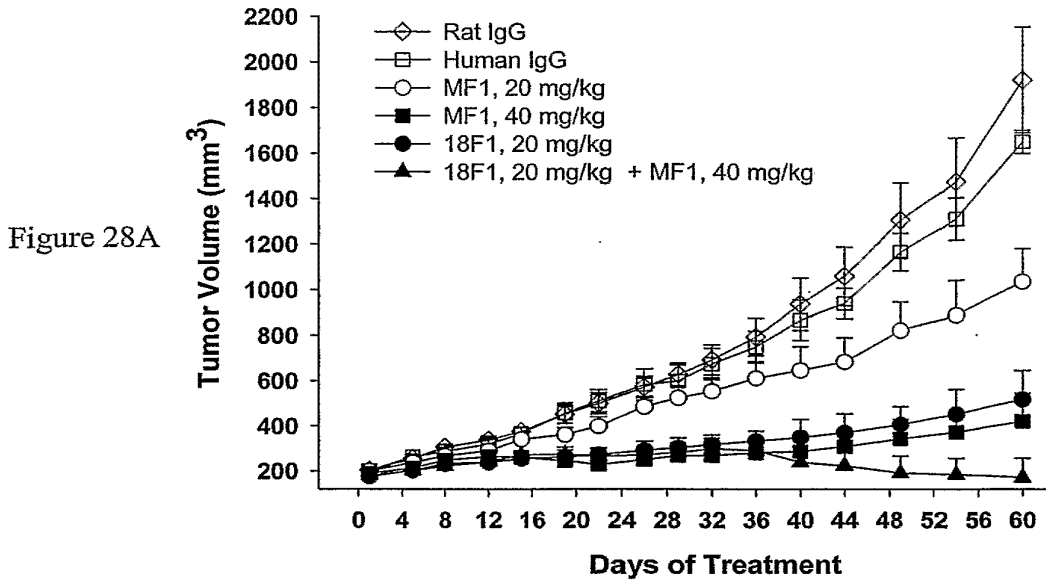


Figure 28A and B: Effect of Combined Inhibition of Mouse and Human VEGFR-1 on Xenograft Growth. Mice with MDA-MB-231 (A) or DU4475 (B) xenografts were treated with 18F1, MF1 or the combination, at the indicated dosages (2x/week for 18F1 and 3x/week for MF1). Mean tumor volume \pm SEM is plotted for n=16-18 per group.

Figure 29

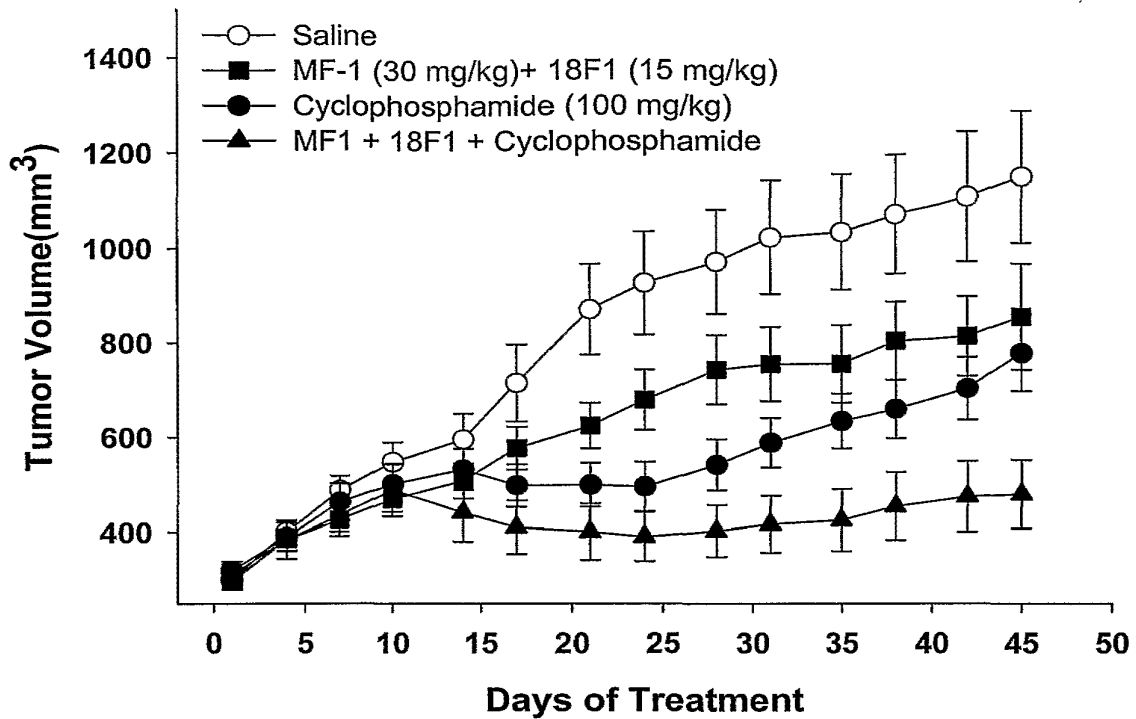


Figure 29: Effect of Cyclophosphamide Treatment in Combination with Anti-mouse and human VEGFR-1 Antibodies on the Growth of MDA-MB-231 Xenografts. Mice with MDA-MB-231 xenografts were treated with 18F1 + MF1 alone (2x/week), cyclophosphamide monotherapy (q7d), or the combination, at the indicated dosages. Mean tumor volume \pm SEM is plotted for n=12 per group.

Figure 30

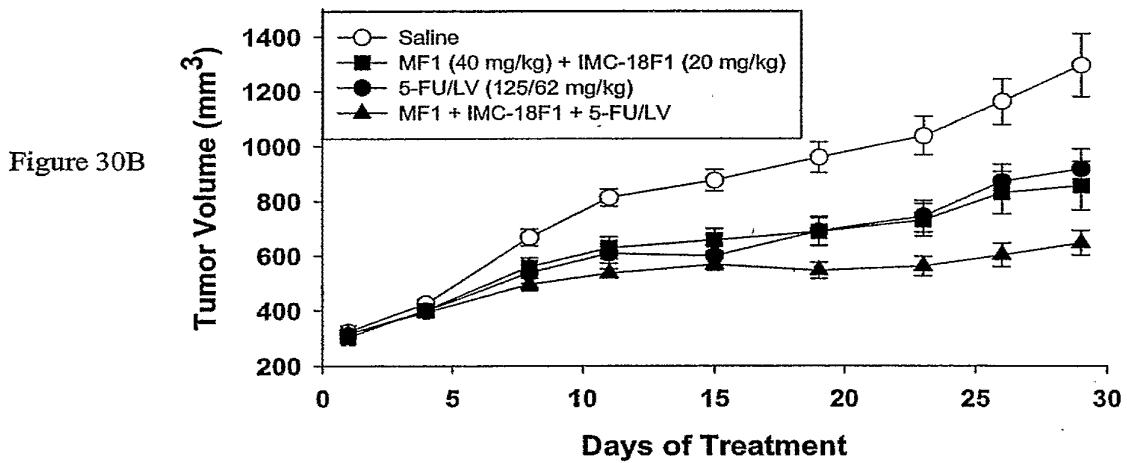
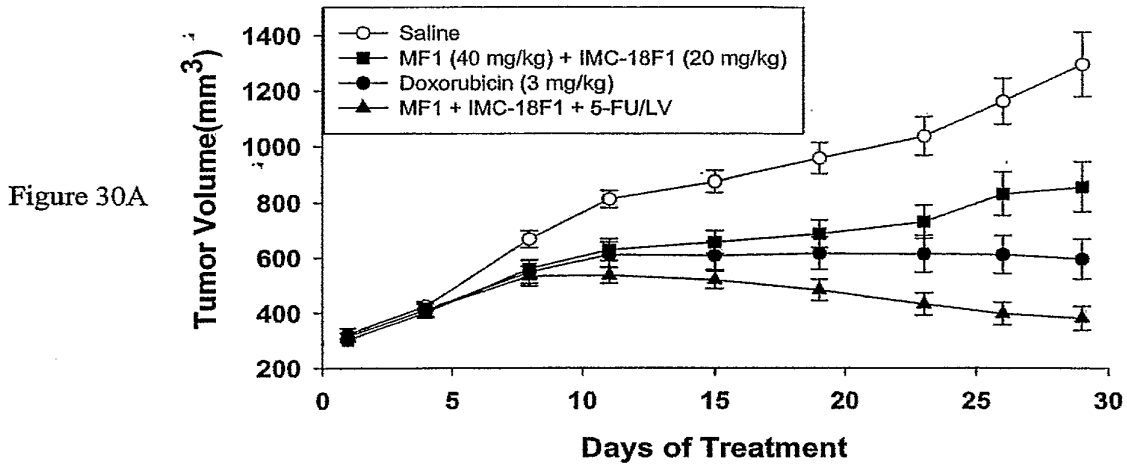


Figure 30A and B: Effect of 5-FU/LV or Doxorubicin Treatment in Combination with Anti-mouse and human VEGFR-1 Antibodies on the Growth of MDA-MB-231 Xenografts. Mice with MDA-MB-231 xenografts were treated with 18F1 + MF1 alone (3x/week), 5-FU/LV monotherapy (q7d) (A), doxorubicin (2x/week) (B) or a combination of antibody plus chemotherapy, at the indicated dosages. Mean tumor volume \pm SEM is plotted for n=12 per group.