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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	03/25/2014	8679487	3005-US-CNT3	8151

22932 7590 03/05/2014

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

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 336 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):

RICHARD J. ARMITAGE, BAINBRIDGE ISLAND, WA;
JOSE CARLOS ESCOBAR, SAMMAMISH, WA;
ARVIA E. MORRIS, SEATTLE, WA;

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/829,231	07/01/2010	1647	2000	3005-US-CNT3	35	1

CONFIRMATION NO. 8151

CORRECTED FILING RECEIPT

22932
IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

OC000000066535822

Date Mailed: 02/10/2014

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

Inventor(s)

RICHARD J. ARMITAGE, BAINBRIDGE ISLAND, WA;
JOSE CARLOS ESCOBAR, SAMMAMISH, WA;
ARVIA E. MORRIS, SEATTLE, WA;

Applicant(s)

RICHARD J. ARMITAGE, BAINBRIDGE ISLAND, WA;
JOSE CARLOS ESCOBAR, SAMMAMISH, WA;
ARVIA E. MORRIS, SEATTLE, WA;

Assignment For Published Patent Application

IMMUNEX CORPORATION

Power of Attorney: The patent practitioners associated with Customer Number 22932

Domestic Priority data as claimed by applicant

This application is a CON of 12/291,702 11/13/2008 ABN
which is a CON of 11/588,696 10/27/2006 PAT 7465450
which is a DIV of 10/324,493 12/19/2002 PAT 7186809
which is a CON of 09/847,816 05/01/2001 ABN

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 07/12/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/829,231**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES

Preliminary Class

424

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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

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CONFIRMATION NO. 8151

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22932
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LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

Date Mailed: 02/04/2014

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JOSE CARLOS ESCOBAR, SAMMAMISH, WA;
ARVIA E. MORRIS, SEATTLE, WA;

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If Required, Foreign Filing License Granted: 07/12/2010

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Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES

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NOT GRANTED

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Electronically Filed January 21, 2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Richard J. Armitage *et al.*	Confirmation No.:	8151
Serial No.:	12/829,231	Group Art Unit No.:	1647
Filed:	July 1, 2010	Examiner:	HAMUD, FOZIA M.
Title:	ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES		
Docket No.:	3005-US-CNT3		

Date of "Notice of Allowance and Base Issue Fee Due" was mailed: **November 5, 2013**

AMENDMENT UNDER 37 CFR 1.312

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

Examiner:

In response to the Notice of Allowance mailed November 5, 2013, please consider the following remarks. Also submitted herewith is a supplemental Application Data Sheet to update the inventorship.

A Listing of the Claims begins on page 2 of this paper.
Remarks begin on page 5 of this paper.

The Director is hereby authorized to charge the fees due under 37 CFR 1.17(i) and any other fees that may be required by the accompanying papers and requests, or credit any overpayment, to Deposit Account No. 09-0089.

CERTIFICATE OF EFS-WEB TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted electronically through EFS-WEB to the Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450, on the date appearing below.

January 21, 2014	/Jae Cho/
Date	Signature

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

Listing of Claims

What is claimed is:

1. (Previously Presented) An isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12.

2. (Previously Presented) The isolated human antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. (Previously Presented) The isolated human antibody of Claim 1, wherein when said isolated human antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human IL-13 interleukin-13 (IL-13) to human IL-4 receptor.

6. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^8.

9. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^9.

10. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^{10}.

11. (Canceled)

12. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a full-length antibody.

13. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fragment of an antibody.

15. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fusion protein.

16. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a single chain antibody (scFv).

17. – 33. (Canceled)

34. (Previously Presented) A composition comprising said isolated human antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. (Previously Presented) A kit comprising said isolated human antibody of Claim 1.

REMARKS

Applicants gratefully acknowledge the Examiner's statement that the claims as pending after entry of the Examiner's Amendment attached to the Notice of Allowance mailed November 5, 2013, are in condition for allowance.

No further amendments to the claims are submitted herewith, therefore no further search or examination of them is required.

However, entry of the Examiner's Amendment, and in particular the cancellation of certain of the claims, necessitates amendment of the inventorship of the claimed invention pursuant to 37 CFR 1.48(b). Specifically, the invention of John D. PLUENNEKE is no longer being claimed and so his name should be removed from the list of co-inventors. Each of the other named co-inventors shall remain a co-inventor. No new co-inventors shall be added.

This change in inventorship is necessitated solely by the cancelation of claims in the Examiner's Amendment and not by an error in inventorship in the Application as filed or previously pending.

Please note that Applicants are also submitting a petition under 37 CFR § 1.324(a) to correct the inventorship of two previously-issued patents in this family, US 7,186,809 and US 7,465,450.

CONCLUSION

The pending claims have been found to be in condition for allowance. The Examiner is invited to call the undersigned attorney at (206) 265-8779 upon receipt and review of this Amendment to discuss any questions or concerns about the present response.

Please send all future correspondence to:

CUSTOMER NO: 22932
Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, WA 98119-3105

Respectfully submitted,

/Nathan A. Machin/

Nathan A. Machin
Attorney/Agent for Applicant(s)
Registration No.: 47,763
Phone: (206) 265-8779
Date: January 21, 2014

PTO/SB/14 (11-06)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3005-US-CNT3
	Application Number	12/829,231
Title of Invention	ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fail under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Richard	J.	ARMITAGE	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Bainbridge Island	State/Province	WA	Country of Residence	US

Citizenship under 37 CFR 1.41(b)	US

Mailing Address of Applicant:

Address 1	5840 Packard Lane		
Address 2			
City	Bainbridge Island	State/Province	WA
Postal Code	98110	Country	US

Applicant 2

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jose	Carlos	ESCOBAR	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Sammamish	State/Province	WA	Country of Residence	US

Citizenship under 37 CFR 1.41(b)	US

Mailing Address of Applicant:

Address 1	1707 East Beaverlake Drive SE		
Address 2			
City	Sammamish	State/Province	WA
Postal Code	98075	Country	US

Applicant 3

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Arvia	E.	MORRIS	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Seattle	State/Province	WA	Country of Residence	US

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3005-US-CNT3
	Application Number	
Title of Invention	ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES	

Citizenship under 37 CFR 1.41(b)	US				
Mailing Address of Applicant:					
Address 1	4535 Thackeray Place NE				
Address 2					
City	Seattle	**State/Province**	WA		
Postal Code	98105	**Country**	US		

Applicant 4

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~John~~	~~D.~~	~~PLUENNEKE~~	

Residence Information (Select One) (•) ~~US Residency~~ ( ) Non US Residency ( ) Active US Military Service

City	~~Parkville~~	**State/Province**	~~MO~~	**Country of Residence**	~~US~~
Citizenship under 37 CFR 1.41(b)	~~US~~				
Mailing Address of Applicant:					
Address 1	~~5816 Hickory Place~~				
Address 2					
City	~~Parkville~~	**State/Province**	~~MO~~		
Postal Code	~~64152~~	**Country**	~~US~~		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	22932		
Email Address	AWA-Patent@amgen.com	Add Email	Remove Email

Application Information:

Title of the Invention	ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES		
Attorney Docket Number	3005-US-CNT3	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	6	**Suggested Figure for Publication (if any)**	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3005-US-CNT3
	Application Number	
Title of Invention	ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22932		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12829231	Continuation of	12291702	2008-11-13

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12291702	Continuation of	11588696	2006-10-27	7465450	2008-12-16

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
11588696	Division of	10324493	2002-12-19	7186809	2007-03-06

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10324493	Continuation of	09847816	2001-05-01

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3005-US-CNT3
	Application Number	
Title of Invention	ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES	

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country[1]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ○ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1

If the Assignee is an Organization check here. ☒

Organization Name	Immunex Corporation		
Mailing Address Information:			
Address 1	One Amgen Center Drive		
Address 2			
City	Thousand Oaks	**State/Province**	CA
Country[1]	US	Postal Code	91320
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature				Date (YYYY-MM-DD)	2014-01-21
First Name	Nathan	Last Name	Machin	Registration Number	47763

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

22932 7590 12/24/2013

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	

NOTIFICATION DATE	DELIVERY MODE
12/24/2013	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):

AWA-Patent@amgen.com
pair_amgen@firsttofile.com

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No. : 12829231
Applicant : Armitage
Filing Date : 07/01/2010
Date Mailed : 12/24/2013

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice, or the time remaining from the Notice of Allowance and Fee(s) Due, whichever is longer, within which to respond.

The application is not in compliance with 37 CFR 1.78, as indicated in the attachment. The consequences of failure to respond within the above-identified time period are set forth in the attachment.

Even if the Office has recognized a benefit claim and has entered it into the Office's database and included it on applicant's filing receipt, the benefit claim is not a proper benefit claim unless the reference in compliance with 37 CFR 1.78 is included, depending upon the application's filing date and as indicated in the attachment, in an application data sheet or in the first sentence(s) of the specification and all other requirements are met.

This period for reply is NOT extendable under 37 CFR 1.136(a).

See attachment.

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Vermel Wilson/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 12829231

APPLICATION FILED PRIOR TO SEPTEMBER 16, 2012, NOT IN COMPLIANCE WITH 37 CFR 1.78

☐ The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification does not indicate the relationship (continuation, division, continuation-in-part) to the prior U.S. nonprovisional application or international application designating the U.S. See document coded dated , listing application number(s) .

☒ The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification following the title does not provide the U.S. nonprovisional application number (series code and serial number) or, with respect to an international PCT application designating the U.S., it provides the international application number or international filing date but not both. See document coded SPEC dated 05/03/2011, in which the following is missing: 09/579,808 is not listed..

☐ The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification following the title shows an incorrect, incomplete, or illegible U.S. nonprovisional application number, international PCT application number, or international PCT filing date. See document coded dated , in which the following error was made: .

☐ The 37 CFR 1.78(a)(2) reference to the prior U.S. nonprovisional application or international application designating the U.S. is not present on an application data sheet or in the first sentence(s) of the specification following the title, thus removing the validating link under 35 U.S.C. 119(a)-(d) to a prior foreign application or under 35 U.S.C. 119(e) to a prior U.S. provisional application.

☐ The 37 CFR 1.78(a)(2) reference to the prior U.S. nonprovisional application or international application designating the U.S. is not present on an application data sheet or in the first sentence(s) of the specification following the title.

☐ The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application is not present on an application data sheet or in first sentence(s) of the specification following the title.

☐ The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application on an application data sheet or in first sentence(s) of the specification following the title does not provide the provisional application number (series code and serial number). See document coded dated , in which the following is missing: .

☐ The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application on an application data sheet or in first sentence(s) of the specification following the title shows an incorrect, incomplete, or illegible U.S. provisional application number. See document coded dated , in which the following error was made: .

☐ Other: .

HOW TO RESPOND

A proper response to this notice would include any one of: (1) a supplemental Application Data Sheet (ADS) pursuant to 37 CFR 1.76(c) which provides benefit information that complies with 37 CFR 1.78(a)(2) or 37 CFR 1.78(a)(5); (2) an amendment to the first sentence(s) of the specification which provides benefit information that complies with 37 CFR 1.78(a)(2) or 37 CFR 1.78(a)(5); or (3) a petition filed pursuant to the provisions of 37 CFR 1.78(a)(3) or 37 CFR 1.78(a)(6) if the benefit information from the document identified above by code and date does not accurately reflect the benefits under 35 U.S.C. 119(e), 120, 121 or 365(c) as claimed by applicant (a grantable petition would include either a supplemental ADS or an amendment to the first sentence(s) of the specification as required by 37 CFR 1.78(a)(3)(i) or 37 CFR 1.78(a)(6)(i)). Such amendments to the specification or supplemental ADS submission may be filed after payment of the issue fee if limited to informalities noted herein. See Waiver of 37 CFR 1.312 for Document Required by Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004).

WARNING: If Applicant fails to timely submit a proper response, the benefit information will be deleted and the patent will be printed without the benefit information present.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

22932 7590 11/05/2013

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER
HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/05/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

TITLE OF INVENTION: ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	02/05/2014

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)

22932 7590 11/05/2013
IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

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

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

TITLE OF INVENTION: ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	02/05/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
HAMUD, FOZIA M	1647	424-130100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

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

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

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

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

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

22932 7590 11/05/2013

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/05/2013

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 400 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 400 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.

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.

Notices of Allowance and Fee(s) Due mailed between October 1, 2013 and December 31, 2013

(Addendum to PTOL-85)

If the "Notice of Allowance and Fee(s) Due" has a mailing date on or after October 1, 2013 and before January 1, 2014, the following information is applicable to this application.

If the issue fee is being timely paid on or after January 1, 2014, the amount due is the issue fee and publication fee in effect January 1, 2014. On January 1, 2014, the issue fees set forth in 37 CFR 1.18 decrease significantly and the publication fee set forth in 37 CFR 1.18(d)(1) decreases to $0.

If an issue fee or publication fee has been previously paid in this application, applicant is not entitled to a refund of the difference between the amount paid and the amount in effect on January 1, 2014.

Notice of Allowability	Application No. 12/829,231	Applicant(s) ARMITAGE ET AL.	
	Examiner FOZIA HAMUD	Art Unit 1647	AIA (First Inventor to File) Status No

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

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

1. ☒ This communication is responsive to *the amendment filed on 13 August 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 *1-10,12-16,34 and 35*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

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

   * Certified copies not received: _____.

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

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

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 08/13/2013
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

DETAILED ACTION

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

1b. Receipt of the response and amendment filed on 13 August 2013 is acknowledged.

Claim Status:

1c. Claims 1-10, 12-16, 20-35 are pending.

Information Disclosure Statement:

2. The information disclosure statement (IDS) submitted on 13 August 2013 has been received and complies with the provisions of 37 CFR §1.97 and §1.98. The references have been considered as to the merits.

Response to Applicant's Argument:

The following rejections are withdrawn in light of Applicants' arguments:

I. The amendment to claim1 has overcome the objection of said claim, because claim 1 ends with a period.

II. The rejections of claims 1-10 and 12-16, 34, 35 made under 35 U.S.C. 103(a) as being unpatentable over Mosley et al. (U.S. Patent 5,717,072), or Tony et al., in view of Aya Jakobovits, are withdrawn.

Applicants' argument that a set of antibodies that bind to a common target, do not all necessarily compete for binding with each other for binding to the target, is persuasive. Applicants submit that United States Patent Number 7,807,159 discloses

antibodies that bind to myostatin and demonstrates that even two antibodies raised against a homodimerized 109 amino acid polypeptide do not necessarily compete for binding to the polypeptide. Applicants' argument that it cannot be concluded that the antibodies of Mosley et al or Tony et al compete for binding with the reference antibody recited in the rejected claims, is found persuasive.

EXAMINER'S AMENDMENT:

3a. 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 *Nathan A. Machin (Applicants' Representative)* on 23 October 2013.

The application has been amended as follows:

In The Claims:

3b. Please cancel claims 20-33 without prejudice or disclaimer.

Conclusion:

4. Claims 1-10, 12-16, 34-35, (now renumbered 1-17, respectively) are allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

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

Fozia Hamud
Patent Examiner
Art Unit 1647
23 October 2013

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

VIA EFS-Web
August 13, 2013

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Richard J. Armitage *et al.*	Confirmation No.:	8151
Serial No.:	12/829,231	Group Art Unit No.:	1647
Filed:	July 1, 2010	Examiner:	HAMUD, Fozia M.
Title:	ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES (as amended)		
Docket No.:	3005-US-CNT3		

RESPONSE TO OFFICE ACTION

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

Sir:

In response to the Office Action mailed May 13, 2013, please consider the following election and remarks.

The Listing of the Claims begins on page 2.

Remarks begin on page 6.

The Director is hereby authorized to charge any additional fees which may be required by the accompanying papers, or credit any overpayment to Deposit Account No. 09-0089.

CERTIFICATE OF EFS-Web TRANSMISSION
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/	August 13, 2013
Jae Cho	Date

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

Listing of the Claims

What is claimed is:

1. (Presently Amended) An isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12.

2. (Previously Presented) The isolated human antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. (Previously Presented) The isolated human antibody of Claim 1, wherein when said isolated human antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human IL-13 interleukin-13 (IL-13) to human IL-4 receptor.

6. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^8.

9. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^9.

10. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^{10}.

11. (Cancelled)

12. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a full-length antibody.

13. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fragment of an antibody.

15. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fusion protein.

16. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a single chain antibody (scFv).

17. – 19. (Cancelled)

20. (Withdrawn) An isolated nucleic acid, wherein said isolated nucleic acid comprises a sequence encoding:

a. the light chain variable domain of said isolated antibody of Claim 1; or

b. the heavy chain variable domain of said isolated antibody of Claim 1; or

c. the light chain variable domain of said isolated antibody of Claim 1 and the heavy chain variable domain of said isolated antibody of Claim 1.

21. (Withdrawn) A vector, wherein said vector comprises said isolated nucleic acid of Claim 20.

22. (Withdrawn) The vector of Claim 21, wherein said vector is an expression vector.

23. (Withdrawn) An isolated cell, wherein said cell comprises said isolated nucleic acid of Claim 20.

24. (Withdrawn) The isolated cell of Claim 23, wherein said isolated cell expresses said isolated antibody.

25. (Withdrawn) A method of reducing IL-4 receptor-dependent signaling in a subject, comprising administering to said subject an effective amount of said isolated antibody of Claim 1.

26. (Withdrawn) The method of Claim 25, wherein said method suppresses a T_H2-type immune response.

27. (Withdrawn) The method of Claim 25, wherein said subject has, or is at risk of developing, a condition responsive to inhibition of IL-4R signaling.

28. (Withdrawn) The method of Claim 27, wherein said condition is an inflammatory condition.

29. (Withdrawn) The method of Claim 27, wherein said condition is an IgE mediated condition.

30. (Withdrawn) The method of Claim 27, wherein said condition is an allergic condition.

31. (Withdrawn) The method of Claim 27, wherein said condition is a condition in which IL-4 mediated epithelial barrier disruption plays a role.

32. (Withdrawn) The method of Claim 27, wherein said condition is asthma, COPD, pulmonary fibrosis, or septic arthritis.

33. (Withdrawn) A method of making an antibody, comprising incubating said cell of Claim 23 under conditions that allow it to express said isolated antibody.

34. (Previously Presented) A composition comprising said isolated human antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. (Previously Presented) A kit comprising said isolated human antibody of Claim 1.

REMARKS

Claim Amendments

Claim 1 has been amended solely to correct a typographical error that was objected to in the instant Office Action. This amendment adds no new matter and is fully supported in the Specification and claims as originally filed. Applicants respectfully request that it be entered and made of record.

Rejections

Applicants gratefully acknowledge the withdrawal of claims 1-10, 12-16, 34 and 35 on the grounds of nonstatutory obviousness-type double patenting and anticipation under 35 §USC 102(b).

35 USC §103(a)

Claims 1-10, 12-16, 34 and 35 are rejected under 35 USC §103(a) as allegedly being unpatentable over US Patent No. 5,717,072 ("Mosley"), in view of Jakobovits, 1998, Expert Opinion on Investigational Drugs 7:607-14. As a *prima facie* case of obviousness has not been made, Applicants respectfully traverse.

A *prima facie* case of obvious must be based on a factual enquiry that comprises: ascertaining the scope and content of the prior art; ascertaining the differences between the claimed invention and the prior art; and resolving the level of ordinary skill in the pertinent art. *See Graham v. John Deere Co.*, 148 USPQ 459 (1966); *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (2007).

The instant rejection is premised primarily on certain antibodies said to be described in Mosley. At the bottom of page 4 of the instant Office Action is a description of these antibodies. This description is almost identical to a passage on page 7 of the Office Action issued on February 3, 2011. As Applicants pointed out in their response filed May 3, 2011, this description is riddled with inaccuracies:

- ¶ The abstract of Mosley does not refer specifically to anti-*human* IL-4 receptor antibodies.

- Lines 10-28 of column 5 of Mosley do not mention anti-IL-4 receptor antibodies. Lines 14-22 refer to the "secretion and expression of antibodies of the IgE and IgG1 isotype" as the result of an IL-4 mediated biological response, not to anti-IL-4 receptor antibodies of IgE or IgG1 isotype.
- The claims of Mosley refer to antibodies that are immunoreactive with either human or murine IL-4 receptor, but provide no other binding characteristics. The claims do not indicate where on the IL-4 receptor these antibodies bind.
- Lines 56-66 of column 2 describe the transformation of COS cells with *murine* IL-4 receptor, not human IL-4 receptor. The passage does not even mention anti-IL-4 receptor antibodies (anti-human or anti-murine).

It is simply impossible for a *prima facie* case of obviousness to rest on so many errors of fact. The instant rejection should be withdrawn for this reason alone.

The rejection is also inadequate for confusing the specific antibodies actually made by Mosley with hypothetical antibodies that might be obtained by following the teachings of Mosley.

The rejection also applies an incorrect legal standard. It alleges that Mosley discloses a non-human antibody that "*would be expected to* compete with the recited [reference?] antibody, absent evidence to the contrary, because both sets of antibodies bind to the extracellular domain of IL-4 receptor. … Since the antibody of Mosley *et al.* competes with the reference antibody, each antibody would *inherently* inhibit the binding of the other with the IL-4 receptor []." (Office Action at pages 4-5; emphases added).

Under certain limited circumstances, a rejection for obviousness under 35 USC §103 can be based, in part, on an inherent property in a cited reference. *See In re Kubin*, 90 USPQ2d 1417 (CAFC 2009). While such situations are rare, the few Federal Circuit cases taking up the issue make it clear that this can be appropriate only if the inherent property is *necessarily* present in the cited art.[1] Applicants are not aware of any Federal Circuit case in which the court has found a claim obvious because the cited art *might have* the allegedly inherent property. The proper legal standard is that the cited art *must* contain the inherent

[1] *See, e.g., Santarus v. Par Pharmaceutical* 104 USPQ2d 1641 (CAFC 2012) ("There is *no dispute* that the blood serum concentrations claimed in the '885 patent are expected in light of the dosages. In fact, a publication [citation omitted] includes a blood serum chart that indicates that the claimed levels are easily achieved []." (emphasis added))

property.[2] It simply cannot be assumed that an antibody in a cited reference "would be expected to" have whatever property would make it a convenient piece of prior art. There must be evidence or sound reasoning indicating that the cited art *must* have the allegedly inherent property.

The instant rejection fails to meet this legal standard. It provides no evidence or reasoning to suggest why the antibodies of Mosley *must* compete with the reference antibody recited in the instant claims. With respect to the antibodies that Mosley actually made, M1 and M2, the sole factual basis for this conclusion is that they allegedly bind to the extracellular domain of IL-4 receptor and are said to block binding of IL-4 to IL-4 receptor. However, M1 and M2 are both anti-*murine* IL-4 receptor antibodies and do not cross-react with *human* IL-4 receptor.[3] Each of the rejected claims recites human anti-*human* IL-4 receptor antibodies. It is impossible for two antibodies to compete for binding to a target if one of them does not even bind to the target. Accordingly, neither M1 nor M2 can support the instant obviousness rejection.

With respect to the prophetic examples of methods of making antibodies of Mosley, it is simply assumed that any hypothetical antibody that binds to the extracellular domain of human IL-4 receptor and inhibits binding of human IL-4 to human IL-4 receptor would *necessarily* compete for binding with the recited reference antibody. But inherency cannot be based on mere conjecture or assumption. No such evidence has been cited and in their previous response[4] Applicants provided four reasons why these hypothetical antibodies would not necessarily have the allegedly inherent properties. None of these reasons has been rebutted and, in spite of Applicants's request, the present rejection provides no documentary evidence under 37 CFR §1.104(c)(2) or affidavit or declaration under 37 CFR §1.104(d)(2).

Because no evidence or reasoning has been provided to show that the allegedly inherent characteristics are necessarily present in the hypothetical antibodies, a *prima facie* case of obviousness has not been made and Applicants are under no obligation to provide counter-evidence. Nonetheless, in the interest of expediting prosecution, Applicants provide

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[2] *See, e.g., Allergan v Sandoz*, 106 USPQ2d 1574, Fn1 (CAFC 2013) (Claim non-obvious because, *inter alia*, "[t]here is … a problem with applying [the inherency] doctrine to this case. … On the present record, we cannot draw a conclusion in favor of either [of two possibilities].")

[3] Evidence and reasons supporting this conclusion were presented on pages 10-11 of the Response filed May 3, 2011, and are not repeated here in the interest of economy. The referred-to passage also proves that M2 fails to block binding of the murine IL-4 ligand to the murine IL-4 receptor.

[4] Response filed October 14, 2011, pages 8-10.

the following example of a set of antibodies that bind to a common target, but do not all compete for binding with each other to the target.

United States Patent Number 7,807,159 discloses antibodies that bind to myostatin. Myostatin is a 109 amino acid polypeptide that forms a homodimer. The '159 patent describes the isolation and characterization of antibodies that bind to myostatin. Example 9 describes a competition binding assay whose results are shown in Figure 8:

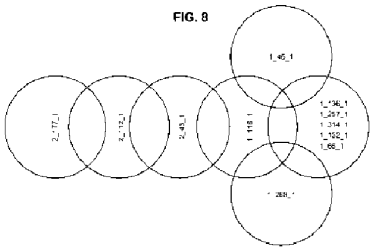

FIG. **8** depicts epitope binning. Epitope binding of the human anti-myostatin antibodies of the invention was mapped by cross-competition experiments using a BIACORE® 3000 instrument. Antibodies are depicted as labeled boxes. Antibodies in one circle compete with antibodies in overlapping circles. For instance, antibody 1_46_1 competes with antibody 1_136_3, but antibody 1_46_1 does not compete with antibody 1_268_1. When two or more antibodies are in the same circle their respective binding cannot be distinguished.

Thus, the '159 patent demonstrates that even two antibodies raised against a homodimerized 109 amino acid polypeptide do not necessarily compete for binding to the polypeptide. In fact, they failed to find even one antibody that competed against all of the other antibodies. Accordingly, it cannot be concluded that the antibodies of Mosley compete for binding with the reference antibody recited in the rejected claims.

Jakobovits fails to cure any of the deficiencies of Mosley. Jakobovits is cited as teaching a method for producing human anti-human antibodies in a genetically engineered mouse strain. It is alleged that the skilled person would have expected to succeed in "*modify[ing]* the IL-4 receptor antibodies of Mosley et al by using the method of Jakobovits to generate fully human antibodies []." (Office Action at page 6; emphasis added). But Jakobovits purports only to provide methods for making and identifying *new* antibodies against a target. For the reasons explained above with respect to Mosley, it simply cannot be assumed that such new anti-IL-4 receptor antibodies would inherently have the properties necessary to make a *prima facie* case.

Thus, the instant rejection simply has too many errors of fact and law for it to rise to the level of a *prima facie* rejection for obviousness. Accordingly, Applicants respectfully request that it be withdrawn.

Claims 1-10, 12-16, 34 and 35 are rejected under 35 USC 103(a) as allegedly being obvious over Tony *et al.*, Eur. J. Biochem, 1994, 225:659-65 ("Tony"), in view of Jakobovits. As a *prima facie* case of obviousness has not been made, Applicants respectfully traverse.

The instant rejection suffers from many of the same deficiencies as the preceding one. In particular, it assumes that the ligand-blocking anti-human IL-4 receptor antibody of Tony will *necessarily* compete for binding with the reference antibody recited in the rejected claims. As explained above, it is legal error to make such an assumption without evidence; it is a factual error as well because there are examples of antibodies that bind to the same small target without competing with each other.

Jakobovits is cited for the same purpose in both rejections but with the same shortcomings: it does not teach how to "modify" the antibody of Tony, only how to make new antibodies, and it simply is not true that an antibody so made would *necessarily* compete for binding with the reference antibody of the rejected claims.

Accordingly, as a *prima facie* case has not been made, Applicants respectfully request that the instant rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the claims as presently pending be allowed. The Examiner is invited to call the undersigned attorney at (206) 265-8779 upon receipt and review of this Response to discuss any questions or concerns about the present response.

Respectfully submitted,

/Nathan A. Machin/
Nathan A. Machin
Attorney for Applicants
Registration No.: 47,763
Phone: (206) 265-8779
Date: August 13, 2013

Please send all future correspondence to:

22932

Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, Washington 98119-3105
(206) 265-7000

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

22932 7590 05/13/2013

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	

NOTIFICATION DATE	DELIVERY MODE
05/13/2013	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):

AWA-Patent@amgen.com
pair_amgen@firsttofile.com

Office Action Summary	Application No. 12/829,231	Applicant(s) ARMITAGE ET AL.	
	Examiner FOZIA HAMUD	Art Unit 1647	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *11/11/2011*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-10,12-16 and 20-35* is/are pending in the application.

5a) Of the above claim(s) *20-33* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10,12-16,34 and 35* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

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

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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

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

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

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

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

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

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

4) ☐ Other: _____.

DETAILED ACTION

1a. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 November 11 has been entered.

1b. The terminal disclaimer (TD) filed on 14 October 2011 has been approved.

Status of claims:

1c. Claims 1-10, 12-16, 20-35 are pending of which claims 1-16 and 34-35 are drawn to the elected invention. Claims 20-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/21/2009. Thus, claims 1-10, 12-16 and 34-35 are under consideration.

Response to Applicant's Argument:

2. The following rejections are withdrawn in light of Applicants' arguments:

I. The amendment to claims 1-7 overcame the objection to claims 1-7, because the recited acronyms are now spelled out.

II. The rejection of claims 1-10, 12-16 and 34-35 made on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8-13, of U.S. Patent No. 7,186,809.

III. The rejection of claims 1-10 and 12-16, 34, 35 made under 35 U.S.C. 102(b), as being anticipated by Mosley et al, U.S. Patent No. 5,717,072, is withdrawn. Applicants' arguments that the Mosley et al reference does not teach human antibodies, has been found persuasive.

New Objections/Rejections:

Claim Objections.

3. Claim 1 is objected to because of the following informalities. Claim 1 is missing a period at the end of the claim.

Claim rejections-35 USC § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4a. Claims 1-10 and 12-16, 34, 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mosley et al. (U.S. Patent 5,717,072), in view of Aya Jakobovits, (Expert Opinion on Investigational Drugs, 1998, Vol. 7; No. 4; pages 607-614).

Claims 1-10 and 12-16 are drawn to an isolated human antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein the reference antibody comprises the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor, said isolated antibody that is a human antibody, wherein the isolated antibody inhibits human IL-4 signaling through human IL-4 receptor, wherein the antibody is humanized, is full length or fragment thereof, wherein the antibody has specific binding affinity, (claims 8-10) or is a composition comprising a buffer, (claim 34) or isolated, (claim 35).

Mosley et al teach an isolated antibody that binds to the extracellular domain of human IL-4 receptor, said antibody that is an IgG1, and fragments of said antibody and inhibits IL-4 mediated activities, (see abstract, column 5, lines 10-28 and claims). Mosley et al disclose that their antibody binds to human cells that express IL-4 receptor and inhibits IL-4 binding to cytotoxic T lymphocyte lines, (CTLL, transfected with IL-4 receptor), (see column 2, lines 56-66 and Example 13). The antibody of Mosley et al. would be expected to compete with the recited antibody, absent evidence to the contrary, because both sets of antibodies bind to the extracellular domain of IL-4 receptor. The Mosley et al antibody inhibits binding of IL-4 to IL-4 receptor and is an IgG1 isotype. Since the antibody of Mosley et al competes with the reference antibody,

each antibody would inherently inhibit the binding of the other with the IL-4 receptor, (claims 2-3). With respect to claims 4 and 6, since the antibody taught by Mosley et al. binds to human IL-4 receptor and inhibits IL-4 binding to IL-4 receptor, it would also inherently inhibit IL-4 signaling through IL-4 receptor. Regarding claims 8-10, the antibody of Mosley et al. would be expected to display said binding affinities, since it was shown to bind to the IL-4 receptor, (see column 33, line 65 to column 34, line 10). Regarding claims 34-35, Mosley et al. teach that their antibody is in a buffer solution thus meeting the limitation recited in claim 34 and is isolated, meeting the limitation of claim 35, (see column 34, lines 4-10 and claims).

However, the Mosley et al reference does not teach human antibodies that bind to the extracellular domain of human IL-4 receptor. Jakobovits teaches that mouse antibody sequences have been shown to be immunogenic in humans, inducing a human antimouse antibody (HAMA) response that leads to rapid clearance of the administered antibodies and a reduction in their efficacy and safety (page 607, 2nd paragraph). Jakobovits states that such limitations could be overcome by fully human monoclonal antibodies, which minimize immunogenic and allergic responses (page 607, 2nd paragraph). Jakobovits discloses an efficient and reliable method of producing fully human antibodies, (see abstract). The researchers engineered mice with human antibody genes to generate and select high affinity, fully human antibodies and utilized the mouse hybridoma technology to derive mAbs from immunized mice, (see page 609, column 1, 2nd paragraph and table 1).

Therefore, it would have been prima facie obvious to the person of ordinary skill

in the art at the time the invention was made to modify/improve the antibodies of Mosley et al, by making fully human antibodies that bind to the extracellular domain of IL-4 receptor, because Jakobovits teaches a method of producing fully human antibodies with reduced immunogenicity. One of ordinary skill in the art would be motivated to generate human antibodies against IL-4R for suppressing IL-4 activities, because IL-4 is involved in allergy and mediates its inflammatory responses through its receptor, (for example see column 3, lines 15-30 of Mosley). Moreover, one skilled in the art would be motivated to produce fully human antibodies following the Jakobovits reference, because the reference teaches a method of producing fully human antibodies that have minimal immunogenic and allergic responses for humans, to be used therapeutically.

The person of ordinary skill in the art would have reasonably expected success to modify the IL-4 receptor antibodies of Mosley et al by using the method of Jakobovits to generate fully human antibodies because fully human antibodies were already being made at the time the instant application was filed.

Therefore, the claimed invention as a whole was clearly prima facie obvious over the prior art.

4b. Claims 1-10 and 12-16, 34, 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tony et al. (Eur. J. Biochem, 2005, Vol. 225, pages 659-665), in view of Aya Jakobovits, (Expert Opinion on Investigational Drugs, 1998, Vol. 7; No. 4; pages 607-614).

Claims 1-10 and 12-13 are drawn to an isolated human antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein the reference

antibody comprises the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor, said isolated antibody that is a human antibody, wherein the isolated antibody inhibits human IL-4 signaling through human IL-4 receptor, wherein the antibody is humanized, is full length or fragment thereof, wherein the antibody has specific binding affinity, (claims 8-10) or is a composition comprising a buffer, (claim 34) or isolated, (claim 35).

Tony et al teach an isolated human antibody that binds to the extracellular domain of human IL-4 receptor, said antibody that is an IgG1, and show that said antibody inhibits both IL-4-dependent and IL-13-dependent responses, (see abstract, page 660, top of column 1, pages 662-663 and figure 4). The antibody of Tony et al binds to IL-4 receptor alpha and inhibits IL-4 or IL-13 activities with high affinity, (see table 5). Thus, the antibody disclosed in the Tony et al reference is expected to compete with the recited antibody, absent evidence to the contrary. Regarding claims 8-10, the antibody of Mosley et al. would be expected to display the recited binding affinities, because Tony et al show that their antibody binds to the extracellular domain of human IL-4 receptor with very low dissociation constant, (k_i), (see table 6 on page 663). It is known in the art that a low dissociation constant is indicative of high affinity binding between the antibody and the antigen, similar to high association constant (K_a). Regarding claims 34-35, Tony et al. teach that their antibody is in a solution thus meeting the limitation recited in claim 34 and is isolated, meeting the limitation of claim 35, (see figure 4).

However, the Tony et al reference does not teach human antibodies that bind to the extracellular domain of human IL-4 receptor. Jakobovits teaches that mouse antibody sequences have been shown to be immunogenic in humans, inducing a human antimouse antibody (HAMA) response that leads to rapid clearance of the administered antibodies and a reduction in their efficacy and safety (page 607, 2nd paragraph). Jakobovits states that such limitations could be overcome by fully human monoclonal antibodies, which minimize immunogenic and allergic responses (page 607, 2nd paragraph). Jakobovits discloses an efficient and reliable method of producing fully human antibodies, (see abstract). The researchers engineered mice with human antibody genes to generate and select high affinity, fully human antibodies and utilized the mouse hybridoma technology to derive mAbs from immunized mice, (see page 609, column 1, 2nd paragraph and table 1).

Therefore, it would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify/improve the antibodies of Tony et al, by making fully human antibodies that bind to the extracellular domain of IL-4 receptor, because Jakobovits teaches a method of producing fully human antibodies with reduced immunogenicity. One of ordinary skill in the art would be motivated to generate antibodies against IL-4R for suppressing IL-4 activities, because IL-4 is involved in allergy and mediates its inflammatory responses through its receptor, (for example see column 3, lines 15-30 of Tony). Moreover, one skilled in the art would be motivated to produce fully human antibodies following the Jakobovits reference, because the reference teaches a method of producing fully human antibodies that have

minimal immunogenic and allergic responses for humans, to be used therapeutically.

The person of ordinary skill in the art would have reasonably expected success to modify the IL-4 receptor antibodies of Tony et al by using the method of Jakobovits to generate fully human antibodies because fully human antibodies were already being made at the time the instant application was filed. Therefore, the claimed invention as a whole was clearly prima facie obvious over the prior art.

Conclusion:

6. No claim is allowed.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

March et al, U.S. PG-Pub: 2002/0076409 (published on 20 June 2002, 102 (e) date: 12 July 2000, via 60/217,888;; post-filing reference;; March et al teach an isolated human antibody that binds to the human IL-4 receptor. March et al disclose that said antibody is an IgG1 antibody, as well as fragments of said antibody and wherein the antibody inhibits IL-4 mediated activities, (see paragraphs 0049, 0104, 0107, 0112, 0210-0214, 0220 and claims). March et al disclose that the antibodies bind to IL-4 receptor and inhibit IL-4 and IL-13 activities, (see paragraph 0107)).

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

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

Fozia Hamud
Patent Examiner
Art Unit 1647
30 April 2013

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

Request for Continued Examination (RCE) Transmittal

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

Application Number	12/829,231
Filing Date	July 1, 2010
First Named Inventor	Richard J. Armitage
Art Unit	1647
Examiner Name	HAMUD, Fozia M.
Attorney Docket Number	3005-US-CNT3

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. .

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 instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   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. 09-0069 .

      i. ☐ RCE fee required under 37 CFR 1.17(e)

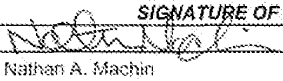
      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   ☐

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature		Date	November 11, 2011
Name (Print/Type)	Nathan A. Machin	Registration No.	47,763

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			
Name (Print/Type)		Date	

VIA EFS-Web
November 11, 2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Richard J. Armitage et al.	**Docket No.**:	3005-US-CNT3
Serial No.:	**12/829,231**	**Confirmation No.**:	8151
Filing Date:	**July 1, 2010**	**Examiner**:	HAMUD, Fozia M.

Title: **ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES (as amended)**

RESPONSE TO ADVISORY ACTION

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

Sir:

In response to the Advisory Action mailed November 1, 2011, please consider the following election and remarks. A one-month extension of time is enclosed thus extending the period for submitting a response until November 14, 2011. Accordingly, this paper is timely filed. Also enclosed herewith is a Request for Continued Examination with appropriate fees.

The Director is hereby authorized to charge any additional fees which may be required by the accompanying papers, or credit any overpayment to Deposit Account No. 09-0089.

CERTIFICATE OF EFS-Web TRANSMISSION
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/	November 11, 2011
Jae Cho	Date

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

Listing of the Claims

What is claimed is:

1. (Previously Presented) An isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12

2. (Previously Presented) The isolated human antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. (Previously Presented) The isolated human antibody of Claim 1, wherein when said isolated human antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human IL-13 interleukin-13 (IL-13) to human IL-4 receptor.

6. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^8.

9. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^9.

10. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^{10}.

11. (Cancelled)

12. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a full-length antibody.

13. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fragment of an antibody.

15. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fusion protein.

16. (Previously Presented) The isolated human antibody of Claim 1, wherein said isolated human antibody is a single chain antibody (scFv).

17. – 19. (Cancelled)

20. (Withdrawn) An isolated nucleic acid, wherein said isolated nucleic acid comprises a sequence encoding:

a. the light chain variable domain of said isolated antibody of Claim 1; or

b. the heavy chain variable domain of said isolated antibody of Claim 1; or

c. the light chain variable domain of said isolated antibody of Claim 1 and the heavy chain variable domain of said isolated antibody of Claim 1.

21. (Withdrawn) A vector, wherein said vector comprises said isolated nucleic acid of Claim 20.

22. (Withdrawn) The vector of Claim 21, wherein said vector is an expression vector.

23. (Withdrawn) An isolated cell, wherein said cell comprises said isolated nucleic acid of Claim 20.

24. (Withdrawn) The isolated cell of Claim 23, wherein said isolated cell expresses said isolated antibody.

25. (Withdrawn) A method of reducing IL-4 receptor-dependent signaling in a subject, comprising administering to said subject an effective amount of said isolated antibody of Claim 1.

26. (Withdrawn) The method of Claim 25, wherein said method suppresses a T_H2-type immune response.

27. (Withdrawn) The method of Claim 25, wherein said subject has, or is at risk of developing, a condition responsive to inhibition of IL-4R signaling.

28. (Withdrawn) The method of Claim 27, wherein said condition is an inflammatory condition.

29. (Withdrawn) The method of Claim 27, wherein said condition is an IgE mediated condition.

30. (Withdrawn) The method of Claim 27, wherein said condition is an allergic condition.

31. (Withdrawn) The method of Claim 27, wherein said condition is a condition in which IL-4 mediated epithelial barrier disruption plays a role.

32. (Withdrawn) The method of Claim 27, wherein said condition is asthma, COPD, pulmonary fibrosis, or septic arthritis.

33. (Withdrawn) A method of making an antibody, comprising incubating said cell of Claim 23 under conditions that allow it to express said isolated antibody.

34. (Previously Presented) A composition comprising said isolated human antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. (Previously Presented) A kit comprising said isolated human antibody of Claim 1.

REMARKS

Applicants gratefully acknowledge entry of the response filed October 14, 2011, and the removal of the nonstatutory obviousness-type double patenting rejection of Claims 1-16, 34 and 35 over Claims 1-3 and 8-13 of U.S. Patent No. 7,186,809.

Rejections

35 USC §102(b)

Claims 1-10, 12-16, 34 and 35 remain rejected under 35 USC 102(b) as allegedly anticipated by US Patent No. 5,717,072 ("Mosley"). As a *prima facie* case has not been advanced, Applicants respectfully traverse.

A claim is anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). See also *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

The rejection does not say so explicitly, but it appears to rely upon a theory of inherent anticipation.

An element is inherently present in a reference only if it necessarily results from the reference's teachings. "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1269 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)) (internal citations omitted; emphasis in original).

The Advisory Action mailed November 1, 2011, summarizes Applicants' previously filed response to the instant rejection, yet fundamentally misconstrues it.

The Advisory Action implies that Applicants' have questioned the validity of Mosley. They have not. Applicants do not dispute that the skilled artisan can make antibodies according to the teachings of Mosley. Rather, Applicants' point is that the properties of Mosley's prophetic antibodies cannot simply be measured or tested because the antibodies do not actually exist. They must be inferred from Mosley's disclosure. So the relevant question is, *if* an antibody according to Mosley were made, would it *necessarily* have all of the properties recited in the rejected claims?

The Advisory Action and its antecedent final Office Action simply assume that it would. In making this assumption, each reason to the contrary listed in Applicants' previous response is impermissibly ignored.

Instead of offering a rebuttal to each of the previous rejection's shortcomings identified by Applicants, the Advisory Action simply re-asserts the basis for the previous rejection:

> "Mosley et al teach an antibody that is immunoreactive, (i.e. binds) to amino acids 1-207 of human IL-4R (see claims). Thus, the antibody of Mosley et al would compete with the reference antibody recited in the instant claims, since both antibodies bind to the same epitope of human IL-4R." (Advisory Action, final paragraph).

In their previous response, Applicants identify at least four independent reasons why this conclusion is not *necessarily* correct, as it must be if it is to satisfy the standard for inherent anticipation. For brevity, Applicants will not repeat those reasons here, although they continue to be true and relevant and are hereby maintained. Applicants respectfully request that, if this rejection is maintained, the perceived flaw in each be specifically explained.

The Advisory Action also fails to acknowledge, much less honor, Applicants' request for either documentary evidence, under 37 CFR 1.104(c)(2), or an affidavit or declaration, under 37 CFR 1.104(d)(2). Applicants' request is maintained. If it is a fact that any two antibodies that bind to the same 207 amino acid polypeptide must *necessarily* compete for binding to the polypeptide, then let the evidence show it. Without such evidence, a *prima facie* case of inherent anticipation has not been made, and the rejection must be withdrawn. There simply is no other alternative. See MPEP § 2144.03.

CONCLUSION

Applicants respectfully request that the claims as presently pending be allowed. The Examiner is invited to call the undersigned attorney at (206) 265-8779 upon receipt and review of this Response to discuss any questions or concerns about the present response.

Respectfully submitted,

Nathan A. Machin
Attorney for Applicants
Registration No.: 47,763
Phone: (206) 265-8779
Date: November 11, 2011

Please send all future correspondence to:
22932
Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, Washington 98119-3105
(206) 265-7000

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

22932 7590 11/01/2011

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
11/01/2011	PAPER

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

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

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/829,231	**Applicant(s)** ARMITAGE ET AL.
	Examiner FOZIA HAMUD	**Art Unit** 1647

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

THE REPLY FILED 14 October 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

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

NOTICE OF APPEAL

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

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-10,12-16,34 and 35*.
   Claim(s) withdrawn from consideration: *20-33*.

AFFIDAVIT OR OTHER EVIDENCE

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

REQUEST FOR RECONSIDERATION/OTHER

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

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claims 1-16 and 34-35 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8-13, of U.S. Patent No. 7,186,809.

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1-10 and 12-16, 34, 35 stand rejected under 35 U.S.C. 102(b), as being anticipated by Mosley et al, U.S. Patent No. 5,717,072, (issued on 10 February 1998), for reasons of record.
Applicants argue that a prima-facie case has not been advanced. Applicants submit that an element is inherently present in a reference only if it necessarily results from the reference's teachings. This rejection fails to make a prima-facie case against the claims as presently amended because it fails to identify where Mosley discloses (either explicitly or inherently) each and every element of the amended claims. Applicants argue that the rejection appears to acknowledge that Mosley does not explicitly disclose an antibody that competes against the recited reference antibody of the rejected claims for binding to human IL-4R. (The only two antibodies actually made and reported in Mosley are M1 and M2, which do not bind to human IL-4R and so cannot compete against the reference antibody as required by the rejected claims.) Instead, the rejection implies that if one made a new antibody according to the cited portions of Mosley, it would inherently have this property.

This argument is not persuasive. It is acknowledged that the Mosley et al reference teaches antibodies that are immunoreactive to mammalian IL-4 receptor, (see abstract). However, the Mosley et al reference teaches human IL-4 receptor, which is identical to the human IL-4 receptor set forth in SEQ ID NO:2 of the instant application, (see figures 4A-4B of Mosley et al). Although Mosley et al. teach M1 and M2, which do not bind to human IL-4R, they disclose that preparations of purified recombinant IL-4 receptor, for example, human or murine IL-4 receptor, transfected COS cells expressing high levels of IL-4 receptor or CTLL 19.4 cells are employed to generate monoclonal antibodies against IL-4 receptor and that such antibodies are useful in interfering with IL-4 binding to IL-4 receptors (column 33, lines 31-38).

Applicants submit that as the Federal Circuit has emphasized, a reference inherently discloses a claim limitation only if the limitation is necessarily present in the cited reference. Applicants argue that the instant rejection fails to meet this standard for multiple reasons, any one of which is sufficient to establish that a primafacie rejection has not been made. First, as acknowledged in the instant Office Action, Example 13 of Mosley teaches methods of making antibodies against murine or human IL-4R, so the skilled artisan is not necessarily led to make an anti-human IL-4R antibody. Second, even if the resulting antibody necessarily bound to human IL-4R, Example 13 provides several choices of antigens for making the antibody (e.g., purified recombinant antigen or antigen displayed on a cell surface). Some such antigens will include the extracellular portion of IL-4R, but others will not and some antigens that include all or part of the extracellular domain will also include other parts of IL-4R. Consequently, an antibody made according to the disclosure of Mosley will not necessarily bind the extracellular domain of human IL-4R. Third, many antigens of the types referred to by Mosley will comprise denatured or mis-folded IL-4R. Antibodies raised against such antigens will not necessarily bind to correctly folded IL-4R. The antibodies referred to in the claims of Mosley do not overcome this deficiency. These too are prophetic antibodies, not antibodies that have actually been made. The claims recite antibodies that bind to polypeptides comprising certain sequences. It is not stated that the antibodies bind to those particular recited sequences. Thus, for example, an antibody that binds to the intracellular portion of full-length IL-4R will bind to a polypeptide "comprising" the IL-4R extracellular domain, as full-length IL-4R comprises both the extracellular and the intracellular domains. Such an antibody would not compete with the reference antibody of the rejected claims. Fourth, the present rejection rests entirely on the assumption that any antibody that binds to the (properly folded) 207 amino acid fragment of IL-4R would necessarily compete for binding with the reference antibody recited in the rejected claims. Applicants respectfully disagree. The art is replete with examples of antibodies that bind a target of 207 amino acids or less but do not compete for binding to the target. Thus it cannot be concluded that an antibody made according to Mosley would necessarily compete for binding with the reference antibody of the rejected claims. Should this rejection be maintained, however, Applicants respectfully request that either documentary evidence, under 37 CFR 1.104(c)(2), or an affidavit or declaration, under 37 CFR 1.104(d)(2), supporting the assumption be provided. See MPEP § 2144.03.

These arguments have been considered, but are not deemed persuasive. The instant claims are drawn to an antibody that competes with a reference antibody that is comprised of the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12. The instant specification describes that antibody 12B5 comprises the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12, (see page 31, lines 20-33). The specification further teaches that the 12B5 antibody binds to human soluble IL-4R that comprises the extracellular domain of human IL-4R, (see page 60, lines 14-27). The instant specification teaches that human soluble IL-4R is comprised of amino acids 1 to 207, (see page 18, lines 33 to page 19, lines 2). Mosley et al teach an antibody that is immunoreactive, (i.e. binds) to amino acids 1-207 of human IL-4R, (see claims). Thus, the antibody of Mosley et al would compete with the reference antibody recited in the instant claims, since both antibodies bind to the same epitope of human IL-4R. Also since Mosley discloses human IL-4 receptor, (figures 4A-4C) and methods of producing antibodies that bind said receptor, as Applicants acknowledge, some such antigens will include the extracellular portion of IL-4R, but others will not, thus, some of the antibodies produced would bind to the extracellular domain of human IL-4R. With respect to Applicants' a argument that the antibodies referred to in the claims of Mosley are prophetic antibodies, i.e. that antibodies have not been actually made, every patent is presumed valid (35 U.S.C. 282) and Affidavits or declarations attacking the operability of a patent cited as a reference must rebut the presumption of operability by a preponderance of the evidence. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). In the instant case Mosley et al teach antibodies that bind to amino acids 1-207 or 1-800 of human IL-4 receptor, (see claim 1) and said antibody would be expected to compete with the claims antibody.

OK TO ENTER: /FH/
10/26/2011

VIA EFS-Web
October 14, 2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Richard J. Armitage et al.	**Docket No.**:	3005-US-CNT3
Serial No.:	**12/829,231**	**Confirmation No.**:	8151
Filing Date:	**July 1, 2010**	**Examiner**:	HAMUD, Fozia M.

Title: **ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES (as amended)**

RESPONSE TO OFFICE ACTION

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

Sir:

In response to the Final Office Action mailed July 14, 2011, please consider the following election and remarks. Also enclosed herewith is a Terminal Disclaimer with appropriate fees.

The Director is hereby authorized to charge any additional fees which may be required by the accompanying papers, or credit any overpayment to Deposit Account No. 09-0089.

CERTIFICATE OF EFS-Web TRANSMISSION
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/	October 14, 2011
Jae Cho	Date

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/829,231	ARMITAGE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 10/14/2011	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Dorethea Lawrence

U.S. Patent and Trademark Office

VIA EFS-Web
October 14, 2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Richard J. Armitage et al.	**Docket No.**:	3005-US-CNT3
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/Jae Cho/	October 14, 2011
Jae Cho	Date

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

Listing of the Claims

What is claimed is:

1. (Presently Amended) An isolated human antibody that competes with a reference antibody for binding to human ~~IL-4~~ interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12

2. (Presently Amended) The isolated human antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. (Presently Amended) The isolated human antibody of Claim 1, wherein when said isolated human antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits the binding of human ~~IL-13~~ interleukin-13 (IL-13) to human IL-4 receptor.

6. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^8.

9. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^9.

10. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^{10}.

11. (Cancelled)

12. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody is a full-length antibody.

13. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fragment of an antibody.

15. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody is a fusion protein.

16. (Presently Amended) The isolated human antibody of Claim 1, wherein said isolated human antibody is a single chain antibody (scFv).

17. – 19. (Cancelled)

20. (Withdrawn) An isolated nucleic acid, wherein said isolated nucleic acid comprises a sequence encoding:

a. the light chain variable domain of said isolated antibody of Claim 1; or

b. the heavy chain variable domain of said isolated antibody of Claim 1; or

c. the light chain variable domain of said isolated antibody of Claim 1 and the heavy chain variable domain of said isolated antibody of Claim 1.

21. (Withdrawn) A vector, wherein said vector comprises said isolated nucleic acid of Claim 20.

22. (Withdrawn) The vector of Claim 21, wherein said vector is an expression vector.

23. (Withdrawn) An isolated cell, wherein said cell comprises said isolated nucleic acid of Claim 20.

24. (Withdrawn) The isolated cell of Claim 23, wherein said isolated cell expresses said isolated antibody.

25. (Withdrawn) A method of reducing IL-4 receptor-dependent signaling in a subject, comprising administering to said subject an effective amount of said isolated antibody of Claim 1.

26. (Withdrawn) The method of Claim 25, wherein said method suppresses a T_H2-type immune response.

27. (Withdrawn) The method of Claim 25, wherein said subject has, or is at risk of developing, a condition responsive to inhibition of IL-4R signaling.

28. (Withdrawn) The method of Claim 27, wherein said condition is an inflammatory condition.

29. (Withdrawn) The method of Claim 27, wherein said condition is an IgE mediated condition.

30. (Withdrawn) The method of Claim 27, wherein said condition is an allergic condition.

31. (Withdrawn) The method of Claim 27, wherein said condition is a condition in which IL-4 mediated epithelial barrier disruption plays a role.

32. (Withdrawn) The method of Claim 27, wherein said condition is asthma, COPD, pulmonary fibrosis, or septic arthritis.

33. (Withdrawn) A method of making an antibody, comprising incubating said cell of Claim 23 under conditions that allow it to express said isolated antibody.

34. (Presently Amended) A composition comprising said isolated human antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. (Presently Amended) A kit comprising said isolated human antibody of Claim 1.

REMARKS

Amendments

Pending claims 1-10, 12-16, 34, and 35 have been amended and claim 11 has been cancelled. Applicants respectfully request entry of these changes.

Claims 1-10, 12-16, 34, and 35 have been amended to recite human antibodies. This amendment is supported in the specification as filed at, for example, page 28, line 33, and in claim 11 as originally filed.

Claims 1 and 5 have been amended such that the first occurrence in the claims of interleukin-4 and interleukin-13, respectively, are spelled out. These amendments are supported by the claims as originally filed.

The claim amendments and cancellation of claim 11 are made without prejudice or disclaimer. Applicants reserve the right to pursue amended or cancelled subject matter in one or more timely filed continuation, continuation-in-part, or divisional applications.

Objection

Claims 1-7 are objected to for using "IL-4" and "IL-13" without first defining them. Claims 1 and 5 have been amended accordingly. Applicants respectfully request that this objection be removed.

Rejections

Obviousness-Type Double Patenting

Claims 1-16, 34 and 35 are rejected on the grounds of nonstatutory obviousness-type double patenting over claims 1-3 and 8-13 of US Pat. No. 7,186,809.

The Terminal Disclaimer filed on May 3, 2011, was not accepted. It is asserted that the proffered Terminal Disclaimer used indefinite language.

Without agreeing with the propriety of this objection, and solely in order to expedite prosecution, Applicants provide herewith a new Terminal Disclaimer. Consequently, Applicants respectfully request that the instant rejection be withdrawn.

35 USC §102(b)

Applicants gratefully acknowledge the withdrawal of the rejection of claims 1-9, 11-16, 34, and 35 over Beckman et al., 1990, J Immunol 144:4212-17.

Claims 1-16, 34 and 35 remain rejected under 35 USC 102(b) as allegedly anticipated by US Patent No. 5,717,072 ("Mosley"). The rejection is moot with respect to canceled claim 11. With respect to the remaining claims, as a *prima facie* case has not been advanced, Applicants respectfully traverse.

A claim is anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). See also *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

An element is inherently present in a reference only if it necessarily results from the reference's teachings. "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1269 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)) (internal citations omitted; emphasis in original).

Pages 5 through 8 of the instant Office Action appear to summarize the original rejection over Mosley and Applicants' previously filed response to it. The present rejection appears on page 9, where it is stated that "Example 13 of Mosely et al … teaches methods for generating anti-murine or anti-human IL-4 receptor antibodies. … Mosely … teaches the

human IL-4 receptor (see example 11), and an antibody that is immunoreactive with said receptor, (see claims). The antibody of Mosley et al binds human IL-4 [receptor], and thus would be expected to compete with the reference antibody recited in the instant claims, since both antibodies bind to the same epitope of human IL-4R." (Final Office Action mailed July 14, 2011, page 9) By "epitope," it is apparently meant the soluble IL-4R comprising amino acids 1 to 207. (See Final Office Action, page 7.)

This rejection fails to make a *prima facie* case against the claims as presently amended because it fails to identify where Mosley discloses (either explicitly or inherently) each and every element of the rejected claims, as required by *Verdegaal*.

First, the rejection fails to identify any passage in Mosley that either explicitly or inherently teaches *human* antibodies having the properties recited in the rejected claims as herein amended.

Second, the rejection appears to acknowledge that Mosley does not *explicitly* disclose an antibody that competes against the recited reference antibody of the rejected claims for binding to human IL-4R. (The only two antibodies actually made and reported in Mosley are M1 and M2, which do not bind to human IL-4R and so cannot compete against the reference antibody as required by the rejected claims.) Instead, the rejection implies that if one made a new antibody according to the cited portions of Mosley, it would *inherently* have this property.

As the Federal Circuit has emphasized in *Continental Can* and other cases, a reference inherently discloses a claim limitation *only* if the limitation is *necessarily* present in the cited reference. The instant rejection fails to meet this standard for multiple reasons, any one of which is sufficient to establish that a *prima facie* rejection has not been made.

First, as acknowledged in the instant Office Action, Example 13 of Mosley teaches methods of making antibodies against murine *or* human IL-4R, so the skilled artisan is not *necessarily* led to make an anti-human IL-4R antibody. And, as the anti-murine IL-4R

antibodies M1 and M2 prove, an antibody against murine IL-4R will not *necessarily* bind to human IL-4R.

Second, even if the resulting antibody necessarily bound to human IL-4R, Example 13 provides several choices of antigens for making the antibody (e.g., purified recombinant antigen or antigen displayed on a cell surface). Some such antigens will include the extracellular portion of IL-4R, but others will not. And some antigens that include all or part of the extracellular domain will also include other parts of IL-4R. Consequently, an antibody made according to the disclosure of Mosley will not *necessarily* bind the extracellular domain of human IL-4R.

Third, many antigens of the types referred to by Mosley will comprise denatured or mis-folded IL-4R. Antibodies raised against such antigens will not *necessarily* bind to correctly folded IL-4R.

The antibodies referred to in the claims of Mosley do not overcome this deficiency. These too are prophetic antibodies, not antibodies that have actually been made. The claims recite antibodies that bind to polypeptides *comprising* certain sequences. It is not stated that the antibodies bind to those particular recited sequences. Thus, for example, an antibody that binds to the intracellular portion of full-length IL-4R will bind to a polypeptide "comprising" the IL-4R extracellular domain, as full-length IL-4R comprises both the extracellular and the intracellular domains. Such an antibody would not compete with the reference antibody of the rejected claims.

Fourth, the present rejection rests entirely on the assumption that any antibody that binds to the (properly folded) 207 amino acid fragment of IL-4R would *necessarily* compete for binding with the reference antibody recited in the rejected claims. Applicants respectfully disagree. The art is replete with examples of antibodies that bind a target of 207 amino acids or less but do not compete for binding to the target. Thus it cannot be concluded that an antibody made according to Mosley would *necessarily* compete for binding with the reference antibody of the rejected claims. Should this rejection be maintained, however, Applicants

respectfully request that either documentary evidence, under 37 CFR 1.104(c)(2), or an affidavit or declaration, under 37 CFR 1.104(d)(2), supporting the assumption be provided. See MPEP § 2144.03.

For completeness, Applicants also point out that the instant Office Action unfairly characterizes the disclosure of the abstract of Mosley. On page 7 of the instant Office Action, it is asserted that the abstract "teaches antibodies that are immunoreactive to human IL-4 receptor." In fact, the first sentence of Mosley's abstract refers to *"[m]ammalian* antibodies that are immunoreactive with Interleukin-4 receptor proteins, DNAs and expression vectors encoding *mammalian* IL-4 receptors, … as well as antibodies that are immunoreactive with IL-4 receptors." The second (and last) sentence of Mosley's abstract does not refer to antibodies at all. Thus, Mosley's abstract does not specifically disclose or suggest antibodies against a *human* anti-IL-4R.

CONCLUSION

Applicants respectfully request that the claims as presently pending be allowed. The Examiner is invited to call the undersigned attorney at (206) 265-8779 upon receipt and review of this Response to discuss any questions or concerns about the present response.

Respectfully submitted,

Nathan A. Machin
Attorney for Applicants
Registration No.: 47,763
Phone: (206) 265-8779
Date: October 14, 2011

Please send all future correspondence to:

22932

Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, Washington 98119-3105
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Filed via EFS-Web
October 14, 2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Richard J. Armitage et al.	Confirmation No.:	8151
Serial No.:	12/829,231	Group Art Unit No.:	1647
Filed:	July 1, 2010	Examiner:	HAMUD, Fozia M.
Title:	**ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES (as amended)**		
Docket No.:	3005-US-CNT3		

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

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

Examiner:

The owner, Immunex Corporation, of 100% interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 7,186,809 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successor or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

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

CERTIFICATE OF EFS-WEB TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted electronically through EFS-WEB to the Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450, on the date appearing below.

October 14, 2011	/Jae Cho/
Date	Signature

Further, the owner does not disclaim any extension of patent term under 35 U.S.C. § 156, which is granted on the instant application.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.*

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

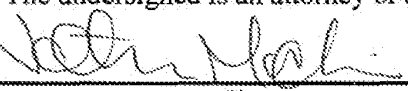
Signature Date

Typed or printed name

Title Telephone Number

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 47,763



October 14, 2011

Signature Date

Nathan A. Machin

Typed or printed name

(206) 265-8779

Telephone Number

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

Please send all future correspondence to:

CUSTOMER NO: 22932
Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, WA 98119-3105

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

22932 7590 07/14/2011

IMMUNEX CORPORATION
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SEATTLE, WA 98119

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
07/14/2011	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)
	12/829,231	ARMITAGE ET AL.
	Examiner	Art Unit
	FOZIA HAMUD	1647

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *03 May 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 20-35* is/are pending in the application.

4a) Of the above claim(s) *20-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2011* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/03/2011*.	6) ☐ Other: _____.

DETAILED ACTION

1a. Receipt of Applicants' amendment and arguments, filed on 03 May 2011is acknowledged.

Status of claims:

1b. Claims 1-16, 20-35 are pending of which claims 1-16 and 34-35 are drawn to the elected invention. Claims 20-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/21/2009.

Specification:

2a. The status of the parent non-provisional application No. 12/291,702 has been updated.

2b. The title of the invention has been changed.

Drawings:

2c. Replacement drawings have been received on 03 May 2011 and are acceptable.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 03 May 2011 has been received and complies with the provisions of 37 CFR §§1.97 and 1.98. The references have been considered as to the merits.

Response to Applicant's Argument:

4. The following rejections are withdrawn in light of Applicants' arguments:

I. The rejections of 1-9, 11-16, 34, and 35 made under 35 U.S.C. 102(b), as being anticipated by Beckmann et al, (Journal of Immunology, 1990, Vol. 144, No. 11, pages 4212-4217), is withdrawn. Applicants' argument that Beckman et al reference teaches two antibodies, M 1 and M2, neither of which binds to human IL-4 receptor, has been found persuasive. Thus, the claimed antibody competes with a reference antibody for binding to human IL-4 receptor, however, the antibodies of Beckmann et al would not be expected to bind to human IL-4 receptor.

Claim Objections:

5. Claims 1-7 stand objected to because of the following informalities:

5a. Claims 1-7 recite ".....IL-4 or IL-13", however, it is suggested that "interleukin 4 or interleukin 13 ", be recited in front of the first independent claim wherein each acronym is recited. Applicants did not address this objection in the response filed on 03 may 2011.

Claim rejections- Obviousness-type Double patenting:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-16 and 34-35 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8-13, of U.S. Patent No. 7,186,809.

The terminal disclaimer (TD) filed on 03 May 2011 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. patent 7,186,809 has been reviewed and is NOT accepted. On page 2, the 1st paragraph contains indefinite language. Please refer to the form at the end of MPEP Chapter 1400 or the form paragraphs in 1490, or utilize language that is clear and complies with the TD rule.

Claim rejections-35 USC § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-16, 34, 35 stand rejected under 35 U.S.C. 102(b), as being anticipated by Mosley et al, U.S. Patent No. 5,717,072, (issued on 10 February 1998; cited in the IDS of 07/01/2010).

Claims 1-16 are drawn to an isolated antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein the reference antibody comprises the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor, said isolated antibody that is a human antibody, wherein the isolated antibody inhibits human IL-4 signaling through human IL-4 receptor, wherein the antibody is humanized, is full length or fragment thereof, wherein the antibody has specific binding affinity, (claims 8-10) or is a composition comprising a buffer, (claim 34) or isolated, (claim 35).

Mosley et al teach an isolated human antibody that binds to human IL-4 receptor, said antibody that is an IgE, Ig1, and fragments of said antibody and inhibits IL-4 mediated activities, (see abstract, column 5, lines 10-28 and claims). Mosley et al disclose that their antibody binds to human cells that express IL-4 receptor and inhibits IL-4 binding to cytotoxic T lymphocyte lines, (CTLL, transfected with IL-4 receptor), (see column 2, lines 56-66 and Example 13).

Thus, the antibody disclosed in the Mosley et al reference meets all the limitations recited in instant claims 1-4, 6, and 12-16, because the antibody of Mosley et al. can compete with the recited antibody, inhibits binding of IL-4 to IL-4 receptor, and is an IgG1. Since the antibody of Mosley et al competes with the reference antibody, each antibody would inherently inhibit the binding of the other with IL-4 receptor, (claims 2-3). With respect to claims 4 and 6, since the antibody taught by Mosley et al. binds to human IL-4 receptor and inhibits IL-4 binding to IL-4 receptor, it would also inherently

inhibit IL-4 signaling through IL-4 receptor. Regarding claims 8-10, the antibody of Mosley et al. would be expected to display said binding affinities, since it was shown to bind to IL-4 receptor, (see column 33, line 65 to column 34, line 10). Regarding claims 34-35, Mosley et al. teach that their antibody is in a buffer solution thus meeting the limitation recited in claim 34 and is isolated, meeting the limitation of claim 35, (see column 34, lines 4-10 and claims).

Thus, the Mosley et al reference anticipates instant claims 1-16, 34, and 35 in the absence of any evidence on the contrary.

Response to Applicants' arguments:

Applicants point out that Mosley et al do not provide an anticipating description of the claimed subject matter. Applicants submit that the abstract of Mosley refers generally to "antibodies that are immunoreactive with IL-4 receptors," and does not refer specifically to anti-human IL-4 receptor antibodies, or to antibodies that inhibit an IL-4 mediated activity, much less to anti-human IL-4 receptor antibodies with the recited properties of the claimed antibodies. Applicants argue that lines 10-28 of column 5 of Mosley et al do not mention anti IL-4 receptor antibodies and lines 14-22 identify "secretion and expression of antibodies of the IgE and IgG1 isotype" as an IL-4 mediated biological response, but these are not stated or implied to be anti-IL-4 receptor antibodies. Applicants submit that the claims of Mosley et al recite antibodies that are immunoreactive with either human or murine IL-4 receptor and no further binding characteristics of the claimed antibodies are provided. Applicants argue that while some of the claims identify specific IL-4 receptor sequences (the smallest of

which are over two hundred amino acids in length), the claims do not require the claimed antibodies to bind to these specific sequences. Applicants submit that Mosley et al. teach that the antibodies, M1 and M2, are capable of immunoprecipitating native mIL-4R protein from CTLL cells or COS-7 cells transfected with IL-4R clones (column 24, lines 1-3). Hence, it is clear that the M1 and M2 antibodies bind mIL-4.

These arguments have been fully considered, but are not deemed persuasive. The Mosley et al reference teaches antibodies that are immunoreactive to human IL-4 receptor, (see abstract). Although the Mosley et al reference does not recite an antibody that "binds", it is understood in the art that an antibody that is immunoreactive, means that said antibody binds to the recited antigen, in the instant case IL-4R. Furthermore, Mosley et al. discloses that preparations of purified recombinant IL-4 receptor, for example, human or murine IL-4 receptor, transfected COS cells expressing high levels of IL-4 receptor or CTLL 19.4 cells are employed to generate monoclonal antibodies against IL-4 receptor and that such antibodies are useful in interfering with IL-4 binding to IL-4 receptors (column 33, lines 31-38). The instant claims are drawn to an antibody that competes with a reference antibody that is comprised of the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12. The instant specification describes that antibody 12B5 comprises the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12, (see page 31, lines 20-33). The specification further teaches that the 12B5 antibody binds to human soluble IL-4R that comprises the extracellular domain of human IL-4R, (see page 60, lines 14-27). The instant specification teaches that human soluble IL-4R is comprised of amino acids 1 to 207, (see page 18, lines 33 to page 19,

lines 2). Mosley et al teach an antibody that is immunoreactive, (i.e. binds) to amino acids 1-207 of human IL-4R, (see claims). Thus, the antibody of Mosley et al would compete with the reference antibody recited in the instant claims, since both antibodies bind to the same epitope of human IL-4R.

Applicants argue that Mosley et al describe the transformation of COS cells with murine, not human, IL-4 receptor. Anti-IL-4 receptor antibodies (either anti-human or anti-murine) are not mentioned. The K_a values appear to be for IL-4 ligand binding to the transformed cells, not antibodies. Applicants submit that the first paragraph of Example 13 provides a brief, prophetic method for generating anti-murine or anti-human IL-4 receptor antibodies. Applicants argue that the second and third paragraphs describe how certain anti-murine IL-4 receptor antibodies were isolated. Applicants submit that as described in Example 2 of Mosley, CTLL 19.4 cells were derived from CTLL cells, which are murine cells expressing murine IL-4 receptor and two anti-murine IL-4 receptor antibodies were generated, M1 and M2. These were shown to bind murine IL-4 receptor, but only M1 was able to inhibit murine IL-4 ligand from binding to murine IL-4 receptor. Applicants argue that a careful reading of the cited portions of Mosley reveals that they (individually or collectively) do not teach "each and every element" as set forth in any of the rejected claims, and so cannot support the instant rejection. Applicants conclude that there is no support for a primafacie rejection because the rejection only assumes that "the antibody" of Mosley (whichever antibody that might refer to) competes for binding against the antibodies in the rejected claims.

These arguments have been considered, but are not deemed persuasive. Example 13 of Mosley et al reference teaches methods for generating anti-murine or anti-human IL-4 receptor antibodies. It is not disputed that the Mosley et al reference does teach two anti-murine IL-4 receptor antibodies were generated, M1 and M2. However, the Mosley et al reference teaches the human IL-4 receptor (see example 11), and an antibody that is immunoreactive with said receptor, (see claims). The antibody of Mosley et al binds human IL-4, and thus would be expected to compete with the reference antibody recited in the instant claims, since both antibodies bind to the same epitope of human IL-4R.

Conclusion:

8. No claim is allowed.

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

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

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery J. Stucker can be reached on (571) 272-0911. 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.

Fozia Hamud
Patent Examiner
Art Unit 1647
10 July 2011

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/829,231	ARMITAGE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 5/3/11	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

On page 2, the 1st paragraph contains indefinite language. Refer to form at the end of Chapter 1400 or the form paragraphs in 1490, or language that is clear and complies with the TD rule.

U.S. Patent and Trademark Office

VIA EFS-Web
May 3, 2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Richard J. Armitage et al.	**Docket No.**:	3005-US-CNT3
Serial No.:	**12/829,231**	**Confirmation No.**:	8151
Filing Date:	**July 1, 2010**	**Examiner**:	HAMUD, Fozia M.

Title: **ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES (as amended)**

RESPONSE TO OFFICE ACTION

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

Sir:

In response to the Non-final Office Action mailed February 3, 2011, please consider the following election and remarks. Also enclosed herewith are a Terminal Disclaimer, an Information Disclosure Statement by Applicant, and replacement drawings, with appropriate fees.

The Director is hereby authorized to charge any additional fees which may be required by the accompanying papers, or credit any overpayment to Deposit Account No. 09-0089.

CERTIFICATE OF EFS-Web TRANSMISSION
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/	May 3, 2011
Jae Cho	Date

Amendment to the Specification

Please replace the title with the following new title:

~~**USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF**~~
ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES

Please replace the paragraph starting at page 1, line 5, with the following:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of US Application Serial No. 12/291,702, filed November 13, 2008, now ~~allowed~~ abandoned, which is a continuation of US Application Serial No. 11/588,696, filed October 27, 2006, now US Patent No. 7,465,450, which is a divisional of US Application Serial No. 10/324,493, filed December 19, 2002, now US Patent 7,186,809, which is a continuation of US Application Serial No. 09/847,816, filed May 1, 2001, abandoned. The above-identified applications are incorporated herein by reference.

Replacement Drawings

Replacement drawings in compliance with 37 CFR 1.121(d) are enclosed herewith.

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

Listing of the Claims

What is claimed is:

1. (Previously Presented) An isolated antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12

2. (Original) The isolated antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. (Original) The isolated antibody of Claim 1, wherein when said isolated antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-13 to human IL-4 receptor.

6. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^8.

9. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^9.

10. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^{10}.

11. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a human, partially human, humanized, or chimeric antibody.

12. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a full-length antibody.

13. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a fragment of an antibody.

15. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a fusion protein.

16. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a single chain antibody (scFv).

17. – 19. (Cancelled)

20. (Withdrawn) An isolated nucleic acid, wherein said isolated nucleic acid comprises a sequence encoding:

a. the light chain variable domain of said isolated antibody of Claim 1; or

b. the heavy chain variable domain of said isolated antibody of Claim 1; or

c. the light chain variable domain of said isolated antibody of Claim 1 and the heavy chain variable domain of said isolated antibody of Claim 1.

21. (Withdrawn) A vector, wherein said vector comprises said isolated nucleic acid of Claim 20.

22. (Withdrawn) The vector of Claim 21, wherein said vector is an expression vector.

23. (Withdrawn) An isolated cell, wherein said cell comprises said isolated nucleic acid of Claim 20.

24. (Withdrawn) The isolated cell of Claim 23, wherein said isolated cell expresses said isolated antibody.

25. (Withdrawn) A method of reducing IL-4 receptor-dependent signaling in a subject, comprising administering to said subject an effective amount of said isolated antibody of Claim 1.

26. (Withdrawn) The method of Claim 25, wherein said method suppresses a T_H2-type immune response.

27. (Withdrawn) The method of Claim 25, wherein said subject has, or is at risk of developing, a condition responsive to inhibition of IL-4R signaling.

28. (Withdrawn) The method of Claim 27, wherein said condition is an inflammatory condition.

29. (Withdrawn) The method of Claim 27, wherein said condition is an IgE mediated condition.

30. (Withdrawn) The method of Claim 27, wherein said condition is an allergic condition.

31. (Withdrawn) The method of Claim 27, wherein said condition is a condition in which IL-4 mediated epithelial barrier disruption plays a role.

32. (Withdrawn) The method of Claim 27, wherein said condition is asthma, COPD, pulmonary fibrosis, or septic arthritis.

33. (Withdrawn) A method of making an antibody, comprising incubating said cell of Claim 23 under conditions that allow it to express said isolated antibody.

34. (Original) A composition comprising said isolated antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. (Original) A kit comprising said isolated antibody of Claim 1.

REMARKS

Amendments to the Specification

The status of parent non-provisional application No 12/291,702 has been updated and the title has been changed by amendment of the Specification as requested.

Applicants respectfully request that the objected-to drawings be replaced with the replacement drawings provided herewith.

Rejections

Obviousness-Type Double Patenting

Claims 1-16, 34 and 35 are rejected on the grounds of nonstatutory obviousness-type double patenting over claims 1-3 and 8-13 of US Pat. No. 7,186,809.

Without agreeing with the propriety of this rejection, and solely in order to expedite prosecution, Applicants provide herewith a terminal disclaimer of the instant Application over US Pat. No. 7,186,809. Consequently, Applicants respectfully request that the instant rejection be withdrawn.

35 USC §102(b)

Claims 1-16, 34 and 35 are rejected under 35 USC 102(b) as allegedly anticipated by US Patent No. 5,717,072 ("Mosley"). As a *prima facie* case has not been advanced, Applicants respectfully traverse.

A claim is anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). See also *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

It is asserted that Mosley teaches an isolated human antibody that binds to human IL-4 receptor and "IgE, Ig1, and fragments of said antibody and inhibits IL-4 mediated activities" in its abstract, at column 5, lines 10-28, and in its claims. Applicants respectfully point out that the cited passages of Mosley, alone or in combination, do not provide an anticipating description of the claimed subject matter.

The abstract of Mosley refers generally to "antibodies that are immunoreactive with IL-4 receptors." It does not refer specifically to anti-*human* IL-4 receptor antibodies, or to antibodies that inhibit an IL-4 mediated activity, much less to anti-human IL-4 receptor antibodies with the recited properties of the claimed antibodies.

Lines 10-28 of column 5 of Mosely do not mention anti-IL-4 receptor antibodies. Lines 14-22 identify "secretion and expression of antibodies of the IgE and IgG1 isotype" as an IL-4 mediated biological response, but these are not stated or implied to be anti-IL-4 receptor antibodies.

The claims of Mosely recite antibodies that are immunoreactive with either human or murine IL-4 receptor. No further binding characteristics of the claimed antibodies are provided. Note that while some of the claims identify specific IL-4 receptor sequences (the smallest of which are over two hundred amino acids in length), the claims do not require the claimed antibodies to bind to these specific sequences.

It is further asserted that Mosely discloses an antibody that "binds to human cells that express IL-4 receptor and inhibits IL-4 binding to cytotoxic T lymphocyte lines" at column 2, lines 56-66 and in Example 13. (Office Action, page 7.) Applicants respectfully point out that this is incorrect.

Lines 56-66 of column 2 describe the transformation of COS cells with *murine*, not human, IL-4 receptor. Anti-IL-4 receptor antibodies (either anti-human or anti-murine) are not mentioned. The K_a values appear to be for IL-4 ligand binding to the transformed cells, not antibodies.

The first paragraph of Example 13 provides a brief, prophetic method for generating anti-murine or anti-human IL-4 receptor antibodies. The second and third paragraphs describe how certain anti-*murine* IL-4 receptor antibodies were isolated. At column 33, lines 39-42, it is stated that CTLL 19.4 cells were used to immunize rats. As described in Example 2 of Mosley, CTLL 19.4 cells were derived from CTLL cells, which are *murine* cells expressing *murine* IL-4 receptor. Two anti-murine IL-4 receptor antibodies were generated, M1 and M2. These were shown to bind *murine* IL-4 receptor, but only M1 was able to inhibit murine IL-4 ligand from binding to murine IL-4 receptor (see Mosley, col. 33, line 64 through col. 34, line 4). Note also that M1 and M2 were also described in Beckmann et al. (1990) J. Immunol. 144:4212-17, discussed below, which states that "[w]e have tested the M1 and M2 antibodies on various human cell lines and have confirmed their inability to recognize the *human* IL-4R." (id. at page 4216; emphasis added.)

Thus, a careful reading of the cited portions of Mosley reveals that they (individually or collectively) do not teach "each and every element" as set forth in any of the rejected claims, and so cannot support the instant rejection.

The rejection concludes "[t]hus, the antibody disclosed in [Mosley] meets all the limitations recited in [the rejected claims] *because the antibody ... can compete with the recited antibody* []. Since *the antibody of Mosley ... competes with the reference antibody*, each antibody would inherently inhibit the binding of the other with IL-4 receptor []." (Office Action, pages 7-8; emphasis added).

This argument cannot support a *prima facie* rejection because it only *assumes* that "the antibody" of Mosley (whichever antibody that might refer to) competes for binding against the antibodies in the rejected claims. This assertion must be proved in order to support the rejection. As the foregoing analysis of the cited passages of Mosley show, this has not been done.

Thus, a *prima facie* case of anticipation has not been made against the rejected claims. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

Claims 1-9, 11-16, 34 and 35 are rejected under 35 USC 102(b) as allegedly anticipated by Beckmann et al. (1990) J. Immunol. 144:4212-17 ("Beckmann"). As a *prima facie* case of anticipation has not been made, Applicants respectfully traverse.

It is asserted that Beckmann teaches an isolated antibody that binds to human IL-4 receptor. This is incorrect. Beckmann actually teaches two antibodies, M1 and M2, neither of which binds to human IL-4 receptor. Beckmann states this explicitly: "We have tested the M1 and M2 antibodies on various human cell lines and have confirmed their inability to recognize the human IL-4R." (Beckmann at page 4216, first full paragraph.) This is consistent with the data in Figure 2, as the CTLL-2 cell line is a *murine* cell line, not a human cell line. ("Mosley et al. described the generation of a subclone of *the murine T cell line CTLL-2* which expressed high levels of IL-4R []" (Beckman at page 4212, first column, last paragraph; citation omitted; emphasis added); "[t]he *murine T-cell line CTLL-2* (ATCC TIB 214) …" (id., first column, first full paragraph; citation omitted; emphasis added.)

As the antibodies of Beckmann do not bind human IL-4 receptor, it follows that they cannot compete with the recited reference antibody for binding to human IL-4 receptor. Thus, a *prima facie* case of anticipation has not been made against the rejected claims. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the claims as presently pending be allowed. The Examiner is invited to call the undersigned attorney at (206) 265-8779 upon receipt and review of this Response to discuss any questions or concerns about the present response.

Respectfully submitted,

Nathan A. Machin
Attorney for Applicants
Registration No.: 47,763
Phone: (206) 265-8779
Date: May 3, 2011

Please send all future correspondence to:

22932

Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, Washington 98119-3105
(206) 265-7000

FIGURE 1A

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ATG GGG TGG CTT TGC TCT GGG CTC CTG TTC CCT GTG AGC TGC CTG -31
Met Gly Trp Leu Cys Ser Gly Leu Leu Phe Pro Val Ser Cys Leu -11

GTC CTG CTG CAG GTG GCA AGC TCT GGG AAC ATG AAG GTC TTG CAG  15
Val Leu Leu Gln Val Ala Ser Ser Gly Asn Met Lys Val Leu Gln   5

GAG CCC ACC TGC GTC TCC GAC TAC ATG AGC ATC TCT ACT TGC GAG  60
Glu Pro Thr Cys Val Ser Asp Tyr Met Ser Ile Ser Thr Cys Glu  20

TGG AAG ATG AAT GGT CCC ACC AAT TGC AGC ACC GAG CTC CGC CTG 105
Trp Lys Met Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu  35

TTG TAC CAG CTG GTT TTT CTG CTC TCC GAA GCC CAC ACG TGT ATC 150
Leu Tyr Gln Leu Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile  50

CCT GAG AAC AAC GGA GGC GCG GGG TGC GTG TGC CAC CTG CTC ATG 195
Pro Glu Asn Asn Gly Gly Ala Gly Cys Val Cys His Leu Leu Met  65

GAT GAC GTG GTC AGT GCG GAT AAC TAT ACA CTG GAC CTG TGG GCT 240
Asp Asp Val Val Ser Ala Asp Asn Tyr Thr Leu Asp Leu Trp Ala  80

GGG CAG CAG CTG CTG TGG AAG GGC TCC TTC AAG CCC AGC GAG CAT 285
Gly Gln Gln Leu Leu Trp Lys Gly Ser Phe Lys Pro Ser Glu His  95

GTG AAA CCC AGG GCC CCA GGA AAC CTG ACA GTT CAC ACC AAT GTC 330
Val Lys Pro Arg Ala Pro Gly Asn Leu Thr Val His Thr Asn Val 110

TCC GAC ACT CTG CTG CTG ACC TGG AGC AAC CCG TAT CCC CCT GAC 375
Ser Asp Thr Leu Leu Leu Thr Trp Ser Asn Pro Tyr Pro Pro Asp 125

AAT TAC CTG TAT AAT CAT CTC ACC TAT GCA GTC AAC ATT TGG AGT 420
Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala Val Asn Ile Trp Ser 140

GAA AAC GAC CCG GCA GAT TTC AGA ATC TAT AAC GTG ACC TAC CTA 465
Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn Val Thr Tyr Leu 155

GAA CCC TCC CTC CGC ATC GCA GCC AGC ACC CTG AAG TCT GGG ATT 510
Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys Ser Gly Ile 170

TCC TAC AGG GCA CGG GTG AGG GCC TGG GCT CAG TGC TAT AAC ACC 555
Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr Asn Thr 185

ACC TGG AGT GAG TGG AGC CCC AGC ACC AAG TGG CAC AAC TCC TAC 600
Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser Tyr 200

AGG GAG CCC TTC GAG CAG CAC CTC CTG CTG GGC GTC AGC GTT TCC 645
Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser 215

TGC ATT GTC ATC CTG GCC GTC TGC CTG TTG TGC TAT GTC AGC ATC 690
Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile 230

ACC AAG ATT AAG AAA GAA TGG TGG GAT CAG ATT CCC AAC CCA GCC 735
Thr Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala 245
```

FIGURE 1B

```
CGC AGC CGC CTC GTG GCT ATA ATA ATC CAG GAT GCT CAG GGG TCA  780
Arg Ser Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser  260

CAG TGG GAG AAG CGG TCC CGA GGC CAG GAA CCA GCC AAG TGC CCA  825
Gln Trp Glu Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro  275

CAC TGG AAG AAT TGT CTT ACC AAG CTC TTG CCC TGT TTT CTG GAG  870
His Trp Lys Asn Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu  290

CAC AAC ATG AAA AGG GAT GAA GAT CCT CAC AAG GCT GCC AAA GAG  915
His Asn Met Lys Arg Asp Glu Asp Pro His Lys Ala Ala Lys Glu  305

ATG CCT TTC CAG GGC TCT GGA AAA TCA GCA TGG TGC CCA GTG GAG  960
Met Pro Phe Gln Gly Ser Gly Lys Ser Ala Trp Cys Pro Val Glu  320

ATC AGC AAG ACA GTC CTC TGG CCA GAG AGC ATC AGC GTG GTG CGA 1005
Ile Ser Lys Thr Val Leu Trp Pro Glu Ser Ile Ser Val Val Arg  335

TGT GTG GAG TTG TTT GAG GCC CCG GTG GAG TGT GAG GAG GAG GAG 1050
Cys Val Glu Leu Phe Glu Ala Pro Val Glu Cys Glu Glu Glu Glu  350

GAG GTA GAG GAA GAA AAA GGG AGC TTC TGT GCA TCG CCT GAG AGC 1095
Glu Val Glu Glu Glu Lys Gly Ser Phe Cys Ala Ser Pro Glu Ser  365

AGC AGG GAT GAC TTC CAG GAG GGA AGG GAG GGC ATT GTG GCC CGG 1140
Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu Gly Ile Val Ala Arg  380

CTA ACA GAG AGC CTG TTC CTG GAC CTG CTC GGA GAG GAG AAT GGG 1185
Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly Glu Glu Asn Gly  395

GGC TTT TGC CAG CAG GAC ATG GGG GAG TCA TGC CTT CTT CCA CCT 1230
Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu Leu Pro Pro  410

TCG GGA AGT ACG AGT GCT CAC ATG CCC TGG GAT GAG TTC CCA AGT 1275
Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe Pro Ser  425

GCA GGG CCC AAG GAG GCA CCT CCC TGG GGC AAG GAG CAG CCT CTC 1320
Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro Leu  440

CAC CTG GAG CCA AGT CCT CCT GCC AGC CCG ACC CAG AGT CCA GAC 1365
His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Asp  455

AAC CTG ACT TGC ACA GAG ACG CCC CTC GTC ATC GCA GGC AAC CCT 1410
Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro  470

GCT TAC CGC AGC TTC AGC AAC TCC CTG AGC CAG TCA CCG TGT CCC 1455
Ala Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro  485

AGA GAG CTG GGT CCA GAC CCA CTG CTG GCC AGA CAC CTG GAG GAA 1500
Arg Glu Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Glu  500

GTA GAA CCC GAG ATG CCC TGT GTC CCC CAG CTC TCT GAG CCA ACC 1545
Val Glu Pro Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr  515
```

FIGURE 1C

```
ACT GTG CCC CAA CCT GAG CCA GAA ACC TGG GAG CAG ATC CTC CGC 1590
Thr Val Pro Gln Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg  530

CGA AAT GTC CTC CAG CAT GGG GCA GCT GCA GCC CCC GTC TCG GCC 1635
Arg Asn Val Leu Gln His Gly Ala Ala Ala Ala Pro Val Ser Ala  545

CCC ACC AGT GGC TAT CAG GAG TTT GTA CAT GCG GTG GAG CAG GGT 1680
Pro Thr Ser Gly Tyr Gln Glu Phe Val His Ala Val Glu Gln Gly  560

GGC ACC CAG GCC AGT GCG GTG GTG GGC TTG GGT CCC CCA GGA GAG 1725
Gly Thr Gln Ala Ser Ala Val Val Gly Leu Gly Pro Pro Gly Glu  575

GCT GGT TAC AAG GCC TTC TCA AGC CTG CTT GCC AGC AGT GCT GTG 1770
Ala Gly Tyr Lys Ala Phe Ser Ser Leu Leu Ala Ser Ser Ala Val  590

TCC CCA GAG AAA TGT GGG TTT GGG GCT AGC AGT GGG GAA GAG GGG 1815
Ser Pro Glu Lys Cys Gly Phe Gly Ala Ser Ser Gly Glu Glu Gly  605

TAT AAG CCT TTC CAA GAC CTC ATT CCT GGC TGC CCT GGG GAC CCT 1860
Tyr Lys Pro Phe Gln Asp Leu Ile Pro Gly Cys Pro Gly Asp Pro  620

GCC CCA GTC CCT GTC CCC TTG TTC ACC TTT GGA CTG GAC AGG GAG 1905
Ala Pro Val Pro Val Pro Leu Phe Thr Phe Gly Leu Asp Arg Glu  635

CCA CCT CGC AGT CCG CAG AGC TCA CAT CTC CCA AGC AGC TCC CCA 1950
Pro Pro Arg Ser Pro Gln Ser Ser His Leu Pro Ser Ser Ser Pro  650

GAG CAC CTG GGT CTG GAG CCG GGG GAA AAG GTA GAG GAC ATG CCA 1995
Glu His Leu Gly Leu Glu Pro Gly Glu Lys Val Glu Asp Met Pro  665

AAG CCC CCA CTT CCC CAG GAG CAG GCC ACA GAC CCC CTT GTG GAC 2040
Lys Pro Pro Leu Pro Gln Glu Gln Ala Thr Asp Pro Leu Val Asp  680

AGC CTG GGC AGT GGC ATT GTC TAC TCA GCC CTT ACC TGC CAC CTG 2085
Ser Leu Gly Ser Gly Ile Val Tyr Ser Ala Leu Thr Cys His Leu  695

TGC GGC CAC CTG AAA CAG TGT CAT GGC CAG GAG GAT GGT GGC CAG 2130
Cys Gly His Leu Lys Gln Cys His Gly Gln Glu Asp Gly Gly Gln  710

ACC CCT GTC ATG GCC AGT CCT TGC TGT GGC TGC TGC TGT GGA GAC 2175
Thr Pro Val Met Ala Ser Pro Cys Cys Gly Cys Cys Cys Gly Asp  725

AGG TCC TCG CCC CCT ACA ACC CCC CTG AGG GCC CCA GAC CCC TCT 2220
Arg Ser Ser Pro Pro Thr Thr Pro Leu Arg Ala Pro Asp Pro Ser  740

CCA GGT GGG GTT CCA CTG GAG GCC AGT CTG TGT CCG GCC TCC CTG 2265
Pro Gly Gly Val Pro Leu Glu Ala Ser Leu Cys Pro Ala Ser Leu  755

GCA CCC TCG GGC ATC TCA GAG AAG AGT AAA TCC TCA TCA TCC TTC 2310
Ala Pro Ser Gly Ile Ser Glu Lys Ser Lys Ser Ser Ser Ser Phe  770

CAT CCT GCC CCT GGC AAT GCT CAG AGC TCA AGC CAG ACC CCC AAA 2355
His Pro Ala Pro Gly Asn Ala Gln Ser Ser Ser Gln Thr Pro Lys  785

ATC GTG AAC TTT GTC TCC GTG GGA CCC ACA TAC ATG AGG GTC TCT 2400
Ile Val Asn Phe Val Ser Val Gly Pro Thr Tyr Met Arg Val Ser  800
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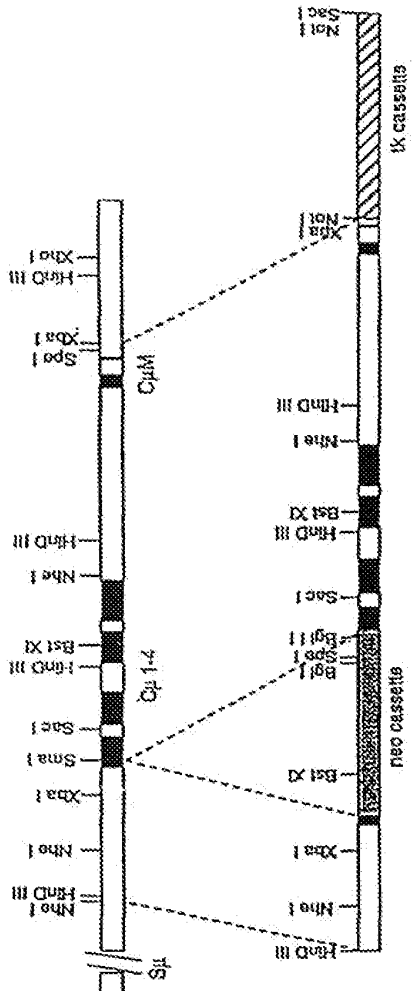


FIGURE 2A

FIGURE 2B

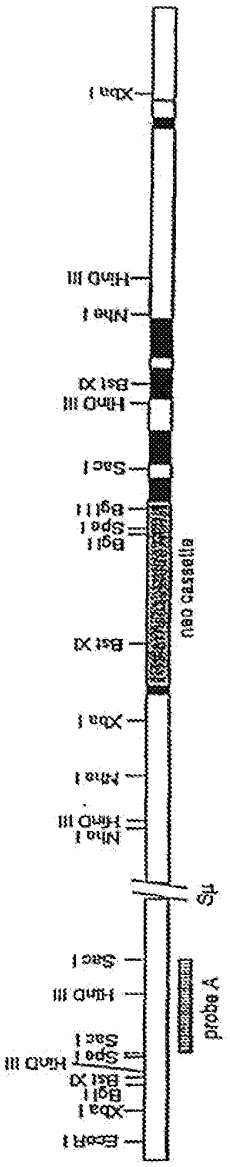


FIGURE 2C

FIGURE 3A

```
AATTAGCGGC CGCTGTCGAC AAGCTTCGAA TTCAGTATCG ATGTGGGGTA   50
CCTACTGTCC CGGGATTGCG GATCCGCGAT GATATCGTTG ATCCTCGAGT  100
GCGGCCGCAG TATGCAAAAA AAAGCCCGCT CATTAGGCGG GCTCTTGGCA  150
GAACATATCC ATCGCGTCCG CCATCTCCAG CAGCCGCACG CGGCGCATCT  200
CGGGCAGCGT TGGGTCCTGG CCACGGGTGC GCATGATCGT GCTCCTGTCG  250
TTGAGGACCC GGCTAGGCTG GCGGGGTTGC CTTACTGGTT AGCAGAATGA  300
ATCACCGATA CGCGAGCGAA CGTGAAGCGA CTGCTGCTGC AAAACGTCTG  350
CGACCTGAGC AACAACATGA ATGGTCTTCG GTTTCCGTGT TTCGTAAAGT  400
CTGGAAACGC GGAAGTCAGC GCCCTGCACC ATTATGTTCC GGATCTGCAT  450
CGCAGGATGC TGCTGGCTAC CCTGTGGAAC ACCTACATCT GTATTAACGA  500
AGCGCTGGCA TTGACCCTGA GTGATTTTTC TCTGGTCCCG CCGCATCCAT  550
ACCGCCAGTT GTTTACCCTC ACAACGTTCC AGTAACCGGG CATGTTCATC  600
ATCAGTAACC CGTATCGTGA GCATCCTCTC TCGTTTCATC GGTATCATTA  650
CCCCCATGAA CAGAAATTCC CCCTTACACG GAGGCATCAA GTGACCAAAC  700
AGGAAAAAAC CGCCCTTAAC ATGGCCCGCT TTATCAGAAG CCAGACATTA  750
ACGCTTCTGG AGAAACTCAA CGAGCTGGAC GCGGATGAAC AGGCAGACAT  800
CTGTGAATCG CTTCACGACC ACGCTGATGA GCTTTACCGC AGCTGCCTCG  850
CGCGTTTCGG TGATGACGGT GAAAACCTCT GACACATGCA GCTCCCGGAG  900
ACGGTCACAG CTTGTCTGTA AGCGGATGCC GGGAGCAGAC AAGCCCGTCA  950
GGGCGCGTCA GCGGGTGTTG GCGGGTGTCG GGGCGCAGCC ATGACCCAGT 1000
CACGTAGCGA TAGCGGAGTG TATACTGGCT TAACTATGCG GCATCAGAG  1050
AGATTGTACT GAGAGTGCAC CATATGCGGT GTGAAATACC GCACAGATGC 1100
GTAAGGAGAA AATACCGCAT CAGGCGCTCT TCCGCTTCCT CGCTCACTGA 1150
CTCGCTGCGC TCGGTCGTTC GGCTGCGGCG AGCGGTATCA GCTCACTCAA 1200
AGGCGGTAAT ACGGTTATCC ACAGAATCAG GGGATAACGC AGGAAAGAAC 1250
ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG AACCGTAAAA AGGCCGCGTT 1300
GCTGGCGTTT TTCCATAGGC TCCGCCCCCC TGACGAGCAT CACAAAAATC 1350
GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAG 1400
GCGTTTCCCC CTGGAAGCTC CCTCGTGCGC TCTCCTGTTC CGACCCTGCC 1450
GCTTACCGGA TACCTGTCCG CCTTTCTCCC TTCGGGAAGC GTGGCGCTTT 1500
CTCATAGCTC ACGCTGTAGG TATCTCAGTT CGGTGTAGGT CGTTCGCTCC 1550
AAGCTGGGCT GTGTGCACGA ACCCCCCGTT CAGCCCGACC GCTGCGCCTT 1600
ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC GACTTATCGC 1650
CACTGGCAGC AGCCAGGCGC GCCTTGGCCT AAGAGGCCAC TGGTAACAGG 1700
ATTAGCAGAG CGAGGTATGT AGGCGGTGCT ACAGAGTTCT TGAAGTGGTG 1750
GCCTAACTAC GGCTACACTA GAAGGACAGT ATTTGGTATC TGCGCTCTGC 1800
TGAAGCCAGT TACCTTCGGA AAAAGAGTTG GTAGCTCTTG ATCCGGCAAA 1850
CAAACCACCG CTGGTAGCGG TGGTTTTTTT GTTTGCAAGC AGCAGATTAC 1900
GCGCAGAAAA AAAGGATCTC AAGAAGATCC TTTGATCTTT TCTACGGGGT 1950
CTGACGCTCA GTGGAACGAA AACTCACGTT AAGGGATTTT GGTCATGAGA 2000
TTATCAAAAA GGATCTTCAC CTAGATCCTT TTAAATTAAA AATGAAGTTT 2050
TAAATCAATC TAAAGTATAT ATGAGTAAAC TTGGTCTGAC AGTTACCAAT 2100
GCTTAATCAG TGAGGCACCT ATCTCAGCGA TCTGTCTATT TCGTTCATCC 2150
ATAGTTGCCT GACTCCCCGT CGTGTAGATA ACTACGATAC GGGAGGGCTT 2200
ACCATCTGGC CCCAGTGCTG CAATGATACC GCGAGACCCA CGCTCACCGG 2250
CTCCAGATTT ATCAGCAATA AACCAGCCAG CCGGAAGGGC CGAGCGCAGA 2300
AGTGGTCCTG CAACTTTATC CGCCTCCATC CAGTCTATTA ATTGTTGCCG 2350
GGAAGCTAGA GTAAGTAGTT CGCCAGTTAA TAGTTTGCGC AACGTTGTTG 2400
```

FIGURE 3B

```
CCATTGCTGC AGGCATCGTG GTGTCACGCT CGTCGTTTGG TATGGCTTCA 2450
TTCAGCTCCG GTTCCCAACG ATCAAGGCGA GTTACATGAT CCCCCATGTT 2500
GTGCAAAAAA GCGGTTAGCT CCTTCGGTCC TCCGATCGTT GTCAGAAGTA 2550
AGTTGGCCGC AGTGTTATCA CTCATGGTTA TGGCAGCACT GCATAATTCT 2600
CTTACTGTCA TGCCATCCGT AAGATGCTTT TCTGTGACTG GTGAGTACTC 2650
AACCAAGTCA TTCTGAGAAT AGTGTATGCG GCGACCGAGT TGCTCTTGCC 2700
CGGCGTCAAC ACGGGATAAT ACCGCGCCAC ATAGCAGAAC TTTAAAAGTG 2750
CTCATCATTG GAAAACGTTC TTCGGGGCGA AAACTCTCAA GGATCTTACC 2800
GCTGTTGAGA TCCAGTTCGA TGTAACCCAC TCGTGCACCC AACTGATCTT 2850
CAGCATCTTT TACTTTCACC AGCGTTTCTG GGTGAGCAAA AACAGGAAGG 2900
CAAAATGCCG CAAAAAAGGG AATAAGGGCG ACACGGAAAT GTTGAATACT 2950
CATACTCTTC CTTTTTCAAT ATTATTGAAG CATTTATCAG GGTTATTGTC 3000
TCATGAGCGG ATACATATTT GAATGTATTT AGAAAAATAA ACAAATAGGG 3050
GTTCCGCGCA CATTTCCCCG AAAAGTGCCA CCTGACGTCT AAGAAACCAT 3100
TATTATCATG ACATTAACCT ATAAAAATAG GCGTATCACG AGGCCCTTTC 3150
GTCTTCAAG                                            3159
```

Filed via EFS-Web
May 3, 2011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Richard J. Armitage et al.	Confirmation No.:	8151
Serial No.:	12/829,231	Group Art Unit No.:	1647
Filed:	July 1, 2010	Examiner:	HAMUD, Fozia M.
Title:	**ANTI-INTERLEUKIN-4 RECEPTOR ANTIBODIES (as amended)**		
Docket No.:	3005-US-CNT3		

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

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

Examiner:

The owner, Immunex Corporation, of 100% interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 7,186,809 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successor or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

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

CERTIFICATE OF EFS-WEB TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted electronically through EFS-WEB to the Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450, on the date appearing below.

May 3, 2011	/Jae Cho/
Date	Signature

Further, the owner does not waive owner's right to obtain, to the full extent provided by law, any patent term extension, restoration and/or pediatric exclusivity.
Check either box 1 ***or*** 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.*

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

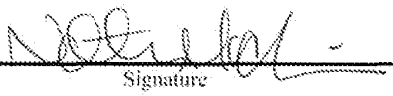
Signature — Date

Typed or printed name

Title — Telephone Number

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 47,763



Signature — May 3, 2011 (Date)

Nathan A. Machin

Typed or printed name

(206) 265-8779

Telephone Number

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

Please send all future correspondence to:

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Seattle, WA 98119-3105

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

22932 7590 02/03/2011

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LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	
MAIL DATE	**DELIVERY MODE**
02/03/2011	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	12/829,231	ARMITAGE ET AL.	
	Examiner	Art Unit	
	FOZIA M. HAMUD	1647	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *07 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 20-35* is/are pending in the application.

4a) Of the above claim(s) *20-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2010* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/01/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction:

1a. Applicant's election without traverse of the invention of Group I, (claims 1-19 and 34-35) in the reply filed on 07 December 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

1b. The restriction requirement to elect a single sequence is moot, since the elected claims recite a single sequence identifier for each heavy chain and light chain.

1c. Regarding the inventions of Groups I and III, if the product claims of Group I is found allowable, the invention of Group III, will be rejoined in accordance with the provisions of MPEP § 821.04, in so far as the claims of Group III depends from or otherwise include all the limitations of the allowable product claims. Furthermore, to be allowable, the rejoined claims must meet all the criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.

The restriction requirement is still deemed proper and is therefore made FINAL.

Status of claims:

1d. Claims 1-16, 20-35 are pending of which claims 1-16 and 34-35 are drawn to the elected invention. Claims 20-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/21/2009.

Specification:

The disclosure is objected to because of the following informalities:

2a. The status of the parent non-provisional application No. 12/291,702 should be updated.

2b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Drawings:

2c. Replacement drawings have been received on 20 September 2010. However, these drawings are not accepted, because they are not labeled at the top of each page as replacement drawings. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required

corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 01 July 2010 has been received and complies with the provisions of 37 CFR §§1.97 and 1.98. The references in Parent U.S. Application Serial Number: 10,324,493 have been considered as to the merits.

Priority:

4. Based on the information given by Applicants and an inspection of the patent applications, the Examiner has concluded that the subject matter defined in claims 1-16 and 34-35 is supported by the disclosure in U.S. Application Serial No. 09/847,816 filed on 01 May 2001, because, this application discloses antibodies that bind to IL-4 receptor, wherein said antibodies comprise the light chain of SEQ ID NO:10 and heavy chain of SEQ ID NO:12. Therefore, claims 1-16 and 34-35 are afforded an effective filing date of 05/01/2001 for purposes of art.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 09/847,816, which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 05/01/2001.

Claim Objections:

5. Claims 1-7 are objected to because of the following informalities:

5a. Claims 1-7 recite ".....IL-4 or IL-13", however, it is suggested that "interleukin 4 or interleukin 13 ", be recited in front of the first independent claim wherein each acronym is recited.

Claim rejections- Obviousness-type Double patenting:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-16 and 34-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8-13, of U.S. Patent No. 7,186,809.

Although the conflicting claims are not identical, they are not patentably distinct from each other because, the instant claim 1 is drawn to an isolated antibody that

competes with a reference antibody for binding to human IL-4 receptor, wherein the light chain of said antibody comprises the amino acid set forth in SEQ ID NO:10 and heavy chain of said antibody comprises the amino acid set forth in SEQ ID NO:12, wherein said antibody inhibits the binding of human IL-14 or human IL-13 to human IL-4 receptor, wherein said antibody is partially human, full length, or a fragment thereof. Claims 1-3, 11-13 of U.S. Patent No. 7,186,809, are drawn to an isolated anti-IL4 receptor antibody comprising a light-chain variable region comprising the amino acid sequence of SEQ ID NO:10 and a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 12, wherein said antibody is a monoclonal antibody, partially human or fragment thereof. The antibody recited in the instant claims as well as the antibody recited in the issued claims both bind human IL-4 receptor; the antibody of the issued claims comprise the light chain of SEQ ID NO:10 and heavy chain of SEQ ID NO:12, while the instantly claimed antibody competes with an antibody that comprises the light chain of SEQ ID NO:10 and heavy chain of SEQ ID NO:12. Thus, both the issued claims and the instant claims encompass an antibody that comprises the light chain of SEQ ID NO:10 and heavy chain of SEQ ID NO:12 or an antibody that competes with said antibody.

Claim rejections-35 USC § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7a. Claims 1-16, 34, 35 are rejected under 35 U.S.C. 102(b), as being anticipated by Mosley et al, U.S. Patent No. 5,717,072, (issued on 10 February 1998; cited in the IDS of 07/01/2010).

Claims 1-16 are drawn to an isolated antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein the reference antibody comprises the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor, said isolated antibody that is a human antibody, wherein the isolated antibody inhibits human IL-4 signaling through human IL-4 receptor, wherein the antibody is humanized, is full length or fragment thereof, wherein the antibody has specific binding affinity, (claims 8-10) or is a composition comprising a buffer, (claim 34) or isolated, (claim 35).

Mosley et al teach an isolated human antibody that binds to human IL-4 receptor, said antibody that is an IgE, Ig1, and fragments of said antibody and inhibits IL-4 mediated activities, (see abstract, column 5, lines 10-28 and claims). Mosley et al disclose that their antibody binds to human cells that express IL-4 receptor and inhibits IL-4 binding to cytotoxic T lymphocyte lines, (CTLL, transfected with IL-4 receptor), (see column 2, lines 56-66 and Example 13).

Thus, the antibody disclosed in the Mosley et al reference meets all the limitations recited in instant claims 1-4, 6, and 12-16, because the antibody of Mosley et al. can compete with the recited antibody, inhibits binding of IL-4 to IL-4 receptor, and is an IgG1. Since the antibody of Mosley et al competes with the reference antibody, each

antibody would inherently inhibit the binding of the other with IL-4 receptor, (claims 2-3). With respect to claims 4 and 6, since the antibody taught by Mosley et al. binds to human IL-4 receptor and inhibits IL-4 binding to IL-4 receptor, it would also inherently inhibit IL-4 signaling through IL-4 receptor. Regarding claims 8-10, the antibody of Mosley et al. would be expected to display said binding affinities, since it was shown to bind to IL-4 receptor, (see column 33, line 65 to column 34, line 10). Regarding claims 34-35, Mosley et al. teach that their antibody is in a buffer solution thus meeting the limitation recited in claim 34 and is isolated, meeting the limitation of claim 35, (see column 34, lines 4-10 and claims).

Thus, the Mosley et al reference anticipates instant claims 1-16, 34, and 35 in the absence of any evidence on the contrary.

7b. Claims 1-9, 11-16, 34, and 35 are rejected under 35 U.S.C. 102(b), as being anticipated by Beckmann et al, (Journal of Immunology, 1990, Vol. 144, No. 11, pages 4212-4217).

Claims 1-16 are drawn to an isolated antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein the reference antibody comprises the light chain of SEQ ID NO:10 and the heavy chain of SEQ ID NO:12, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor, said isolated antibody that is a human antibody, wherein the isolated antibody inhibits human IL-4 signaling through human IL-4 receptor, wherein the antibody is humanized, is full

length or fragment thereof, wherein the antibody has specific binding affinity, (claims 8-10) or is a composition comprising a buffer, (claim 34) or isolated, (claim 35).

Beckmann et al. teach an isolated human antibody that binds to human IL-4 receptor, said antibody that is IgG2, and inhibits IL-4 induced proliferation, (see abstract, page 4213, column 1). Beckmann et al disclose that their antibody binds to human cells that express IL-4 receptor and inhibits IL-4 binding to cytotoxic T lymphocyte lines, (CTLL), (see figure 2). Beckmann et al. also teach that their antibody binds to IL-4 receptor at binding affinity of k_a of 1×10^9, (see page 4212, top of column 2, page 4213, column 2 and figure 3).

Thus, the antibody disclosed in the Beckmann et al reference meets all the limitations recited in instant claims 1-4, 6, and 12-16, because the antibody of Beckmann et al can compete with the recited antibody, inhibits binding of IL-4 to IL-4 receptor, and is an IgG2. Since the antibody of Beckmann et al competes with the reference antibody, each antibody would inherently inhibit the binding of the other with IL-4 receptor, (claims 2-3). With respect to claims 4 and 6, since the antibody taught by Beckmann et al binds to human IL-4 receptor and inhibits IL-4 binding to IL-4 receptor and IL-4 induced activity, it would also inherently inhibit IL-4 signaling through IL-4 receptor. Regarding claims 34-35, Beckmann et al. teach that their antibody is in a buffer solution thus meeting the limitation recited in claim 34 and is isolated, meeting the limitation of claim 35, (page 4213, column 1).

Thus, the Beckmann et al reference anticipates instant claims 1-16, 34, and 35 in the absence of any evidence on the contrary.

Conclusion:

8. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery J. Stucker can be reached on (571) 272-0911. 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.

Fozia Hamud
Patent Examiner
Art Unit 1647
22 January 2011

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3

CONFIRMATION NO. 8151

22932
IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

PUBLICATION NOTICE

Title:USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

Publication No.US-2011-0002913-A1
Publication Date:01/06/2011

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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

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

VIA EFS-Web
December 7, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Richard J. Armitage et al.	**Docket No.**:	3005-US-CNT3
Serial No.:	**12/829,231**	**Confirmation No.**:	8151
Filing Date:	**July 1, 2010**	**Examiner**:	HAMUD, Fozia M.

Title: USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

RESPONSE TO RESTRICTION REQUIREMENT

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

Sir:

In response to the Restriction Requirement mailed November 8, 2010, please consider the following election and remarks.

The Listing of the Claims begins on page 2.
Remarks begin on page 6.

The Director is hereby authorized to charge any additional fees which may be required by the accompanying papers, or credit any overpayment to Deposit Account No. 09-0089.

CERTIFICATE OF EFS-Web TRANSMISSION
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/	December 7, 2010
Jae Cho	Date

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

Listing of the Claims

What is claimed is:

1. (Currently Amended) An isolated antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein~~:~~

~~a.~~ the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12~~; or~~

~~b. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:14 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:16; or~~

~~c. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:18 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:20; or~~

~~d. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:22 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:24~~.

2. (Original) The isolated antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. (Original) The isolated antibody of Claim 1, wherein when said isolated antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-13 to human IL-4 receptor.

6. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1×10^8.

9. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1×10^9.

10. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1×10^{10}.

11. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a human, partially human, humanized, or chimeric antibody.

12. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a full-length antibody.

13. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a fragment of an antibody.

15. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a fusion protein.

16. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a single chain antibody (scFv).

17. – 19. (Cancelled)

20. (Withdrawn) An isolated nucleic acid, wherein said isolated nucleic acid comprises a sequence encoding:

a. the light chain variable domain of said isolated antibody of Claim 1; or

b. the heavy chain variable domain of said isolated antibody of Claim 1; or

c. the light chain variable domain of said isolated antibody of Claim 1 and the heavy chain variable domain of said isolated antibody of Claim 1.

21. (Withdrawn) A vector, wherein said vector comprises said isolated nucleic acid of Claim 20.

22. (Withdrawn) The vector of Claim 21, wherein said vector is an expression vector.

23. (Withdrawn) An isolated cell, wherein said cell comprises said isolated nucleic acid of Claim 20.

24. (Withdrawn) The isolated cell of Claim 23, wherein said isolated cell expresses said isolated antibody.

25. (Withdrawn) A method of reducing IL-4 receptor-dependent signaling in a subject, comprising administering to said subject an effective amount of said isolated antibody of Claim 1.

26. (Withdrawn) The method of Claim 25, wherein said method suppresses a T_H2-type immune response.

27. (Withdrawn) The method of Claim 25, wherein said subject has, or is at risk of developing, a condition responsive to inhibition of IL-4R signaling.

28. (Withdrawn) The method of Claim 27, wherein said condition is an inflammatory condition.

29. (Withdrawn) The method of Claim 27, wherein said condition is an IgE mediated condition.

30. (Withdrawn) The method of Claim 27, wherein said condition is an allergic condition.

31. (Withdrawn) The method of Claim 27, wherein said condition is a condition in which IL-4 mediated epithelial barrier disruption plays a role.

32. (Withdrawn) The method of Claim 27, wherein said condition is asthma, COPD, pulmonary fibrosis, or septic arthritis.

33. (Withdrawn) A method of making an antibody, comprising incubating said cell of Claim 23 under conditions that allow it to express said isolated antibody.

34. (Original) A composition comprising said isolated antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. (Original) A kit comprising said isolated antibody of Claim 1.

REMARKS

Restriction Requirement

First Restriction Requirement

The instant Restriction Requirement divides the pending claims into three groups:

- Group I (Claims 1-19, 34, and 35) is said to be drawn to an isolated antibody that binds a specific polypeptide, a composition comprising said antibody, and a kit comprising said antibody;
- Group II (Claims 20-24 and 33) is said to be drawn to an isolated polynucleotide encoding an antibody, an expression system, a host cell, and a method of making the encoded antibody; and
- Group III (Claims 25-32) is said to be drawn to a method of reducing IL-4 dependent signaling in a subject by administering an isolated antibody.

Applicants choose the claims of Group I (Claims 1-19, 34-35) for immediate prosecution on their merits.

Applicant gratefully acknowledges the Examiner's statement that Groups I and III are related as product and process of use claims and that withdrawn process claims that depend from or otherwise require all of the limitations of an allowable product claim will be considered for rejoinder.

Second Restriction Requirement

The instant Restriction Requirement further states that "Applicant is additionally required to elect a single polypeptide … sequence. This requirement is not to be considered as a requirement of an election of species, since each of the compounds recited in alternative form is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention."

The pending claims are not directed to single isolated polypeptides *per se* and thus it is not clear how they could be so amended without fundamentally altering the nature of the claimed subject matter. It is believed that what is actually sought is restriction to a single *reference antibody* having one light chain and one heavy chain polypeptide sequence as

defined in pending Claim 1. Accordingly, Applicants choose the reference antibody whose light chain comprises the amino acid sequence of SEQ ID NO:10 and whose heavy chain comprises the amino acid sequence of SEQ ID NO:12 for immediate prosecution. Claim 1 has been amended accordingly.

If Applicants' interpretation of this requirement differs from that which was intended, further guidance is respectfully requested.

Claim Amendments

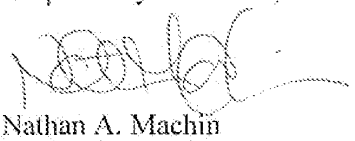
Claims 20- 33 are withdrawn. Claim 1 is amended as shown in the Listing of the Claims. Claims 17-19 are cancelled.

Applicants makes these elections, amendments, and cancellations without traverse, prejudice, or disclaimer and reserve the right to select any non-elected, withdrawn, cancelled, or amended subject matter for further prosecution by amendment or in one or more timely filed divisional, continuation, or continuation-in-part applications.

CONCLUSION

Applicants respectfully request that the claims as herein restricted and amended be allowed. The Examiner is invited to call the undersigned attorney at (206) 265-8779 upon receipt and review of this Response to the Restriction Requirement to discuss any questions or concerns about the present response.

Respectfully submitted,



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3	8151

22932 7590 11/08/2010

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
11/08/2010	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	12/829,231	ARMITAGE ET AL.	
	Examiner	Art Unit	
	FOZIA M. HAMUD	1647	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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

Status

1)☒ Responsive to communication(s) filed on *20 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election Restriction:

Status of Claims:

1. Claims 1-35 are pending and under consideration.

2 Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-19, 34-35, drawn to an isolated antibody that binds a specific polypeptide, a composition comprising said antibody and a kit comprising said antibody, classified in class 530, subclass 387.9.

II. Claims 20-24 and 33, drawn to an isolated polynucleotide encoding an antibody, an expression system, a host cell and a method of making the encoded antibody classified in class 435, subclass 69.1.

III Claims 25-32, drawn to a method of reducing IL-4 dependent signaling in a subject, by administering an isolated antibody, classified in class 424, sub class 143.1.

The inventions are distinct, each from the other because of the following reasons:

The antibody of Group I and the nucleic acid of Group II are patentably distinct inventions for the following reasons. Antibodies are polypeptides, which are composed of amino acids, and nucleic acids, which are composed of purine and pyrimidine units, are structurally distinct molecules, any relationship between a nucleic acid and polypeptide is dependent upon the information provided by the nucleic acid sequence open reading frame as it corresponds to the primary amino acid sequence of the encoded antibody. In the present claims, a nucleic acid of Group II does not necessarily encode an antibody of Group I. For example, the information provided by the nucleic acid of Group II can be used to make a materially different antibody than that of Group I.

In addition, while an antibody of Group I can made by methods other than using the nucleic acid of Group II, it can also be recovered from a natural source using by biochemical means. For instance, immunizing an animal with a polypeptide that binds to said antibody. For these reasons, the inventions of Groups I and II are patentably distinct. Furthermore, searching the inventions of Groups I and II together would impose a serious search burden. In the instant case, the search of the antibodies, (polypeptides) and the nucleic acids are not coextensive. The inventions of Groups I and II have a separate status in the art as shown by their different classifications. In cases such as this one where descriptive sequence information is provided, the sequences are searched in appropriate databases. The databases used to search the sequences of polypeptides are not the same databases used to search nucleic acid sequences. As such, it would be burdensome to search the inventions of Groups I and II together.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the antibody of Group I as claimed can also be used to purify the polypeptide that binds it.

Inventions II and III, are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §

806.04, MPEP § 808.01). In the instant case the polynucleotide of Group II is neither used nor produced in the method of Group III.

Additional Restriction Requirement:

The claims of Groups I-III recite a multitude of light and heavy chain sequences (SEQ ID NO: 10/ SEQ ID NO:12; SEQ ID NO:16/ SEQ ID NO:18; or SEQ ID NO:22/ SEQ ID NO:24) and nucleic acids encoding such. This constitutes a recitation of an implied, mis-joined Markush group that contains multiple, independent and distinct inventions. Each of the antibodies having said light and heavy chain sequences and polynucleotides encoding such are independent and distinct because no common structural or functional properties are shared. Accordingly, these claims are subject to restriction under 35 U.S.C. 121.

Upon election of one of Groups I-III, Applicant is additionally required to elect a single polypeptide or polynucleotide sequence. This requirement is not to be considered as a requirement of an election of species, since each of the compounds recited in alternative from is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if

the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and

recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has prima facie shown a serious burden of search (see MPEP § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because at least the following reason(s) apply:

- the inventions have acquired a separate status in the art in view of their different classification,

- the inventions have acquired a separate status in the art due to their recognized divergent subject matter

- the inventions require a different field of search (e.g., searching different classes /subclasses or electronic resources, or employing different search strategies or search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time

of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

3. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery J. Stucker can be reached on (571) 272-0911. 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.

Fozia Hamud
Patent Examiner
Art Unit 1647
26 October 2010

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/829,231	07/01/2010	1646	2000	3005-US-CNT3	35	1

CONFIRMATION NO. 8151

UPDATED FILING RECEIPT

22932
IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

Date Mailed: 09/30/2010

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

Applicant(s)

RICHARD J. ARMITAGE, BAINBRIDGE ISLAND, WA;
JOSE CARLOS ESCOBAR, SAMMAMISH, WA;
ARVIA E. MORRIS, SEATTLE, WA;
JOHN D. PLUENNEKE, PARKVILLE, MO;

Assignment For Published Patent Application

IMMUNEX CORPORATION

Power of Attorney: The patent practitioners associated with Customer Number 22932

Domestic Priority data as claimed by applicant

This application is a CON of 12/291,702 11/13/2008 ABN
which is a CON of 11/588,696 10/27/2006 PAT 7,465,450
which is a DIV of 10/324,493 12/19/2002 PAT 7,186,809
which is a CON of 09/847,816 05/01/2001 ABN

Foreign Applications

If Required, Foreign Filing License Granted: 07/12/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/829,231**

Projected Publication Date: 01/06/2011

Non-Publication Request: No

Early Publication Request: No

Title

USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

Preliminary Class

530

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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

VIA EFS-Web
September 20, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Richard J. Armitage et al.	**Docket No.:**	3005-US-CNT3
Serial No.:	**12/829,231**	**Confirmation No.:**	8151
Filing Date:	**July 1, 2010**	**Examiner:**	not yet assigned

Title: USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

RESPONSE TO NOTICE TO FILE MISSING PARTS

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

Sir:

In response to the Notice to File Missing Parts of Nonprovisional Application mailed July 20, 2010, please consider the following amendments and remarks.

The Listing of the Claims begins on page 2.

Remarks begin on page 7.

The fee of $130 as set forth in 37 CFR 1.16(f) has been paid via EFS-Web on September 20, 2010.

The Director is hereby authorized to charge any additional fees which may be required by the accompanying papers, or credit any overpayment to Deposit Account No. 09-0089.

CERTIFICATE OF EFS-Web TRANSMISSION
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/ — Jae Cho

September 20, 2010 — Date

REMARKS

The Oath/Declaration

Properly signed declarations in compliance with 37 CFR 1.63, identifying the application by the Application Number and Filing Date of the present application are submitted herewith.

Replacement Drawing

Replacement Figures 1-3 (six of six sheets) are submitted herewith.

Correction of the Inventorship

Richard J. Armitage, Jose Carlos Escobar and Arvia E. Morris are being added as inventors of the present application.

Inventorship of priority filings that are now abandoned are hereby corrected as follows:

- For U.S. Pat. App. No. 09/847,816, filed May 1, 2001 (3005-US-CIP3), now abandoned, the correct inventorship is Richard J. Armitage and John D. Plunneke.
- For U.S. Pat. App. No. 12/291,702, filed November 13, 2008 (3005-US-CNT3), now abandoned, the correct inventorship is Richard J. Armitage, Jose Carlos Escobar and Arvia E. Morris.

Re-issue applications are being filed in connection with related U.S. Patents Number 7,186,809, granted March 6, 2007, and 7,465,450, granted December 16, 2008, to correct their inventorship.

Priority

As noted in the Specification of the present application, priority for the instant application begins with U.S. Pat. App. No. 09/847,816, filed May 1, 2001 (3005-US-CIP3). Priority is not claimed to any of U.S. Pat. App. No. 09/579,808, filed May 26, 2000 (3005-US-NP), 09/665,343, filed September 19, 2000 (3005-US-CIP), or 09/785,934, filed February 15, 2001, published January 3, 2002 as U.S. Pub. No. 2002-0002132 (3005-US-CIP2).

CONCLUSION

Applicant respectfully requests that the claims be allowed. The Examiner is invited to call the undersigned attorney at (206) 265-8779 to discuss any questions or concerns.

Respectfully submitted,

Nathan A. Machin
Attorney/Agent for Applicant(s)
Registration No.: 47,763
Phone: (206) 265-8779
Date: September 20, 2010

Please send all future correspondence to:
22932
Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, Washington 98119-3105
(206) 265-7000

Docket No.: 3005-US-CNT3

DECLARATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first, and sole inventor (if only one name is listed below) or a joint inventor (if plural names are listed below) of the invention entitled

USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

which is described and claimed in the specification which:

☐ is attached hereto.

☒ was filed on July 1, 2010
as Application Serial No. 12/829,231
and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

Please send all future correspondence to:

Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, WA 98119-3105
(206) 265-7000

Direct Telephone Calls To:

Nathan A. Machin
Attorney for Applicant(s)
Registration No.: 47,763
Phone: (206) 265-8779

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full Name of Sole or First Inventor:	Richard J. Armitage
Inventor's Signature:	R Bud Date: 9/16/2010
Residence and Post Office Address:	5840 Packard Lane, Bainbridge Island, WA 98110, USA (Address, City, State, Zip Code, Country)
Citizenship:	US

DECLARATION(cont'd)

Full Name of Second Joint Inventor, if Any:	Jose Carlos Escobar
Inventor's Signature:	Date: 9/14/10
Residence and Post Office Address:	1707 East Beaverlake Drive SE, Sammamish, WA 98075, USA (Address, City, State, Zip Code, Country)
Citizenship:	US
Full Name of Third Joint Inventor, if Any:	Arvia E. Morris
Inventor's Signature:	Date: September 16, 2010
Residence and Post Office Address:	4535 Thackeray Place NE, Seattle, WA 98105, USA (Address, City, State, Zip Code, Country)
Citizenship:	US

DECLARATION

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe that I am an original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

the specification of which

☐ is attached hereto.

OR

☒ was filed on May 1, 2001 as United States Application No. or PCT International Application No. 09/847,816.

I hereby state that I have reviewed and understand the contents of said specification, including the claims. I acknowledge the duty to disclose information that is known to me and material to patentability of the subject claimed invention in accordance with 37 C.F.R. §1.56.

☒ I hereby claim the benefit under 35 U.S.C. §120 of the United States application(s) and PCT international application(s) designating the United States that are listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) or PCT international application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application.

Application No.	Filed
09/785,934	February 15, 2001
09/665,343	September 19, 2000
09/579,808	May 26, 2000

☐ I hereby claim the benefit under 35 U.S.C. §119(e) of the United States provisional patent application(s) listed below:

Application No.	Filed

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature _____ Date 8/7/01

Inventor John D. Pluenneke
Post Office Address 51 University Street
Seattle, Washington 98101
U.S.A.
Residence Parkville, Missouri U.S.A.
Citizenship U.S.A.

cf053102 7/18/01

FIGURE 1A

```
ATG GGG TGG CTT TGC TCT GGG CTC CTG TTC CCT GTG AGC TGC CTG -31
Met Gly Trp Leu Cys Ser Gly Leu Leu Phe Pro Val Ser Cys Leu -11

GTC CTG CTG CAG GTG GCA AGC TCT GGG AAC ATG AAG GTC TTG CAG  15
Val Leu Leu Gln Val Ala Ser Ser Gly Asn Met Lys Val Leu Gln   5

GAG CCC ACC TGC GTC TCC GAC TAC ATG AGC ATC TCT ACT TGC GAG  60
Glu Pro Thr Cys Val Ser Asp Tyr Met Ser Ile Ser Thr Cys Glu  20

TGG AAG ATG AAT GGT CCC ACC AAT TGC AGC ACC GAG CTC CGC CTG 105
Trp Lys Met Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu  35

TTG TAC CAG CTG GTT TTT CTG CTC TCC GAA GCC CAC ACG TGT ATC 150
Leu Tyr Gln Leu Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile  50

CCT GAG AAC AAC GGA GGC GCG GGG TGC GTG TGC CAC CTG CTC ATG 195
Pro Glu Asn Asn Gly Gly Ala Gly Cys Val Cys His Leu Leu Met  65

GAT GAC GTG GTC AGT GCG GAT AAC TAT ACA CTG GAC CTG TGG GCT 240
Asp Asp Val Val Ser Ala Asp Asn Tyr Thr Leu Asp Leu Trp Ala  80

GGG CAG CAG CTG CTG TGG AAG GGC TCC TTC AAG CCC AGC GAG CAT 285
Gly Gln Gln Leu Leu Trp Lys Gly Ser Phe Lys Pro Ser Glu His  95

GTG AAA CCC AGG GCC CCA GGA AAC CTG ACA GTT CAC ACC AAT GTC 330
Val Lys Pro Arg Ala Pro Gly Asn Leu Thr Val His Thr Asn Val 110

TCC GAC ACT CTG CTG CTG ACC TGG AGC AAC CCG TAT CCC CCT GAC 375
Ser Asp Thr Leu Leu Leu Thr Trp Ser Asn Pro Tyr Pro Pro Asp 125

AAT TAC CTG TAT AAT CAT CTC ACC TAT GCA GTC AAC ATT TGG AGT 420
Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala Val Asn Ile Trp Ser 140

GAA AAC GAC CCG GCA GAT TTC AGA ATC TAT AAC GTG ACC TAC CTA 465
Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn Val Thr Tyr Leu 155

GAA CCC TCC CTC CGC ATC GCA GCC AGC ACC CTG AAG TCT GGG ATT 510
Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys Ser Gly Ile 170

TCC TAC AGG GCA CGG GTG AGG GCC TGG GCT CAG TGC TAT AAC ACC 555
Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr Asn Thr 185

ACC TGG AGT GAG TGG AGC CCC AGC ACC AAG TGG CAC AAC TCC TAC 600
Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser Tyr 200

AGG GAG CCC TTC GAG CAG CAC CTC CTG CTG GGC GTC AGC GTT TCC 645
Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser 215

TGC ATT GTC ATC CTG GCC GTC TGC CTG TTG TGC TAT GTC AGC ATC 690
Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile 230

ACC AAG ATT AAG AAA GAA TGG TGG GAT CAG ATT CCC AAC CCA GCC 735
Thr Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala 245
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FIGURE 1B

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CGC AGC CGC CTC GTG GCT ATA ATA ATC CAG GAT GCT CAG GGG TCA  780
Arg Ser Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser  260

CAG TGG GAG AAG CGG TCC CGA GGC CAG GAA CCA GCC AAG TGC CCA  825
Gln Trp Glu Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro  275

CAC TGG AAG AAT TGT CTT ACC AAG CTC TTG CCC TGT TTT CTG GAG  870
His Trp Lys Asn Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu  290

CAC AAC ATG AAA AGG GAT GAA GAT CCT CAC AAG GCT GCC AAA GAG  915
His Asn Met Lys Arg Asp Glu Asp Pro His Lys Ala Ala Lys Glu  305

ATG CCT TTC CAG GGC TCT GGA AAA TCA GCA TGG TGC CCA GTG GAG  960
Met Pro Phe Gln Gly Ser Gly Lys Ser Ala Trp Cys Pro Val Glu  320

ATC AGC AAG ACA GTC CTC TGG CCA GAG AGC ATC AGC GTG GTG CGA 1005
Ile Ser Lys Thr Val Leu Trp Pro Glu Ser Ile Ser Val Val Arg  335

TGT GTG GAG TTG TTT GAG GCC CCG GTG GAG TGT GAG GAG GAG GAG 1050
Cys Val Glu Leu Phe Glu Ala Pro Val Glu Cys Glu Glu Glu Glu  350

GAG GTA GAG GAA GAA AAA GGG AGC TTC TGT GCA TCG CCT GAG AGC 1095
Glu Val Glu Glu Glu Lys Gly Ser Phe Cys Ala Ser Pro Glu Ser  365

AGC AGG GAT GAC TTC CAG GAG GGA AGG GAG GGC ATT GTG GCC CGG 1140
Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu Gly Ile Val Ala Arg  380

CTA ACA GAG AGC CTG TTC CTG GAC CTG CTC GGA GAG GAG AAT GGG 1185
Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly Glu Glu Asn Gly  395

GGC TTT TGC CAG CAG GAC ATG GGG GAG TCA TGC CTT CTT CCA CCT 1230
Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu Leu Pro Pro  410

TCG GGA AGT ACG AGT GCT CAC ATG CCC TGG GAT GAG TTC CCA AGT 1275
Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe Pro Ser  425

GCA GGG CCC AAG GAG GCA CCT CCC TGG GGC AAG GAG CAG CCT CTC 1320
Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro Leu  440

CAC CTG GAG CCA AGT CCT CCT GCC AGC CCG ACC CAG AGT CCA GAC 1365
His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Asp  455

AAC CTG ACT TGC ACA GAG ACG CCC CTC GTC ATC GCA GGC AAC CCT 1410
Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro  470

GCT TAC CGC AGC TTC AGC AAC TCC CTG AGC CAG TCA CCG TGT CCC 1455
Ala Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro  485

AGA GAG CTG GGT CCA GAC CCA CTG CTG GCC AGA CAC CTG GAG GAA 1500
Arg Glu Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Glu  500

GTA GAA CCC GAG ATG CCC TGT GTC CCC CAG CTC TCT GAG CCA ACC 1545
Val Glu Pro Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr  515
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FIGURE 1C

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ACT GTG CCC CAA CCT GAG CCA GAA ACC TGG GAG CAG ATC CTC CGC 1590
Thr Val Pro Gln Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg  530

CGA AAT GTC CTC CAG CAT GGG GCA GCT GCA GCC CCC GTC TCG GCC 1635
Arg Asn Val Leu Gln His Gly Ala Ala Ala Ala Pro Val Ser Ala  545

CCC ACC AGT GGC TAT CAG GAG TTT GTA CAT GCG GTG GAG CAG GGT 1680
Pro Thr Ser Gly Tyr Gln Glu Phe Val His Ala Val Glu Gln Gly  560

GGC ACC CAG GCC AGT GCG GTG GTG GGC TTG GGT CCC CCA GGA GAG 1725
Gly Thr Gln Ala Ser Ala Val Val Gly Leu Gly Pro Pro Gly Glu  575

GCT GGT TAC AAG GCC TTC TCA AGC CTG CTT GCC AGC AGT GCT GTG 1770
Ala Gly Tyr Lys Ala Phe Ser Ser Leu Leu Ala Ser Ser Ala Val  590

TCC CCA GAG AAA TGT GGG TTT GGG GCT AGC AGT GGG GAA GAG GGG 1815
Ser Pro Glu Lys Cys Gly Phe Gly Ala Ser Ser Gly Glu Glu Gly  605

TAT AAG CCT TTC CAA GAC CTC ATT CCT GGC TGC CCT GGG GAC CCT 1860
Tyr Lys Pro Phe Gln Asp Leu Ile Pro Gly Cys Pro Gly Asp Pro  620

GCC CCA GTC CCT GTC CCC TTG TTC ACC TTT GGA CTG GAC AGG GAG 1905
Ala Pro Val Pro Val Pro Leu Phe Thr Phe Gly Leu Asp Arg Glu  635

CCA CCT CGC AGT CCG CAG AGC TCA CAT CTC CCA AGC AGC TCC CCA 1950
Pro Pro Arg Ser Pro Gln Ser Ser His Leu Pro Ser Ser Ser Pro  650

GAG CAC CTG GGT CTG GAG CCG GGG GAA AAG GTA GAG GAC ATG CCA 1995
Glu His Leu Gly Leu Glu Pro Gly Glu Lys Val Glu Asp Met Pro  665

AAG CCC CCA CTT CCC CAG GAG CAG GCC ACA GAC CCC CTT GTG GAC 2040
Lys Pro Pro Leu Pro Gln Glu Gln Ala Thr Asp Pro Leu Val Asp  680

AGC CTG GGC AGT GGC ATT GTC TAC TCA GCC CTT ACC TGC CAC CTG 2085
Ser Leu Gly Ser Gly Ile Val Tyr Ser Ala Leu Thr Cys His Leu  695

TGC GGC CAC CTG AAA CAG TGT CAT GGC CAG GAG GAT GGT GGC CAG 2130
Cys Gly His Leu Lys Gln Cys His Gly Gln Glu Asp Gly Gly Gln  710

ACC CCT GTC ATG GCC AGT CCT TGC TGT GGC TGC TGC TGT GGA GAC 2175
Thr Pro Val Met Ala Ser Pro Cys Cys Gly Cys Cys Cys Gly Asp  725

AGG TCC TCG CCC CCT ACA ACC CCC CTG AGG GCC CCA GAC CCC TCT 2220
Arg Ser Ser Pro Pro Thr Thr Pro Leu Arg Ala Pro Asp Pro Ser  740

CCA GGT GGG GTT CCA CTG GAG GCC AGT CTG TGT CCG GCC TCC CTG 2265
Pro Gly Gly Val Pro Leu Glu Ala Ser Leu Cys Pro Ala Ser Leu  755

GCA CCC TCG GGC ATC TCA GAG AAG AGT AAA TCC TCA TCA TCC TTC 2310
Ala Pro Ser Gly Ile Ser Glu Lys Ser Lys Ser Ser Ser Ser Phe  770

CAT CCT GCC CCT GGC AAT GCT CAG AGC TCA AGC CAG ACC CCC AAA 2355
His Pro Ala Pro Gly Asn Ala Gln Ser Ser Ser Gln Thr Pro Lys  785

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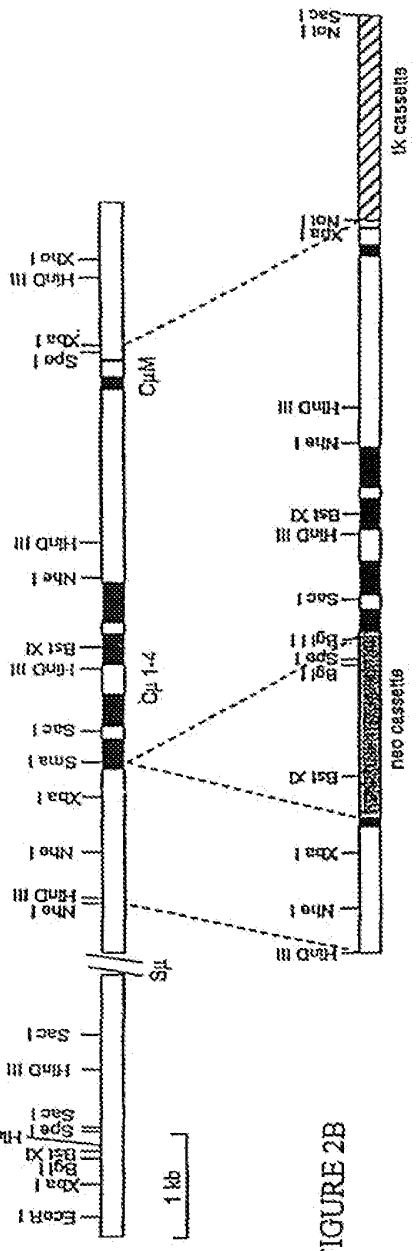

FIGURE 2A

FIGURE 2B

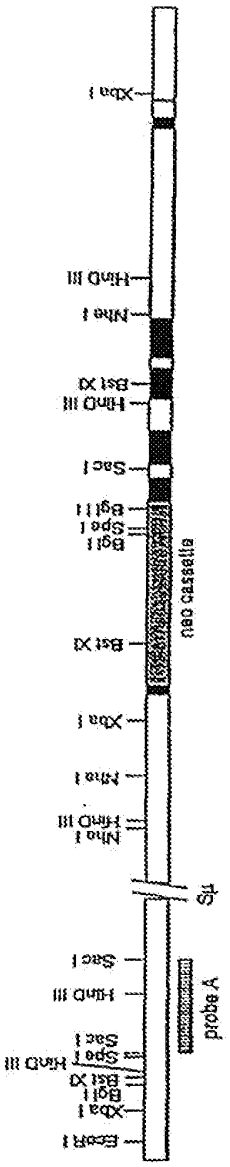

FIGURE 2C

FIGURE 3A

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GAACATATCC ATCGCGTCCG CCATCTCCAG CAGCCGCACG CGGCGCATCT  200
CGGGCAGCGT TGGGTCCTGG CCACGGGTGC GCATGATCGT GCTCCTGTCG  250
TTGAGGACCC GGCTAGGCTG GCGGGGTTGC CTTACTGGTT AGCAGAATGA  300
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CGCAGGATGC TGCTGGCTAC CCTGTGGAAC ACCTACATCT GTATTAACGA  500
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CCCCCATGAA CAGAAATTCC CCCTTACACG GAGGCATCAA GTGACCAAAC  700
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CACGTAGCGA TAGCGGAGTG TATACTGGCT TAACTATGCG GCATCAGAG  1050
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TGAAGCCAGT TACCTTCGGA AAAAGAGTTG GTAGCTCTTG ATCCGGCAAA 1850
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FIGURE 3B

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GTCTTCAAG                                            3159
```

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

Listing of the Claims

What is claimed is:

1. (Original) An isolated antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein:

a. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12; or

b. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:14 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:16; or

c. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:18 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:20; or

d. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:22 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:24.

2. (Original) The isolated antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. (Original) The isolated antibody of Claim 1, wherein when said isolated antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-13 to human IL-4 receptor.

6. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. (Original) The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1×10^8.

9. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1×10^9.

10. (Original) The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1×10^{10}.

11. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a human, partially human, humanized, or chimeric antibody.

12. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a full-length antibody.

13. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a fragment of an antibody.

15. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a fusion protein.

16. (Original) The isolated antibody of Claim 1, wherein said isolated antibody is a single chain antibody (scFv).

17. (Original) The isolated antibody of Claim 1, wherein:

a. the light chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:14 and the heavy chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:16; or

b. the light chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:18 and the heavy chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:20; or

c. the light chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:22 and the heavy chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:24.

18. (Original) The isolated antibody of Claim 1, wherein:

a. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:14; or

b. the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:16; or

c. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:18; or

d. the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:20; or

e. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:22; or

f. the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:24.

19. (Original) The isolated antibody of Claim 1, wherein:

a. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:14 and the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:16; or

b. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:18 and the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:20; or

c. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:22 and the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:24.

20. (Original) An isolated nucleic acid, wherein said isolated nucleic acid comprises a sequence encoding:

a. the light chain variable domain of said isolated antibody of Claim 1; or

b. the heavy chain variable domain of said isolated antibody of Claim 1; or

c. the light chain variable domain of said isolated antibody of Claim 1 and the heavy chain variable domain of said isolated antibody of Claim 1.

21. (Original) A vector, wherein said vector comprises said isolated nucleic acid of Claim 20.

22. (Original) The vector of Claim 21, wherein said vector is an expression vector.

23. (Original) An isolated cell, wherein said cell comprises said isolated nucleic acid of Claim 20.

24. (Original) The isolated cell of Claim 23, wherein said isolated cell expresses said isolated antibody.

25. (Original) A method of reducing IL-4 receptor-dependent signaling in a subject, comprising administering to said subject an effective amount of said isolated antibody of Claim 1.

26. (Original) The method of Claim 25, wherein said method suppresses a T_H2-type immune response.

27. (Original) The method of Claim 25, wherein said subject has, or is at risk of developing, a condition responsive to inhibition of IL-4R signaling.

28. (Original) The method of Claim 27, wherein said condition is an inflammatory condition.

29. (Original) The method of Claim 27, wherein said condition is an IgE mediated condition.

30. (Original) The method of Claim 27, wherein said condition is an allergic condition.

31. (Original) The method of Claim 27, wherein said condition is a condition in which IL-4 mediated epithelial barrier disruption plays a role.

32. (Original) The method of Claim 27, wherein said condition is asthma, COPD, pulmonary fibrosis, or septic arthritis.

33. (Original) A method of making an antibody, comprising incubating said cell of Claim 23 under conditions that allow it to express said isolated antibody.

34. (Original) A composition comprising said isolated antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. (Original) A kit comprising said isolated antibody of Claim 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/829,231	07/01/2010	RICHARD J. ARMITAGE	3005-US-CNT3

CONFIRMATION NO. 8151

22932
IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

FORMALITIES LETTER

OC000000042613078

Date Mailed: 07/20/2010

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

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

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings must be reasonably free from erasures and must be free from alterations, overwriting, interlineations, folds, and copy marks. See Figure(s) 2A-2C.

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

The applicant needs to satisfy supplemental fees problems indicated below.

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

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**130** for a non-small entity
- $**130** Surcharge.

Replies should be mailed to:

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

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

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/ygizaw/

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

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/829,231	07/01/2010	1646	1870	3005-US-CNT3	35	1

CONFIRMATION NO. 8151

22932
IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

FILING RECEIPT

OC000000042613077

Date Mailed: 07/20/2010

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

Applicant(s)

RICHARD J. ARMITAGE, Residence Not Provided;
JOSE CARLOS ESCOBAR, Residence Not Provided;
ARVIA E. MORRIS, Residence Not Provided;
JOHN D. PLUENNEKE, Residence Not Provided;

Assignment For Published Patent Application

IMMUNEX CORPORATION

Power of Attorney: The patent practitioners associated with Customer Number 22932

Domestic Priority data as claimed by applicant

This application is a CON of 12/291,702 11/13/2008 ABN
which is a CON of 11/588,696 10/27/2006 PAT 7,465,450
which is a DIV of 10/324,493 12/19/2002 PAT 7,186,809
which is a CON of 09/847,816 05/01/2001 ABN

Foreign Applications

If Required, Foreign Filing License Granted: 07/12/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/829,231**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

Preliminary Class

530

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

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

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/829,231	07/01/2010	Richard J. Armitage	3005-US-CNT3

CONFIRMATION NO. 8151

22932
IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

POA ACCEPTANCE LETTER

OC000000042574808

Date Mailed: 07/20/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/01/2010.

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

/lchau/

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

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If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).
Reviewer: Saleem, Syed (ASRC)
Timestamp: [year=2010; month=7; day=12; hr=10; min=2; sec=39; ms=890;]
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Escobar, Jose Carlos
Morris, Arvia E.
Pluenneke, John D.

<120> USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

<130> 3005-US-CNT3

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aat ggt ccc acc aat tgc agc acc gag ctc cgc ctg ttg tac cag ctg        192
Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu Leu Tyr Gln Leu
    25                  30                  35

gtt ttt ctg ctc tcc gaa gcc cac acg tgt atc cct gag aac aac gga        240
Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile Pro Glu Asn Asn Gly
40                  45                  50                  55

ggc gcg ggg tgc gtg tgc cac ctg ctc atg gat gac gtg gtc agt gcg        288
Gly Ala Gly Cys Val Cys His Leu Leu Met Asp Asp Val Val Ser Ala
                60                  65                  70

gat aac tat aca ctg gac ctg tgg gct ggg cag cag ctg ctg tgg aag        336
Asp Asn Tyr Thr Leu Asp Leu Trp Ala Gly Gln Gln Leu Leu Trp Lys
            75                  80                  85

ggc tcc ttc aag ccc agc gag cat gtg aaa ccc agg gcc cca gga aac        384
Gly Ser Phe Lys Pro Ser Glu His Val Lys Pro Arg Ala Pro Gly Asn
        90                  95                  100

ctg aca gtt cac acc aat gtc tcc gac act ctg ctg ctg acc tgg agc        432
Leu Thr Val His Thr Asn Val Ser Asp Thr Leu Leu Leu Thr Trp Ser
    105                 110                 115

aac ccg tat ccc cct gac aat tac ctg tat aat cat ctc acc tat gca        480
Asn Pro Tyr Pro Pro Asp Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala
120                 125                 130                 135

gtc aac att tgg agt gaa aac gac ccg gca gat ttc aga atc tat aac        528
Val Asn Ile Trp Ser Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn
                140                 145                 150

gtg acc tac cta gaa ccc tcc ctc cgc atc gca gcc agc acc ctg aag        576
Val Thr Tyr Leu Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys
            155                 160                 165

tct ggg att tcc tac agg gca cgg gtg agg gcc tgg gct cag tgc tat        624
Ser Gly Ile Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr
        170                 175                 180

aac acc acc tgg agt gag tgg agc ccc agc acc aag tgg cac aac tcc        672
Asn Thr Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser
    185                 190                 195

tac agg gag ccc ttc gag cag cac ctc ctg ctg ggc gtc agc gtt tcc        720
Tyr Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser
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tgc att gtc atc ctg gcc gtc tgc ctg ttg tgc tat gtc agc atc acc        768
Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile Thr
                220                 225                 230

aag att aag aaa gaa tgg tgg gat cag att ccc aac cca gcc cgc agc        816
Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala Arg Ser
            235                 240                 245

cgc ctc gtg gct ata ata atc cag gat gct cag ggg tca cag tgg gag        864
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Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser Gln Trp Glu
        250                 255                 260

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Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro His Trp Lys Asn
    265                 270                 275

tgt ctt acc aag ctc ttg ccc tgt ttt ctg gag cac aac atg aaa agg        960
Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu His Asn Met Lys Arg
280                 285                 290                 295

gat gaa gat cct cac aag gct gcc aaa gag atg cct ttc cag ggc tct       1008
Asp Glu Asp Pro His Lys Ala Ala Lys Glu Met Pro Phe Gln Gly Ser
                300                 305                 310

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Gly Lys Ser Ala Trp Cys Pro Val Glu Ile Ser Lys Thr Val Leu Trp
            315                 320                 325

cca gag agc atc agc gtg gtg cga tgt gtg gag ttg ttt gag gcc ccg       1104
Pro Glu Ser Ile Ser Val Val Arg Cys Val Glu Leu Phe Glu Ala Pro
        330                 335                 340

gtg gag tgt gag gag gag gag gag gta gag gaa gaa aaa ggg agc ttc       1152
Val Glu Cys Glu Glu Glu Glu Glu Val Glu Glu Glu Lys Gly Ser Phe
    345                 350                 355

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Cys Ala Ser Pro Glu Ser Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu
360                 365                 370                 375

ggc att gtg gcc cgg cta aca gag agc ctg ttc ctg gac ctg ctc gga       1248
Gly Ile Val Ala Arg Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly
                380                 385                 390

gag gag aat ggg ggc ttt tgc cag cag gac atg ggg gag tca tgc ctt       1296
Glu Glu Asn Gly Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu
            395                 400                 405

ctt cca cct tcg gga agt acg agt gct cac atg ccc tgg gat gag ttc       1344
Leu Pro Pro Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe
        410                 415                 420

cca agt gca ggg ccc aag gag gca cct ccc tgg ggc aag gag cag cct       1392
Pro Ser Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro
    425                 430                 435

ctc cac ctg gag cca agt cct cct gcc agc ccg acc cag agt cca gac       1440
Leu His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Asp
440                 445                 450                 455

aac ctg act tgc aca gag acg ccc ctc gtc atc gca ggc aac cct gct       1488
Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro Ala
                460                 465                 470

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Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro Arg Glu
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            475                 480                 485

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        490                 495                 500

gag atg ccc tgt gtc ccc cag ctc tct gag cca acc act gtg ccc caa       1632
Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr Thr Val Pro Gln
    505                 510                 515

cct gag cca gaa acc tgg gag cag atc ctc cgc cga aat gtc ctc cag       1680
Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg Arg Asn Val Leu Gln
520                 525                 530                 535

cat ggg gca gct gca gcc ccc gtc tcg gcc ccc acc agt ggc tat cag       1728
His Gly Ala Ala Ala Ala Pro Val Ser Ala Pro Thr Ser Gly Tyr Gln
                540                 545                 550

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Glu Phe Val His Ala Val Glu Gln Gly Gly Thr Gln Ala Ser Ala Val
            555                 560                 565

gtg ggc ttg ggt ccc cca gga gag gct ggt tac aag gcc ttc tca agc       1824
Val Gly Leu Gly Pro Pro Gly Glu Ala Gly Tyr Lys Ala Phe Ser Ser
        570                 575                 580

ctg ctt gcc agc agt gct gtg tcc cca gag aaa tgt ggg ttt ggg gct       1872
Leu Leu Ala Ser Ser Ala Val Ser Pro Glu Lys Cys Gly Phe Gly Ala
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agc agt ggg gaa gag ggg tat aag cct ttc caa gac ctc att cct ggc       1920
Ser Ser Gly Glu Glu Gly Tyr Lys Pro Phe Gln Asp Leu Ile Pro Gly
600                 605                 610                 615

tgc cct ggg gac cct gcc cca gtc cct gtc ccc ttg ttc acc ttt gga       1968
Cys Pro Gly Asp Pro Ala Pro Val Pro Val Pro Leu Phe Thr Phe Gly
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ctg gac agg gag cca cct cgc agt ccg cag agc tca cat ctc cca agc       2016
Leu Asp Arg Glu Pro Pro Arg Ser Pro Gln Ser Ser His Leu Pro Ser
            635                 640                 645

agc tcc cca gag cac ctg ggt ctg gag ccg ggg gaa aag gta gag gac       2064
Ser Ser Pro Glu His Leu Gly Leu Glu Pro Gly Glu Lys Val Glu Asp
        650                 655                 660

atg cca aag ccc cca ctt ccc cag gag cag gcc aca gac ccc ctt gtg       2112
Met Pro Lys Pro Pro Leu Pro Gln Glu Gln Ala Thr Asp Pro Leu Val
    665                 670                 675

gac agc ctg ggc agt ggc att gtc tac tca gcc ctt acc tgc cac ctg       2160
Asp Ser Leu Gly Ser Gly Ile Val Tyr Ser Ala Leu Thr Cys His Leu
680                 685                 690                 695

tgc ggc cac ctg aaa cag tgt cat ggc cag gag gat ggt ggc cag acc       2208
Cys Gly His Leu Lys Gln Cys His Gly Gln Glu Asp Gly Gly Gln Thr
                700                 705                 710
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            715                 720                 725

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Ser Pro Pro Thr Thr Pro Leu Arg Ala Pro Asp Pro Ser Pro Gly Gly
        730                 735                 740

gtt cca ctg gag gcc agt ctg tgt ccg gcc tcc ctg gca ccc tcg ggc       2352
Val Pro Leu Glu Ala Ser Leu Cys Pro Ala Ser Leu Ala Pro Ser Gly
    745                 750                 755

atc tca gag aag agt aaa tcc tca tca tcc ttc cat cct gcc cct ggc       2400
Ile Ser Glu Lys Ser Lys Ser Ser Ser Ser Phe His Pro Ala Pro Gly
760                 765                 770                 775

aat gct cag agc tca agc cag acc ccc aaa atc gtg aac ttt gtc tcc       2448
Asn Ala Gln Ser Ser Ser Gln Thr Pro Lys Ile Val Asn Phe Val Ser
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gtg gga ccc aca tac atg agg gtc tct tat                              2478
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<400> 2

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Leu Leu Gln Val Ala Ser Ser Gly Asn Met Lys Val Leu Gln Glu Pro
                -5              -1  1               5

Thr Cys Val Ser Asp Tyr Met Ser Ile Ser Thr Cys Glu Trp Lys Met
        10                  15                  20

Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu Leu Tyr Gln Leu
    25                  30                  35

Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile Pro Glu Asn Asn Gly
40                  45                  50                  55

Gly Ala Gly Cys Val Cys His Leu Leu Met Asp Asp Val Val Ser Ala
                60                  65                  70
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Asp Asn Tyr Thr Leu Asp Leu Trp Ala Gly Gln Gln Leu Leu Trp Lys
            75                  80                  85

Gly Ser Phe Lys Pro Ser Glu His Val Lys Pro Arg Ala Pro Gly Asn
        90                  95                  100

Leu Thr Val His Thr Asn Val Ser Asp Thr Leu Leu Leu Thr Trp Ser
    105                 110                 115

Asn Pro Tyr Pro Pro Asp Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala
120                 125                 130                 135

Val Asn Ile Trp Ser Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn
                140                 145                 150

Val Thr Tyr Leu Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys
            155                 160                 165

Ser Gly Ile Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr
        170                 175                 180

Asn Thr Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser
    185                 190                 195

Tyr Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser
200                 205                 210                 215

Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile Thr
                220                 225                 230

Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala Arg Ser
            235                 240                 245

Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser Gln Trp Glu
        250                 255                 260

Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro His Trp Lys Asn
    265                 270                 275

Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu His Asn Met Lys Arg
280                 285                 290                 295

Asp Glu Asp Pro His Lys Ala Ala Lys Glu Met Pro Phe Gln Gly Ser
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                300                 305                 310

Gly Lys Ser Ala Trp Cys Pro Val Glu Ile Ser Lys Thr Val Leu Trp
            315                 320                 325

Pro Glu Ser Ile Ser Val Val Arg Cys Val Glu Leu Phe Glu Ala Pro
        330                 335                 340

Val Glu Cys Glu Glu Glu Glu Glu Val Glu Glu Glu Lys Gly Ser Phe
    345                 350                 355

Cys Ala Ser Pro Glu Ser Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu
360                 365                 370                 375

Gly Ile Val Ala Arg Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly
                380                 385                 390

Glu Glu Asn Gly Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu
            395                 400                 405

Leu Pro Pro Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe
        410                 415                 420

Pro Ser Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro
    425                 430                 435

Leu His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Asp
440                 445                 450                 455

Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro Ala
                460                 465                 470

Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro Arg Glu
            475                 480                 485

Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Glu Val Glu Pro
        490                 495                 500

Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr Thr Val Pro Gln
    505                 510                 515

Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg Arg Asn Val Leu Gln
520                 525                 530                 535
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His Gly Ala Ala Ala Ala Pro Val Ser Ala Pro Thr Ser Gly Tyr Gln
                540                 545                 550

Glu Phe Val His Ala Val Glu Gln Gly Gly Thr Gln Ala Ser Ala Val
            555                 560                 565

Val Gly Leu Gly Pro Pro Gly Glu Ala Gly Tyr Lys Ala Phe Ser Ser
        570                 575                 580

Leu Leu Ala Ser Ser Ala Val Ser Pro Glu Lys Cys Gly
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DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 12829231 Document Date: 07/01/2010

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Sequence Listing

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 12829231 Document Date: 07/01/2010

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Design Drawing

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Form Revision Date: February 8, 2006

Via EFS-Web
July 1, 2010

DIVISION - CONTINUATION - CONTINUATION-IN-PART APPLICATION TRANSMITTAL FORM	Attorney Docket No.: 3005-US-CNT3

Anticipated Classification Of This Application: Class:	Subclass:	Prior Application: Examiner: HAMUD, Fozia M.	Art Unit: 1647

To the Commissioner for Patents:

This is a request for filing a ☒ continuation ☐ divisional ☐ continuation-in-part application, under 37 CFR 1.53(b), of pending prior application Serial No. 12/291,702 filed on November 13, 2010,

of Richard J. Armitage, Jose Carlos Escobar, Arvia E. Morris and John D. Pluenneke

for USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

For CONTINUATION or DIVISIONAL APPLNs only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 1b, below, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

1. ☒ Transmitted herewith are:

☒ 62 pages of specification, 5 pages of claim(s) and 1 page of abstract, **totaling** 68 pages.

☒ 6 sheet(s) of drawings.

☐ __pages of Oath or Declaration by the applicant(s):
- ☐ a. Newly executed (original or copy)
- ☐ b. Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional applns. only)*

☒ 24 pages of Sequence Listing (Text File); 1 page Sequence Statement.

2. ☒ The filing fee is calculated below:

For	Number Filed		Number Extra		Rate		Fee
Total Claims	35	- 20 =	15	x	$52.00	=	$ 780.00
Independent Claims	4	- 3 =	1	x	$220.00	=	$ 220.00
Multiple Dependent Claims	0			+	$390.00	=	$ 0.00
Basic Filing Fee					$330.00	=	$330.00
Basic Search Fee					$540.00	=	$540.00
Basic Examination Fee					$220.00	=	$220.00
Excess Page Fee (per 50)	63	- 100 =	0	x	$270.00	=	$ 0.00
					Total Filing		$2,090.00

3. ☒ Total of $2090.00 has been paid via EFS-Web on July 1, 2010.

4. ☒ Throughout the prosecution of this application, if any extension of time is necessary, please consider this a request therefore.

5. ☒ The Commissioner is hereby authorized to charge any additional filing fees which may be required by the accompanying application, any additional fees which may be required during pendency of this application as required by 37 CFR 1.16 or 1.17, or credit any overpayment to Deposit Account No. 09-0089 throughout the prosecution of this application.

6. ☐ Cancel in this application original claims _____ of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

CERTIFICATE OF EFS-Web TRANSMISSION

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/ — Jae Cho

July 1, 2010 — Date

7. ☐ Transfer the drawings from the prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in the prior application file. (May only be used if signed by person authorized by § 1.138 and before payment of base issue fee.)

7a. ☐ New formal drawings are enclosed.

8. ☐ Priority of application Serial No. _____ filed on _____ in _____ is claimed under 35 USC 119.

8a. ☐ The certified copy has been filed in prior application Serial No. _____ filed _____.

9. ☒ The prior application is assigned of record to Immunex Corporation at Reel 012104, Frame 0560.

10. ☐ A preliminary amendment is enclosed.

11. ☒ Also enclosed: Information Disclosure Statement; PTO-1449

12. ☐ Other: _____

13. ☒ The power of attorney in the prior application is to: Practitioners at Customer Number 22932

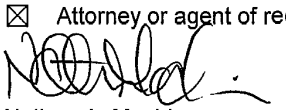
a. ☐ The power appears in the original papers in the prior application.

b. ☒ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

14. ☒ Address all future communications to Nathan A. Machin at the address below.

Signator: ☐ Assignee of complete interest

☒ Attorney or agent of record



Nathan A. Machin
Attorney for Applicants
Registration No.: 47,763
Phone: (206) 265-8779
Date: July 1, 2010

Please send all future correspondence to:

22932

Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, WA 98119-3105
(206) 265-7000

TITLE

USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of US Application Serial No. 12/291,702, filed November 13, 2008, now allowed, which is a continuation of US Application Serial No. 11/588,696, filed October 27, 2006, now US Patent No. 7,465,450, which is a divisional of US Application Serial No. 10/324,493, filed December 19, 2002, now US Patent 7,186,809, which is a continuation of US Application Serial No. 09/847,816, filed May 1, 2001, abandoned. The above-identified applications are incorporated herein by reference.

REFERENCE TO THE SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format via EFS-Web. The Sequence Listing is provided as a text file entitled 3005USCNT3st25.txt, created June 30, 2010, which is 55,527 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Interleukin-4 (IL-4), previously known as B cell stimulating factor, or BSF-1, was originally characterized by its ability to stimulate the proliferation of B cells in response to low concentrations of antibodies directed to surface immunoglobulin. IL-4 has been shown to possess a far broader spectrum of biological activities, including growth co-stimulation of T cells, mast cells, granulocytes, megakaryocytes, and erythrocytes. In addition, IL-4 stimulates the proliferation of several IL-2- and IL-3-dependent cell lines, induces the expression of class II major histocompatibility complex molecules on resting B cells, and enhances the secretion of IgE and IgG1 isotypes by stimulated B cells. IL-4 is associated with a TH2-type immune response, being one of the cytokines secreted by TH2 cells.

Murine and human IL-4 have been identified and characterized, including cloning of IL-4 cDNAs and determination of the nucleotide and encoded amino acid sequences. (See Yokota et al., *Proc. Natl. Acad. Sci. USA 83*:5894, 1986; Noma et al., *Nature 319*:640, 1986; Grabstein et al., *J. Exp. Med. 163*:1405, 1986; and U.S. Patent 5,017,691.)

IL-4 binds to particular cell surface receptors, which results in transduction of a biological signal to cells such as various immune effector cells. IL-4 receptors are described, and DNA and amino acid sequence information presented, in Mosley et al., *Cell* 59:335-348, October 20, 1989 (murine IL-4R); Idzerda et al., *J. Exp. Med*. 171:861-873, March 1990 (human IL-4R); and U.S. Patent 5,599,905. The IL-4 receptor described in these publications is sometimes referred to as IL-4Rα.

Other proteins have been reported to be associated with IL-4Rα on some cell types, and to be components of multi-subunit IL-4 receptor complexes. One such subunit is IL-2Rγ, also known as IL-2Rγc. (See the discussion of IL-4R complexes in Sato et al., *Current Opinion in Cell Biology*, 6:174-179, 1994.) IL-4Rα has been reported to be a component of certain multi-subunit IL-13 receptor complexes (Zurawski et al., *J. Biol. Chem*. 270 (23), 13869, 1995; de Vries, *J. Allergy Clin. Immunol*. 102(2):165, August 1998; and Callard et al. *Immunology Today*, 17(3):108, March 1996).

IL-4 has been implicated in a number of disorders, examples of which are allergy and asthma. Studies of biological properties of IL-4 continue, in an effort to identify additional activities associated with this pleiotrophic cytokine, and to elucidate the role IL-4 may play in various biological processes and diseases.

SUMMARY OF THE INVENTION

The present invention provides methods for treating certain conditions induced by IL-4, comprising administering an IL-4 antagonist to a patient afflicted with such a condition. Also provided are compositions for use in such methods, comprising an effective amount of an IL-4 antagonist and a suitable diluent, excipient, or carrier. Endogenous IL-4 may be contacted with an IL-4 antagonist in alternative methods, such as those involving *ex vivo* procedures.

Among the conditions to be treated in accordance with the present invention are septic arthritis, dermatitis herpetiformis, chronic idiopathic urticaria, ulcerative colitis, scleroderma, hypertrophic scarring, Whipple's Disease, benign prostate hyperplasia, lung disorders in which IL-4 plays a role, conditions in which IL-4-induced epithelial barrier disruption plays a role, disorders of the digestive system in which IL-4 plays a role, allergic reactions to medication, Kawasaki disease, sickle cell crisis, Churg-Strauss syndrome, Grave's disease, pre-eclampsia, Sjogren's syndrome, autoimmune lymphoproliferative syndrome, autoimmune hemolytic anemia, Barrett's esophagus, autoimmune uveitis,

tuberculosis, and nephrosis. IL-4 antagonists also find use as adjuvants to allergy immunotherapy and as vaccine adjuvants.

IL-4 antagonists include, but are not limited to, IL-4 receptors (IL-4R), antibodies that bind IL-4, antibodies that bind IL-4R, IL-4 muteins that bind to IL-4R but do not induce a biological response, molecules that inhibit IL-4-induced signal transduction, and other compounds that inhibit a biological effect that results from the binding of IL-4 to a cell surface IL-4R.

Examples of IL-4 receptors are soluble forms of the human IL-4 receptor of SEQ ID NO:2. Particular antibodies provided herein include human monoclonal antibodies generated by procedures involving immunization of transgenic mice. Such human antibodies may be directed against human IL-4 receptor, for example.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES 1A-C present the nucleotide sequence of the coding region of a human IL-4 receptor cDNA. The amino acid sequence encoded by the cDNA is presented as well. The cDNA clone was isolated from a cDNA library derived from a human T cell line T22. The encoded protein comprises (from N- to C-terminus) an N-terminal signal peptide, followed by an extracellular domain, a transmembrane region (underlined), and a cytoplasmic domain, as discussed further below. The DNA and amino acid sequences of Figures 1A to 1C are also presented in SEQ ID NOS:1 and 2, respectively.

Figures 2A to 2C depict targeted insertion of a neo cassette into the Sma I site of the μ1 exon. The construct was employed in generating transgenic mice, as described in Example 2. Figure 2A is a schematic diagram of the genomic structure of the μ locus. The filled boxes represent the μ exons. Figure 2B is a schematic diagram of the CmD targeting vector. The dotted lines denote those genomic μ sequences included in the construct. Plasmid sequences are not shown. Figure 2C is a schematic diagram of the targeted μ locus in which the neo cassette has been inserted into μ1.

Figures 3A and 3B present the nucleotide sequence of a vector designated pGP1k, as described in Example 3 below. This nucleotide sequence also is presented in SEQ ID NO:4.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for treating certain conditions induced by IL-4, and for inhibiting biological activities of interleukin-4 (IL-4) *in vivo*. One method comprises

administering an IL-4 antagonist to a patient afflicted with such a condition. Compositions for use in such methods for treating IL-4-induced conditions also are provided.

Among the conditions to be treated in accordance with the present invention are septic/reactive arthritis, dermatitis herpetiformis, chronic idiopathic urticaria, scleroderma, hypertrophic scarring, Whipple's Disease, benign prostate hyperplasia, lung disorders in which IL-4 plays a role, conditions in which IL-4-induced epithelial barrier disruption plays a role, disorders of the digestive system in which IL-4 plays a role, including inflammatory bowel disease and other inflammatory conditions in the gastrointestinal tract, allergic reactions to medication, Kawasaki disease, sickle cell disease (including sickle cell crisis), Churg-Strauss syndrome, Grave's disease, pre-eclampsia, Sjogren's syndrome, autoimmune lymphoproliferative syndrome, autoimmune hemolytic anemia, Barrett's esophagus, autoimmune uveitis, tuberculosis, and nephrosis, as described in more detail below. IL-4 antagonists also find use as adjuvants to allergy immunotherapy and as vaccine adjuvants.

IL-4 antagonists that may be employed include those compounds that inhibit a biological activity of IL-4. Biological activity(ies) of IL-4 that are inhibited by an antagonist in accordance with methods provided herein are activities that play a role in the particular disease to be treated.

Suitable antagonists include, but are not limited to, IL-4 receptors (IL-4R), antibodies that bind IL-4, antibodies that bind IL-4R, IL-4 muteins that bind to IL-4R but do not induce biological responses, molecules that inhibit IL-4-induced signal transduction, and other compounds that inhibit a biological effect that results from the binding of IL-4 to a cell surface IL-4R. Examples of such IL-4 antagonists are described in more detail below. Particular embodiments of the invention are directed to novel antibodies, polypeptides, and nucleic acid molecules, as described below. Antibodies provided herein include, but are not limited to, human monoclonal antibodies that bind to human IL-4 receptor, and that function as antagonists of both IL-4 and IL-13.

Indications

The present invention provides methods comprising administering an IL-4 antagonist to a patient afflicted with any of a number of conditions induced by IL-4. IL-4-induced conditions include conditions caused or exacerbated, directly or indirectly, by IL-4. Other factors or cytokines also may play a role in such conditions, but IL-4 induces or mediates the condition to some degree, i.e., at least in part.

The biological activities of IL-4 are mediated through binding to specific cell surface receptors, referred to as interleukin-4 receptors (IL-4R). IL-4-induced conditions include those arising from biological responses that result from the binding of IL-4 to a native IL-4 receptor on a cell, or which may be inhibited or suppressed by preventing IL-4 from binding to an IL-4 receptor. Conditions that may be treated include, but are not limited to, medical disorders characterized by abnormal or excess expression of IL-4, or by an abnormal host response to IL-4 production. Further examples are conditions in which IL-4-induced antibody production, or proliferation or influx of a particular cell type, plays a role. IL-4-induced disorders include those in which IL-4 induces upregulation of IL-4 receptors or enhanced production of another protein that plays a role in a disease (e.g., another cytokine).

A method for treating a mammal, including a human patient, who has such a medical disorder comprises administering an IL-4 antagonist to the mammal or otherwise contacting endogenous IL-4 with an antagonist, e.g., in an *ex vivo* procedure. Conditions that may be treated in accordance with the present invention include, but are not limited to, septic/reactive arthritis, dermatitis herpetiformis, urticaria (especially chronic idiopathic urticaria), ulcers, gastric inflammation, mucosal inflammation, ulcerative colitis, Crohn's Disease, inflammatory bowel disease, other disorders of the digestive system in which IL-4 plays a role (e.g., IL-4-induced inflammation of part of the gastrointestinal tract), conditions in which IL-4-induced barrier disruption plays a role (e.g., conditions characterized by decreased epithelial barrier function in the lung or gastrointestinal tract), scleroderma, hypertrophic scarring, Whipple's Disease, benign prostate hyperplasia, IL-4-induced pulmonary conditions (including those listed below), allergic reactions to medication, Kawasaki disease, sickle cell disease or crisis, Churg-Strauss syndrome, Grave's disease, pre-eclampsia, Sjogren's syndrome, autoimmune lymphoproliferative syndrome, autoimmune hemolytic anemia, Barrett's esophagus, autoimmune uveitis, tuberculosis, nephrosis, pemphigus vulgaris or bullous pemphigoid (autoimmune blistering diseases), and myasthenia gravis (an autoimmune muscular disease). IL-4 antagonists also find use as

adjuvants to allergy immunotherapy and as vaccine adjuvants, especially when directing the immune response toward a TH1 response would be beneficial in treating or preventing the disease in question.

Septic/reactive arthritis

IL-4 antagonists may be employed in treating septic arthritis, which also is known as reactive arthritis or bacterial arthritis. Septic arthritis can be triggered by (result from, or develop subsequent to) infection with such microbes as *Staphylococcus aureus, Chlamydia trachomatis, Yersinia* e.g., *Y. enterocolitica, Salmonella,* e.g., *S. enteritidis, Shigella* and *Campylobacter*. *S. aureus* has been reported to be the major human pathogen in septic arthritis, responsible for the majority of cases.

IL-4 and IL-4-dependent Th2 responses play roles in promoting septic arthritis. IL-4 antagonist(s) are employed in accordance with the invention, to inhibit IL-4 and also to suppress the Th2 response in patients having septic arthritis or at risk for developing septic arthritis.

IL-4 increases bacterial burden and bacterial persistence in joints, by inhibiting clearance of the bacteria. IL-4 antagonists may be employed to assist in the clearance of bacteria associated with reactive arthritis, thereby reducing clinical manifestations such as swelling in joints. IL-4 antagonists may be administered to a human patient afflicted with septic arthritis, to reduce IL-4-mediated joint inflammation. In one approach, an antagonist is injected into a joint, e.g., into synovial fluid in the knee.

The use of IL-4 antagonists may benefit patients having (or at risk for) septic arthritis by suppressing a TH2 response and promoting a TH1 response against the infection. TH2 cytokines may contribute to bacterial persistence in the joint, whereas a TH1 response plays a role in eliminating the bacteria.

The antagonists may be administered to patients infected with bacteria or other microbes such as those listed above, to prevent development of septic arthritis. Antagonist(s) may be administered after diagnosis with such an infection, but before development of clinical symptoms of septic arthritis.

Whipple's Disease

Tropheryma whippelii is the causative bacterium for Whipple's Disease, also known as intestinal lipodystrophy and lipophagia granulomatosis. The disease is characterized by steatorrhea, frequently generalized lymphadenopathy, arthritis, fever, and cough. Also

reported in Whipple's Disease patients are an abundance of "foamy" macrophages in the jejunal lamina propria, and lymph nodes containing periodic acid-schiff positive particles appearing bacilliform by electron microscopy (*Steadman's Medical Dictionary,* 26th Edition, Williams & Wilkins, Baltimore, MD, 1995).

The use of IL-4 antagonist(s) may benefit patients having (or at risk for developing) Whipple's Disease, by restoring a normal balance between the TH1 and TH2 components of the patient's immune response. Increased production of IL-4 (a TH2-type cytokine) and decreased levels of certain TH1-type cytokines have been associated with Whipple's Disease. TH2 cytokines may contribute to bacterial persistence, whereas a TH1 response plays a role in clearing the causative bacteria. IL-4 antagonists may be administered to patients infected with *T. whippelii*, whether or not the patient exhibits clinical symptoms of Whipple's Disease.

Dermatitis herpetiformis

Dermatitis herpetiformis, also known as Duhring's disease, is a chronic skin condition characterized by blistering skin lesions, cutaneous IgA deposits, and itching. Patients have an immunobullous skin disorder with an associated gluten sensitive enteropathy, which is mediated by a Th2 immune response. IL-4 antagonist(s) are administered in accordance with the present invention, to inhibit IL-4 and the Th2 response, thus promoting healing of current lesions and reducing or preventing the formation of blisters on the extensor body surfaces.

Hypertrophic scarring

In accordance with the present invention, IL-4 antagonist(s) are administered to patients who have, or are susceptible to developing, hypertrophic scarring. In one method provided herein, an IL-4 antagonist is administered to a burn patient. An immune response to burns and other injury is believed to play a role in the pathogenesis of hypertrophic scarring. Increased production of TH2-type cytokines, including IL-4, and reduced levels of certain TH1-type cytokines have been reported in burn patients who have hypertropic scarring. The use of IL-4 antagonists may benefit patients having (or at risk for developing) hypertrophic scarring, by suppressing a TH2-type immune response.

Urticaria

Urticaria, especially chronic forms thereof such as chronic idiopathic urticaria (CIU), may be treated with an IL-4 antagonist in accordance with the present invention. CIU patients have higher serum levels of IL-4 than controls, and may have a predominantly TH2-type cytokine profile. Mast cells and Th2-type T cells are implicated as primary effector cells in chronic urticaria. IL-4 stimulates mast cell proliferation. Mast cell degranulation leads to histamine release, subsequent erythema, eosinophilia, redness of skin, and itching. IL-4 antagonists are administered to inhibit IL-4 and reduce the TH2-type response, thereby helping to control a patient's urticaria.

Ulcerative colitis; other disorders of the gastrointestinal tract

IL-4 is implicated in the pathogenesis of ulcerative colitis. Th2-type cytokines including IL-4 may predominate in the colonic mucosa of patients with this disorder. The use of IL-4 antagonist(s) to suppress the TH2 response may alleviate this condition.

In addition to ulcerative colitis, other disorders of the gastrointestinal tract or digestive system may be treated with IL-4 antagonist(s). Examples of such disorders include, but are not limited to, inflammatory bowel disease (IBD), with ulcerative colitis and Crohn's Disease being forms of IBD, gastritis, ulcers, and mucosal inflammation.

Any gastrointestinal condition in which IL-4 plays a role may be treated with an IL-4 antagonist in accordance with the present invention. For example, conditions involving IL-4-induced inflammation of part of the gastrointestinal tract may be treated with an IL-4 antagonist. Particular embodiments are directed to treatment of chronic inflammatory conditions in the gastrointestinal tract.

Other embodiments are directed to conditions in which IL-4-induced barrier disruption plays a role, e.g., conditions characterized by decreased epithelial barrier function in at least a portion of the gastrointestinal tract. Such conditions may, for example, involve damage to the epithelium that is induced by IL-4, directly or indirectly.

The intestinal epithelium forms a relatively impermeable barrier between the lumen and the submucosa. Disruption of the epithelial barrier has been associated with conditions such as inflammatory bowel disease. See the discussion in Youakim, A. and M. Ahdieh (*Am. J. Physiol.* 276 (*Gastrointest. Liver Physiol.* 39):G1279-G1288, 1999), hereby incorporated by reference in its entirety. A damaged or "leaky" barrier can allow antigens to cross the barrier, which in turn elicits an immune response that may cause further damage to gastrointestinal tissue. Such an immune response may include recruitment of neutrophils

or T cells, for example. An IL-4 antagonist may be administered to inhibit undesirable stimulation of an immune response.

Lung disorders

Methods for treating IL-4-induced pulmonary disorders are provided herein. Such disorders include, but are not limited to, lung fibrosis, including chronic fibrotic lung disease, other conditions characterized by IL-4-induced fibroblast proliferation or collagen accumulation in the lungs, pulmonary conditions in which a TH2-type immune response plays a role, conditions characterized by decreased barrier function in the lung (e.g., resulting from IL-4-induced damage to the epithelium), or conditions in which IL-4 plays a role in an inflammatory response.

Cystic fibrosis is characterized by the overproduction of mucus and development of chronic infections. Inhibiting IL-4 and the Th2 response will reduce mucus production and help control infections such as allergic bronchopulmonary aspergillosis (ABPA).

Allergic bronchopulmonary mycosis occurs primarily in patients with cystic fibrosis or asthma, where a Th2 immune response is dominant. Inhibiting IL-4 and the Th2 response will help clear and control these infections.

Chronic obstructive pulmonary disease is associated with mucus hypersecrection and fibrosis. Inhibiting IL-4 and the Th2 response will reduce the production of mucus and the development of fibrous thereby improving respiratory function and delaying disease progression.

Bleomycin-induced pneumopathy and fibrosis, and radiation-induced pulmonary fibrosis are disorders characterized by fibrosis of the lung which is manifested by the influx of Th2, $CD4^+$ cells and macrophages, which produce IL-4 which in turn mediates the development of fibrosis. Inhibiting IL-4 and the Th2 response will reduce or prevent the development of these disorders.

Pulmonary alveolar proteinosis is characterized by the disruption of surfactant clearance. IL-4 increases surfactant product. Use of IL-4 antagonists will decrease surfactant production and decrease the need for whole lung lavage.

Adult respiratory distress syndrome (ARDS) may be attributable to a number of factors, one of which is exposure to toxic chemicals. One patient population susceptible to ARDS is critically ill patients who go on ventilators. ARDS is a frequent complication in such patients. IL-4 antagonists may alleviate ARDS by reducing inflammation and adhesion molecules, although methods for treating such patients in accordance with the present

invention are not limited by a particular mechanism of action. IL-4 antagonists may be used to prevent or treat ARDS.

Sarcoidosis is characterized by granulomatus lesions. Use of IL-4 antagonists to treat sarcoidosis, particularly pulmonary sarcoidosis, is contemplated herein.

Conditions in which IL-4-induced barrier disruption plays a role (e.g., conditions characterized by decreased epithelial barrier function in the lung) may be treated with IL-4 antagonist(s). Damage to the epithelial barrier in the lungs may be induced by IL-4 directly or indirectly. The epithelium in the lung functions as a selective barrier that prevents contents of the lung lumen from entering the submucosa. A damaged or "leaky" barrier allows antigens to cross the barrier, which in turn elicits an immune response that may cause further damage to lung tissue. Such an immune response may include recruitment of eosinophils or mast cells, for example. An IL-4 antagonist may be administered to inhibit such undesirable stimulation of an immune response.

IL-4 antagonists may be employed to promote healing of lung epithelium, thus restoring barrier function. IL-4 antagonists may be employed to promote healing of lung epithelium in asthmatics, for example. Alternatively, the antagonist is administered for prophylactic purposes, to prevent IL-4-induced damage to lung epithelium.

Tuberculosis

A TH2-type immune response is implicated in playing a role in causing tissue damage (e.g., necrosis of lung tissue) in tuberculosis (TB) patients. Elevated levels of IL-4 are associated with TB. IL-4 production may be particularly elevated in cavitary tuberculosis (i.e., in TB patients who have developed pulmonary cavities, which can be detected/visualized by such techniques as radiographs of the chest).

IL-4 antagonists may benefit TB patients (especially those with cavitary TB) by suppressing a TH2-type immune response, or by binding (and inactivating) excess secreted IL-4. Methods for treating such patients in accordance with the present invention are not limited by a particular mechanism of action, however. IL-4 antagonists advantageously are administered in an amount that restores the desired balance between the TH1 and TH2 components of the immune response, and reduces IL-4-induced tissue damage in a patient.

Churg-Strauss syndrome

Churg-Strauss syndrome, a disease also known as allergic granulomatous angiitis, is characterized by inflammation of the blood vessels in persons with a history of asthma or

allergy, and by eosinophilia. IL-4 antagonist(s) may be administered to alleviate inflammation in patients with this syndrome. The use of IL-4 antagonists to suppress a TH2-type immune response, and to combat eosinophilia, would benefit the patients.

Pre-eclampsia

Pre-eclampsia is a toxemia of late pregnancy. The condition is characterized by a sharp rise in blood pressure, generally accompanied by edema and albuminuria, during the third term of pregnancy.

Elevated TH1-type and TH2-type immune responses may play a role in the condition. One method provided herein comprises administering an IL-4 antagonist to a pregnant woman who has developed pre-eclampsia. The IL-4 antagonist is administered in an amount, and for a period of time, sufficient to reduce the level of IL-4 (or of TH2-type cytokines collectively) to a level that is considered normal during pregnancy. In general, the IL-4 antagonist is administered repeatedly throughout the duration of the pregnancy.

Scleroderma

IL-4 antagonist(s) are administered to scleroderma patients in accordance with the invention. The antagonists reduce IL-4-induced collagen synthesis by fibroblasts in the patients. The antagonists may be employed in preventing or reducing fibrosis in skin and lung tissues, as well as other tissues in which fibrosis occurs in scleroderma patients, suppressing collagen synthesis in such tissues, and in treating scleroderma-related pulmonary disease.

Benign Prostate Hyperplasia

Benign prostate hyperplasia (BPH), also known as benign prostate hypertrophy, may be treated with IL-4 antagonist(s). While not wishing to be bound by a particular mechanism of action, administration of an IL-4 inhibitor may benefit a patient with BPH by suppressing IL-4-induced inflammation, or by suppressing a TH2-type immune response.

Grave's Disease

Antibodies directed against thyrotropin receptor play an important role in Grave's Disease, a disorder characterized by hyperthyroidism. Studies of cytokine production in Grave's Disease patients show a shift toward a TH2-type cytokine response. Use of an IL-4

antagonist to suppress the TH2-type immune response, and suppress antibody production, would benefit Grave's Disease patients.

Sickle Cell Disease

Sickle cell disease patients typically experience intermittent periods of acute exacerbation called crises, with the crises being categorized as anemic or vaso-occlusive. IL-4 antagonists find use in treating or preventing sickle cell crisis, especially in patients with elevated IL-4 levels or in whom the immune response has shifted toward a TH2-type response. Sickle cell disease (especially sickle cell crisis) has been associated with increased susceptibility to infectious diseases, including bacterial infections. Administering IL-4 antagonists to sickle cell disease patients may help the patient mount an immune response against infectious diseases.

Sjogren's syndrome

The autoimmune disease known as Sjogren's syndrome or sicca syndrome typically combines dry eyes and dry mouth with a disorder of the connective tissues, such as rheumatoid arthritis, lupus, scleroderma, or polymyositis. The vast majority of patients are middle age (or older) females. Sjogren's syndrome is an inflammatory disease of glands (e.g., lacrimal and salivary glands) and other tissues of the body. The syndrome typically is associated with autoantibody production.

IL-4 antagonists may be administered to reduce the inflammatory response (such as inflammation of glands, including lacrimal glands) in such patients. IL-4 antagonists may benefit Sjogren's syndrome patients by suppressing a TH2-type immune response, or by binding (and inactivating) excess IL-4 at inflammatory lesions. Methods for treating patients in accordance with the present invention are not limited by a particular mechanism of action, however.

Autoimmune lymphoproliferative syndrome

Manifestations of autoimmune lymphoproliferative syndrome include lymphoproliferation and autoantibody production. Patients with the syndrome reportedly have an inherited deficiency in apoptosis. IL-4 antagonists may benefit patients with this syndrome by suppressing a TH2-type immune response, or by binding (and inactivating) excess IL-4 at sites of inflammation. Methods for treating such patients in accordance with the present invention are not limited by a particular mechanism of action, however.

Autoimmune hemolytic anemia

Excessive IL-4 secretion, and a deficiency in TH1-type cytokines, are implicated in contributing to the pathogenesis of autoimmune hemolytic anemia. IL-4 antagonists are administered in accordance with the present invention, to benefit the patients by reducing autoantibody production, and by restoring a more normal balance between the TH1 and TH2 components of the immune response.

Autoimmune uveitis

Uveitis involves inflammation of the uvea (generally considered to include the iris, ciliary body, and choroid, considered together). Excess IL-4 secretion is implicated as playing a role in pathogenesis of this sight-threatening inflammatory eye disease. In accordance with the present invention, IL-4 antagonist(s) are administered to a uveitis patient to reduce disease severity. In one embodiment, IL-4 antagonist(s) are administered to an individual who has autoimmune uveoretinitis.

Kawasaki Disease

Also known as the mucocutaneous lymph node syndrome, Kawasaki disease (KD) mainly afflicts young children. The disease is characterized by particular changes in the mucus membranes lining the lips and mouth, and by enlarged, tender lymph glands. Symptoms typically include fever, conjunctivitis, inflammation of the lips and mucous membranes of the mouth, swollen glands in the neck, and a rash covering the hands and feet, leading to hardened, swollen and peeling skin on hands and feet. In children with Kawasaki Disease (KD), inflammation of arteries (vasculitis) may develop. Due to the effect of the disease on the vascular system, KD reportedly is the main cause of acquired heart disease in children.

IL-4 antagonists may be administered to patients with Kawasaki Disease, to reduce the elevated levels of IL-4 in the patient. Excessive IL-4 secretion and a deficiency in TH1-type cytokines contribute to the pathogenesis of the disease.

Barrett's esophagus

Barrett's esophagus is a condition characterized by alteration (subsequent to irritation) of the cells in the epithelial tissue that lines the lower portion of the esophagus. Frequent reflux of the stomach contents into the esophagus, over time, can lead to Barrett

esophagus. Patients with Barrett esophagus are at risk for developing esophageal cancer (e.g., adenocarcinoma). While not wishing to be bound by a particular mechanism of action, administration of an IL-4 antagonist may benefit a patient with Barrett's esophagus by suppressing a TH2-type immune response. In one embodiment, an IL-4 antagonist is administered to a patient with esophagitis, to inhibit progression to Barrett's esophagus.

Nephrosis

Nephrosis, also known as nephrotic syndrome, is kidney disease that is non-inflammatory and non-malignant. In the condition known as minimal change nephrosis, glomerular damage (believed to arise from structural changes in glomerular visceral epithelial cells) results in abnormalities that include proteinuria. A TH2-type immune response (especially secretion of the TH2-type cytokines IL-4 and IL-13) are implicated as playing a role in pathogenesis of minimal change nephrosis.

Other indications

Additional examples of conditions that may be treated in accordance with the present invention include but are not limited to the following. IL-4 antagonists may be employed in treating or preventing hyper IgE syndrome, idiopathic hypereosinophil syndrome, allergic reactions to medication, autoimmune blistering diseases (e.g., pemphigus vulgaris or bullous pemphigoid), myasthenia gravis (an autoimmune muscular disease), and chronic fatigue syndrome. IL-4 inhibitors may be employed in treating GVHD; particular methods for treating GVHD combination therapy with other therapeutic agents as described below. IL-4 inhibitors also find use in treating or preventing hepatotoxicity induced by drugs such as diclofenac (a non-steroidal anti-inflammatory drug).

An IL-4 antagonist may be employed as an adjuvant to allergy immunotherapy treatment. IL-4 antagonists find further use as vaccine adjuvants, such as adjuvants for cancer vaccines and infectious disease vaccines. The use of IL-4 antagonists is especially advantageous when favoring a TH1-type immune response would be beneficial in preventing or treating the condition for which the vaccine is being administered. IL-4 antagonists may be employed when reducing an antibody-mediated immune response and/or promoting a T-cell-mediated immune response is desired.

IL-4 Antagonists

IL-4 antagonists that may be employed in accordance with the present invention include compounds that inhibit a biological activity of IL-4. The IL-4-induced biological activities to be inhibited by the methods provided herein are activities that directly or indirectly play a role in the condition to be treated.

Examples of IL-4 antagonists include, but are not limited to, IL-4 receptors (IL-4R), antibodies, other IL-4-binding molecules, and IL-4 muteins as discussed further below. The antibodies may bind IL-4 or may bind an IL-4 receptor, for example.

Antagonists that bind IL-4 include but are not limited to IL-4 receptors and anti-IL-4 antibodies. Endogenous IL-4 that becomes bound to such an antagonist is thereby prevented from binding its natural receptor on cell surfaces *in vivo*, and thus cannot manifest IL-4-mediated biological activities.

Different types of antagonists may act at different sites or by different mechanisms of action. Examples include but are not limited to antagonists that interfere with binding of IL-4 to cell surface receptors or that inhibit signal transduction. The site of action may be intracellular (e.g., by interfering with an intracellular signaling cascade), on a cell surface, or extracellular. Antagonists that act by interfering with the interaction of IL-4 with IL-4R may bind to either IL-4 or to the receptor. An antagonist need not completely inhibit an IL-4 induced activity to find use in the present invention; rather, antagonists that reduce a particular activity of IL-4 are contemplated for use as well.

The above-presented discussions of particular mechanisms of action for IL-4 antagonists in treating particular diseases are illustrative only, and the methods presented herein are not bound thereby. The mechanisms of action by which IL-4 antagonists ameliorate diseases are not limited to those discussed above.

In treating particular disorders, an IL-4 antagonist may reduce the amount of active IL-4 at a particular site within the body that is involved in the disorder. Antagonists that bind IL-4 such that it no longer can bind to endogenous cellular receptors functionally reduce the amount of active IL-4 available for inducing biological responses.

An IL-4 antagonist may alleviate a disorder by reducing the amount of free endogenous IL-4 that is circulating in the body, e.g., in the bloodstream or in a particular tissue. When the action of IL-4 on such tissue plays a role in pathogenesis of the disease, the antagonist serves to block action of IL-4 in the tissue, thereby alleviating the disorder. In a further example, antagonists may inhibit IL-4-induced recruitment of cells to a site or tissue within the body, wherein such recruitment plays a role in causing or exacerbating a disease.

The antagonists may inhibit an IL-4-mediated influx of cells involved in an immune or inflammatory response. An antagonist may act by reducing proliferation, activation, migration, influx, or accumulation of a particular cell type, or by inhibiting a biological response directly or indirectly attributable to a particular cell type. Examples of particular cell types are fibroblasts, mast cells, and eosinophils.

As discussed above, some conditions may be treated by suppressing a TH2-type immune response. IL-4 is associated with a TH2 response, and is one of the cytokines secreted by T-helper cells of type 2 (TH2 cells). An IL-4 antagonist may be administered to reduce a TH2-type immune response. The IL-4 antagonist may be said to reduce proliferation of TH2 cells, to suppress a TH2 response, to shift the immune response toward a TH1 response, or to favor a TH1-type response. The use of antagonists of other cytokines associated with a TH2-type immune response is discussed below. Antagonists of other TH2-type cytokine(s), such as IL-5, IL-10, or IL-13, may be administered to patients who have a disorder involving elevated levels of such cytokines. Techniques for measuring the amount of such cytokines in a patient, e.g., in the patient's serum, are well known.

One embodiment of the invention is directed to a method for inhibiting IL-4-induced damage to epithelium, comprising administering an IL-4 antagonist to an individual who has, or is at risk of developing, a condition in which IL-4-mediated epithelial barrier disruption plays a role. In accordance with the present invention, barrier function studies revealed that IL-4 plays a role in reduction of barrier function in models of lung epithelium and intestinal epithelium, and that a soluble human IL-4 receptor polypeptide (an IL-4 antagonist) inhibits the IL-4-mediated reduction of barrier function (see example 7).

Particular embodiments of methods provided herein comprise administering an IL-4 antagonist to inhibit IL-4-induced damage to epithelium in the gastrointestinal tract or lung. Such methods may be employed to prevent epithelial damage, or to restore epithelial barrier function (i.e., promote repair or healing of the epithelium). The ability of an IL-4 antagonist to inhibit IL-4-induced damage to epithelium may be confirmed in any of a number of suitable assays, such as those described in example 7 below.

Any inflammation associated with (or subsequent to) an infection also may be treated with an IL-4 antagonist. The antagonist may be administered to inhibit any IL-4-induced component of an inflammatory response resulting from microbial infection in the gastrointestinal tract, for example.

Combinations of two or more antagonists may be employed in methods and compositions of the present invention. Examples of suitable IL-4 antagonists are as follows.

IL-4 Receptor

A preferred IL-4 antagonist is an IL-4 receptor (IL-4R). When administered *in vivo*, IL-4R polypeptides circulate in the body and bind to circulating endogenous IL-4 molecules, preventing interaction of IL-4 with endogenous cell surface IL-4 receptors, thus inhibiting transduction of IL-4-induced biological signals.

IL-4 receptors are described in U.S. Patent 5,599,905; Idzerda et al., *J. Exp. Med.* 171:861-873, March 1990 (human IL-4R); and Mosley et al., *Cell* 59:335-348, October 20, 1989 (murine IL-4R); each of which is hereby incorporated by reference. The protein described in those three references is sometimes referred to in the scientific literature as IL-4Rα. Unless otherwise specified, the terms "IL-4R" and "IL-4 receptor" as used herein encompass this protein in various forms that are capable of functioning as IL-4 antagonists, including but not limited to soluble fragments, fusion proteins, oligomers, and variants that are capable of binding IL-4, as described in more detail below.

The nucleotide sequence of a human IL-4R cDNA, and the amino acid sequence encoded thereby, are set forth in Figures 1A-1C. The cDNA clone was isolated from a cDNA library derived from a $CD4^+/CD8^-$ human T cell clone designated T22, as described in Idzerda et al., *J. Exp. Med.*, 171:861, March 1990, and in U.S. Patent 5,599,905, which are hereby incorporated by reference in their entirety. The DNA and amino acid sequences of Figures 1A-1C are presented in SEQ ID NO:1 and SEQ ID NO:2, respectively.

The encoded human IL-4R protein comprises (from N- to C-terminus) an N-terminal signal peptide, followed by an extracellular domain, a transmembrane region, and a cytoplasmic domain. The transmembrane region, which is underlined in Figure 1A, corresponds to amino acids 208 through 231. The cytoplasmic domain comprises amino acids 232 through 800.

A signal peptide includes amino acids -25 to -1 of SEQ ID NO:2. An alternative signal peptide cleavage site occurs between residues -3 and -2 of SEQ ID NO:2, such that the signal peptide corresponds to residues -25 through -3.

As is recognized in the pertinent field, the signal peptide cleavage site for a given protein may vary according to such factors as the particular expression system (especially the host cells) in which the protein is expressed. The exact boundaries of the signal peptide, and thus the extracellular domain, of a given recombinant protein thus may depend on the expression system employed. Further, the signal peptide may be cleaved at more

than one position, generating more than one species of polypeptide in a preparation of recombinant protein.

In one embodiment, in which an expression vector comprises DNA encoding amino acids -25 through 207 of SEQ ID NO:2, the expressed recombinant IL-4R includes two species of mature soluble human IL-4R. The expressed polypeptides include a major species corresponding to amino acids -2 to 207 and a minor species corresponding to amino acids 1 to 207 of SEQ ID NO:2. Two alternate forms of the extracellular domain of human IL-4R thus correspond to residues -2 to 207 and 1 to 207 of SEQ ID NO:2. The term "mature" refers to a protein in a form lacking a signal peptide or leader sequence, as is understood in the pertinent art.

Among the IL-4 receptors suitable for use herein are IL-4R fragments. Truncated IL-4R polypeptides may occur naturally, e.g., as a result of proteolytic cleavage, post-translational processing, or alternative splicing of mRNA. Alternatively, fragments may be constructed by deleting terminal or internal portions of an IL-4R sequence, e.g., *via* recombinant DNA technology. Fragments that retain the ability to bind IL-4 may be identified in conventional binding assays. Such fragments may be soluble fragments, as discussed below.

In a preferred embodiment of the invention, the antagonist comprises a soluble form of the IL-4R. A soluble IL-4 receptor is a polypeptide that is secreted from the cell in which it is expressed, rather than being retained on the cell surface. The full length human IL-4R protein of SEQ ID NO:2 is a transmembrane protein, which, as described above, comprises an N-terminal signal peptide, followed by an extracellular domain, a transmembrane region, and a C-terminal cytoplasmic domain. Soluble IL-4R polypeptides lack the transmembrane region that would cause retention on the cell, and the soluble polypeptides consequently are secreted into the culture medium. The transmembrane region and intracellular domain of IL-4R may be deleted or substituted with hydrophilic residues to facilitate secretion of the receptor into the cell culture medium.

Particular embodiments of soluble IL-4R polypeptides lack the transmembrane region but comprise the extracellular domain (the complete extracellular domain or a fragment thereof that is capable of binding IL-4). As one option, the polypeptide comprises all or part of the cytoplasmic domain, as well as the extracellular domain (or fragment of the extracellular domain), but lacks the transmembrane region.

Examples of soluble human IL-4R polypeptides include, but are not limited to, polypeptides comprising amino acid residues x to y of SEQ ID NO:2, wherein x represents 1

or -2 and y represents an integer from 197 to 207. Preferred embodiments include polypeptides comprising residues 1 to 207 or -2 to 207 of SEQ ID NO:2.

A protein preparation administered as an IL-4 antagonist may comprise more than one form of IL-4R. For example, the preparation may comprise polypeptide molecules consisting of amino acids 1 to 207 of SEQ ID NO:2, as well as polypeptides consisting of amino acids -2 to 207 of SEQ ID NO:2.

IL-4R polypeptides arising from alternative mRNA constructs, e.g., which can be attributed to different mRNA splicing events following transcription, and which yield polypeptide translates capable of binding IL-4, are among the IL-4R polypeptides disclosed herein. Such alternatively spliced mRNAs may give rise to soluble polypeptides.

Further examples of IL-4 receptors that may be employed in the methods provided herein are variants having amino acid sequences which are substantially similar to the native interleukin-4 receptor amino acid sequence of SEQ ID NO:2, or fragments thereof. Variant IL-4 receptor polypeptides that are capable of functioning as IL-4 antagonists may be employed in the methods of the present invention.

Any of a number of conventional assay techniques may be employed to confirm that a given form of IL-4R (e.g., an IL-4R fragment or variant) functions as an IL-4 antagonist. Examples include binding assays or assays that test the ability of a given IL-4R polypeptide to inhibit transduction of an IL-4-induced biological signal. Examples of suitable *in vitro* assays are described below.

"Substantially similar" IL-4 receptors include those having amino acid or nucleic acid sequences that vary from a native sequence by one or more substitutions, deletions, or additions, but retain a desired biological activity of the IL-4R protein. Examples of nucleic acid molecules encoding IL-4 receptors include, but are not limited to: (a) DNA derived from the coding region of a native mammalian IL-4R gene; (b) DNA that is capable of hybridization to a DNA of (a) under moderately stringent conditions and which encodes an IL-4R having a biological activity of a native IL-4R; or (c) DNA that is degenerate as a result of the genetic code to a DNA defined in (a) or (b) and which encodes an IL-4R having a biological activity of a native IL-4R. Due to code degeneracy, there can be considerable variation in nucleotide sequences encoding the same amino acid sequence.

Variants may be naturally occurring, such as allelic variants or those arising from alternative splicing of mRNA. Alternatively, variants may be prepared by such well known techniques as *in vitro* mutagenesis.

A variant sequence identified by Idzerda et al., *supra*, comprises a GTC codon encoding the amino acid valine (Val) at position 50, instead of isoleucine (Ile). The variant sequence is otherwise identical to the sequence of SEQ ID NOS:1 and 2. IL-4R fragments, such as soluble fragments, comprising Val at position 50 are provided herein.

In particular embodiments, an IL-4 receptor DNA or amino acid sequence is at least 80 percent identical to the sequence of a native IL-4R. Preferably, an IL-4R DNA or polypeptide comprises a sequence that is at least 90 percent identical to a native IL-4R DNA or amino acid sequence. One example is a human IL-4R comprising an amino acid sequence that is at least 80 percent identical to the sequence presented in SEQ ID NO:2. Another example is a soluble IL-4R comprising an amino acid sequence at least 80 percent identical to the sequence of the extracellular domain of human IL-4R. Further examples are polypeptides comprising amino acid sequences that are at least 90 percent identical to the sequence presented in SEQ ID NO:2, or a fragment thereof. In a particular embodiment, the polypeptide comprises no more than 10 amino acid substitutions. IL-4R polypeptides that retain the ability to bind IL-4 may be identified in conventional binding assays.

Percent similarity or percent identity may be determined, for example, by comparing DNA or amino acid sequence information using the GAP computer program, version 6.0, available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol. 48*:443, 1970), as revised by Smith and Waterman (*Adv. Appl. Math. 2*:482, 1981). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids) which are similar, divided by the total number of symbols in the shorter of the two sequences. The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res. 14*:6745, 1986, as described by Schwartz and Dayhoff, ed., *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

IL-4R polypeptides that vary from native proteins but possess a desired property may be constructed by, for example, substituting or deleting residues not needed for the particular biological activity. Substitutions may be conservative substitutions, such that a desired biological property of the protein is retained. Amino acids may be replaced with residues having similar physicochemical characteristics.

Cysteine residues can be deleted or replaced with other amino acids to prevent formation of incorrect intramolecular disulfide bridges upon renaturation. Other alterations of a native sequence involve modification of adjacent dibasic amino acid residues, to enhance expression in yeast host cells in which KEX2 protease activity is present.

The present invention also includes IL-4R with or without associated native-pattern glycosylation. The glycosylation pattern may vary according to the type of host cells in which the protein is produced. Another option is inactivation of N-glycosylation sites by site-specific mutagenesis. N-glycosylation sites in eukaryotic proteins are characterized by the amino acid triplet Asn-A_1-Z, where A_1 is any amino acid except Pro, and Z is Ser or Thr. In this sequence, asparagine provides a side chain amino group for covalent attachment of carbohydrate. Such a site can be eliminated by substituting another amino acid for Asn or for residue Z, deleting Asn or Z, or inserting a non-Z amino acid between A_1 and Z, or an amino acid other than Asn between Asn and A_1.

Oligonucleotide-directed site-specific mutagenesis procedures can be employed to provide an altered gene having particular codons altered according to the substitution, deletion, or insertion required. Examples of techniques for making such alterations are described in Walder et al. (*Gene 42*:133, 1986); Bauer et al. (*Gene 37*:73, 1985); Craik (*BioTechniques*, January 1985, 12-19); Smith et al. (*Genetic Engineering: Principles and Methods*, Plenum Press, 1981); and U.S. Patent Nos. 4,518,584 and 4,737,462.

IL-4 receptors that may be employed also include derivatives, e.g., various structural forms of the primary protein which retain a desired biological activity. Due to the presence of ionizable amino and carboxyl groups, for example, an IL-4R protein may be in the form of acidic or basic salts, or in neutral form. Individual amino acid residues may also be modified by oxidation or reduction. The primary amino acid structure may be modified by forming covalent or aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like, or by creating amino acid sequence mutants. PEGylated derivatives (modified with polyethylene glycol) are contemplated. Covalent derivatives may be prepared by linking particular functional groups to IL-4R amino acid side chains or at the N- or C-termini. IL-4R derivatives may also be obtained by cross-linking agents, such as M-maleimidobenzoyl succinimide ester and N-hydroxysuccinimide, at cysteine and lysine residues. IL-4R proteins may also be covalently bound through reactive side groups to various insoluble substrates, such as cyanogen bromide-activated,

bisoxirane-activated, carbonyldiimidazole-activated or tosyl-activated agarose structures, or by adsorbing to polyolefin surfaces (with or without glutaraldehyde cross-linking).

Other derivatives of IL-4R within the scope of this invention include covalent or aggregative conjugates of IL-4R or its fragments with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an IL-4R polypeptide. For example, the conjugated peptide may be a heterologous signal (or leader) polypeptide, e.g., the yeast α-factor leader, or a peptide such as an epitope tag. IL-4R-containing fusion proteins can comprise peptides added to facilitate purification or identification of IL-4R (e.g., poly-His). Specific examples of poly-His fusion constructs that is biologically active are soluble human IL-4R (e.g., comprising residues -2 to 207 or 1-207 of SEQ ID NO:2) His His and soluble human IL-4R His His His His His His. An amino acid sequence of IL-4 receptor can also be linked to the Flag® peptide Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (DYKDDDDK) (SEQ ID NO:3) as described in Hopp et al., *Bio/Technology* 6:1204, 1988, and U.S. Patent 5,011,912. The Flag® peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the Flag® peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, MO).

Oligomers that contain IL-4R polypeptides may be employed as IL-4 antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more IL-4R polypeptides are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, heterotrimers, and the like, which comprise an IL-4R polypeptide as well as at least one polypeptide that is not derived from the IL-4R of SEQ ID NO:2.

One embodiment is directed to oligomers comprising multiple IL-4R polypeptides joined *via* covalent or non-covalent interactions between peptide moieties fused to the IL-4R polypeptides. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of IL-4R polypeptides attached thereto, as described in more detail below.

In particular embodiments, the oligomers comprise from two to four IL-4R polypeptides. The IL-4R moieties of the oligomer may be in any of the forms described above, e.g., variants or fragments. Preferably, the oligomers comprise soluble IL-4R polypeptides.

As one alternative, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al. (*PNAS USA* 88:10535, 1991); Byrn et al. (*Nature* 344:677, 1990); and Hollenbaugh and Aruffo ("Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1 - 10.19.11, 1992).

One embodiment of the present invention is directed to a dimer comprising two fusion proteins created by fusing IL-4R to the Fc region of an antibody. A gene fusion encoding the IL-4R/Fc fusion protein is inserted into an appropriate expression vector. IL-4R/Fc fusion proteins are expressed in host cells transformed with the recombinant expression vector, and allowed to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield divalent IL-4R.

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization are also included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 (hereby incorporated by reference), is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Patent 5,457,035 and in Baum et al., (*EMBO J.* 13:3992-4001, 1994). The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

In other embodiments, IL-4R may be substituted for the variable portion of an antibody heavy or light chain. If fusion proteins are made with both heavy and light chains of an antibody, it is possible to form an oligomer with as many as four IL-4R extracellular regions.

Soluble recombinant fusion proteins comprising an IL-4R and various portions of the constant region of an immunoglobulin are described in EP 464,533, along with procedures

for preparing such fusion proteins and dimers thereof. Among the fusion proteins described in EP 464,533 are those comprising the extracellular portion of human IL-4R and an Fc polypeptide.

Alternatively, the oligomer is a fusion protein comprising multiple IL-4R polypeptides, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233.

Another method for preparing oligomeric IL-4R involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., *Science* 240:1759, 1988), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al. (*FEBS Letters* 344:191, 1994), hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al. (*Semin. Immunol.* 6:267-278, 1994). In one approach, recombinant fusion proteins comprising a soluble IL-4R polypeptide fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric IL-4R that forms is recovered from the culture supernatant.

One example of a heterodimer comprises an IL-4R polypeptide derived from the human IL-4R of SEQ ID NO:2, and an IL-2Rγ polypeptide. IL-2Rγ (also known as IL-2Rγ_c) is described in U.S. Patent 5,510,259 and in Takeshita et al. (*Science* 257:379, 17 July 1992), which are incorporated by reference herein. The polypeptides may be in one of the various forms described herein, e.g., soluble fragments, variants, and the like, derived from the indicated proteins. One embodiment of such a heterodimer comprises a soluble IL-4R/Fc fusion protein and a soluble IL-2Rγ/Fc fusion protein. Such heterodimers are described in WO 96/11213, along with IL-4R homodimers.

Other examples of heterodimers comprise an IL-4R subunit (preferably a soluble fragment of the protein of SEQ ID NO:2) and at least one IL-13 receptor subunit. IL-13 receptor (IL-13R) complexes and IL-13R polypeptides (such as polypeptides designated IL-13Rα1 and IL-13Rα2) are described in Zurawski et al., *J. Biol. Chem.* 270 (23), 13869, 1995; de Vries, *J. Allergy Clin. Immunol.* 102(2):165, August 1998; Callard et al.

Immunology Today, 17(3):108, March 1996, and U.S. Patent 5,710,023, each of which is incorporated by reference herein. In one embodiment, a heterodimer comprises a soluble human IL-4R and a soluble IL-13R (preferably a soluble form of the polypeptide described in U.S. Patent 5,710,023 or IL-13Rα1). The components of heterodimers may be any suitable form of the polypeptides that retains the desired activity, such as fragments, variants, or fusion proteins (e.g., fusions of soluble receptor polypeptides with Fc polypeptides, leucine zipper peptides, peptide linkers, or epitope tags).

IL-4 receptor polypeptides and fusion proteins described herein may be prepared by any of a number of conventional techniques. IL-4R polypeptides may be purified from cells that naturally express the receptor (such as the cells discussed in Park et al., *Proc. Natl. Acad. Sci. USA* 84:1669-673, 1987), or may be produced in recombinant expression systems, using well known techniques. Expression systems for use in producing IL-4R include those described in U.S. Patent 5,599,905, which is hereby incorporated by reference.

A variety of expression systems are known for use in producing recombinant proteins. In general, host cells are transformed with a recombinant expression vector that comprises DNA encoding a desired IL-4R polypeptide. Among the host cells that may be employed are prokaryotes, yeast or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or bacilli. Higher eukaryotic cells include insect cells and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman et al., *Cell 23*:175, 1981), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, BHK (ATCC CRL 10) cell lines, and the CVI/EBNA cell line derived from the African green monkey kidney cell line CVI (ATCC CCL 70) as described by McMahan et al. (*EMBO J.* 10: 2821, 1991). Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (*Cloning Vectors: A Laboratory Manual*, Elsevier, New York, 1985).

The transformed cells are cultured under conditions that promote expression of the IL-4R, and the polypeptide is recovered by conventional protein purification procedures. One such purification procedure includes the use of affinity chromatography, e.g., over a matrix having IL-4 bound thereto. Expressed IL-4R will be deposited in the cell membrane or secreted into the culture supernatant, depending on the IL-4R DNA selected.

Polypeptides contemplated for use herein include substantially homogeneous recombinant mammalian IL-4R polypeptides substantially free of contaminating endogenous materials.

Antibodies

Antibodies that function as IL-4 antagonists may be employed in the methods of the present invention. The antibodies preferably are monoclonal antibodies or antigen-binding fragments thereof. Advantageously, humanized or chimeric monoclonal antibodies are employed. Most preferred are human monoclonal antibodies prepared using transgenic mice, as described below.

Examples of suitable antibodies are those that interfere with the binding of IL-4 to an IL-4 receptor. Such antibodies, referred to herein as blocking antibodies, may be raised against either IL-4 or IL-4R, and screened in conventional assays for the ability to interfere with binding of IL-4 to IL-4 receptors. Examples of suitable assays are assays that test the antibodies for the ability to inhibit binding of IL-4 to cells expressing IL-4R, or that test antibodies for the ability to reduce a biological or cellular response that results from the binding of IL-4 to cell surface IL-4 receptors.

It has been reported that IL-4Rα is a component of certain multi-subunit IL-13 receptor complexes (Zurawski et al., *J. Biol. Chem.* 270 (23), 13869, 1995; de Vries, *J. Allergy Clin. Immunol*. 102(2):165, August 1998; and Callard et al. Immunology Today, 17(3):108, March 1996, each incorporated by reference herein). Thus, some antibodies raised against IL-4Rα may interfere with the binding of IL-13 to such receptor complexes.

In one embodiment, antibodies directed against IL-4R block binding of IL-4 and also IL-13 to cells. The antibodies inhibit IL-4-induced biological activity and also inhibit IL-13-induced activity, and thus may be employed in treating conditions induced by either or both cytokines. Examples of such conditions include but are not limited to IgE-mediated conditions, asthma, allergic conditions, allergic rhinitis, and dermatitis including atopic dermatitis.

Antibodies that bind to IL-4R and inhibit IL-4 binding may be screened in various conventional assays to identify those antibodies that also interfere with the binding of IL-13 to such receptor complexes. Antibodies may be screened in binding assays or tested for the ability to inhibit an IL-4-induced and an IL-13-induced biological activity. An example of a suitable assay is illustrated in Example 5 below.

Antibodies specific for IL-4 or IL-4R may be prepared by well known procedures. See, for example, *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Kennet et al. (eds.), Plenum Press, New York (1980); and *Antibodies: A Laboratory Manual*, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1988).

Antigen-binding fragments of such antibodies may be produced by conventional techniques. Examples of such fragments include, but are not limited to, Fab and $F(ab')_2$ fragments. Antibody fragments and derivatives produced by genetic engineering techniques are also contemplated for use. Unless otherwise specified, the terms "antibody" and "monoclonal antibody" as used herein encompass both whole antibodies and antigen-binding fragments thereof.

Additional embodiments include chimeric antibodies, e.g., humanized versions of murine monoclonal antibodies. Such humanized antibodies may be prepared by known techniques, and offer the advantage of reduced immunogenicity when the antibodies are administered to humans. In one embodiment, a humanized monoclonal antibody comprises the variable region of a murine antibody (or just the antigen binding site thereof) and a constant region derived from a human antibody. Alternatively, a humanized antibody fragment may comprise the antigen binding site of a murine monoclonal antibody and a variable region fragment (lacking the antigen-binding site) derived from a human antibody. Procedures for the production of chimeric and further engineered monoclonal antibodies include those described in Riechmann et al. (*Nature 332*:323, 1988), Liu et al. (*PNAS 84*:3439, 1987), Larrick et al. (*Bio/Technology 7*:934, 1989), and Winter and Harris (*TIPS 14*:139, May, 1993).

A method for producing an antibody comprises immunizing a non-human animal, such as a transgenic mouse, with an IL-4R polypeptide, whereby antibodies directed against the IL-4R polypeptide are generated in said animal. Procedures have been developed for generating human antibodies in non-human animals. The antibodies may be partially human, or preferably completely human. For example, transgenic mice into which genetic material encoding one or more human immunoglobulin chains has been introduced may be employed. Such mice may be genetically altered in a variety of ways. The genetic manipulation may result in human immunoglobulin polypeptide chains replacing endogenous immunoglobulin chains in at least some (preferably virtually all) antibodies produced by the animal upon immunization.

Mice in which one or more endogenous immunoglobulin genes have been inactivated by various means have been prepared. Human immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes. Antibodies produced in the animals incorporate human immunoglobulin polypeptide chains encoded by the human genetic material introduced into the animal.

Examples of techniques for production and use of such transgenic animals are described in U.S. Patents 5,814,318, 5,569,825, and 5,545,806, which are incorporated by reference herein. Examples 2-4 below provide further description of the preparation of transgenic mice useful for generating human antibodies directed against an antigen of interest.

Antibodies produced by immunizing transgenic non-human animals with an IL-4R polypeptide are provided herein. Transgenic mice into which genetic material encoding human immunoglobulin polypeptide chain(s) has been introduced are among the suitable transgenic animals. Examples of such mice include, but are not limited to, those containing the genetic alterations described in the examples below. One example of a suitable immunogen is a soluble human IL-4R, such as a polypeptide comprising the extracellular domain of the protein of SEQ ID NO:2, or other immunogenic fragment of the protein of SEQ ID NO:2.

Monoclonal antibodies may be produced by conventional procedures, e.g., by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells may be fused with myeloma cells to produce hybridomas, by conventional procedures.

A method for producing a hybridoma cell line comprises immunizing such a transgenic animal with an IL-4R immunogen; harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; and identifying a hybridoma cell line that produces a monoclonal antibody that binds an IL-4R polypeptide. Such hybridoma cell lines, and anti-IL-4R monoclonal antibodies produced therefrom, are encompassed by the present invention. Monoclonal antibodies secreted by the hybridoma cell line are purified by conventional techniques. Hybridomas or MAbs may be further screened to identify MAbs with particular properties, such as the ability to block an IL-4-induced activity, and to block an IL-13-induced activity (see the assay in example 5).

Human antibodies that bind IL-4R are provided by the present invention. In one embodiment of the invention, human antibodies raised against IL-4R and produced by

techniques involving use of transgenic mice, block binding of IL-4 and also IL-13 to cells. Such antibodies are IL-4 antagonists and additionally function as IL-13 antagonists.

Among the uses of antibodies directed against an IL-4R is use in assays to detect the presence of IL-4R polypeptides, either *in vitro* or *in vivo*. The antibodies also may be employed in purifying IL-4R proteins by immunoaffinity chromatography. Those antibodies that additionally can block binding of IL-4 to IL-4R may be used to inhibit a biological activity that results from such binding. Blocking antibodies find use in the methods of the present invention. Such antibodies which function as IL-4 antagonists may be employed in treating any IL-4-induced condition, including but not limited to asthma and allergies, e.g., allergic rhinitis, contact dermatitis, and atopic dermatitis. In one embodiment, a human anti-IL-4R monoclonal antibody generated by procedures involving immunization of transgenic mice is employed in treating such conditions.

Antibodies may be employed in an *in vitro* procedure, or administered *in vivo* to inhibit an IL-4-induced biological activity. Disorders caused or exacerbated (directly or indirectly) by the interaction of IL-4 with cell surface IL-4 receptors thus may be treated. A therapeutic method involves *in vivo* administration of a blocking antibody to a mammal in an amount effective for reducing an IL-4-induced biological activity.

Antibodies of the invention include, but are not limited to, partially human (preferably fully human) monoclonal antibodies that inhibit a biological activity of IL-4 and also inhibit a biological activity of IL-13. One embodiment is directed to a human monoclonal antibody that at least partially blocks binding of IL-4 to a cell, and at least partially blocks binding of IL-13 to a cell.

Antibodies of the present invention include but are not limited to antibodies generated by immunizing a transgenic mouse with an IL-4 receptor immunogen, wherein the transgenic mouse is selected from the mouse strains described in example 3 below. The desired antibodies are at least partially human, and preferably fully human. In one embodiment, the immunogen is a human IL-4 receptor polypeptide. Hybridoma cell lines derived from the thus-immunized mice, wherein the hybridoma secretes a monoclonal antibody that binds IL-4R, also are provided herein. Examples of antibodies produced by immunizing such transgenic mice are the human monoclonal antibodies designated 6-2 (described in example 6); 12B5 (described in example 8); and MAbs 63, 1B7, 5A1, and 27A1 (all described in example 9). Monoclonal antibodies 6-2, 12B5, 63, 1B7, 5A1, and 27A1 are fully human antibodies, and are capable of inhibiting activity of both IL-4 and IL-13. MAbs 12B5, 63, and 1B7 are preferred antagonists of human IL-4 and human IL-13.

Particular monoclonal antibodies of the invention are selected from the group consisting of MAb 6-2; a Mab that is cross-reactive with 6-2; a MAb that binds to the same epitope as 6-2; a MAb that competes with 6-2 for binding to a cell that expresses human IL-4R; a MAb that possesses a biological activity of 6-2; and an antigen-binding fragment of any of the foregoing antibodies. In one embodiment, the antibody has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of 6-2 for human IL-4R. MAb 6-2 is an IgM antibody. MAbs of other isotypes (including but not limited to IgG1 and IgG4), derived from 6-2, also are encompassed by the present invention. Hybridoma cell lines that produce any such monoclonal antibodies also are provided by the present invention.

One example of a biological activity of 6-2 is the ability to function as both an IL-4 antagonist and an IL-13 antagonist. In one embodiment, a MAb of the invention possesses IL-4-blocking activity substantially equivalent to that of 6-2; and possesses IL-13-blocking activity substantially equivalent to that of 6-2. Such activity may be measured in any suitable conventional assay (e.g., as measured in the CD23 expression assay described in example 5).

The DNA sequence of the variable region of the light chain of MAb 6-2 is presented in SEQ ID NO:5, and the encoded amino acid sequence is presented in SEQ ID NO:6. The DNA sequence for the variable region of the heavy chain of MAb 6-2 is presented as SEQ ID NO:7, and the encoded amino acid sequence is presented in SEQ ID NO:8. Antibodies of the present invention include, but are not limited to, monoclonal antibodies that comprise, in their light chain, residues 1 to 107 of SEQ ID NO:6; and antibodies that additionally or alternatively comprise, in their heavy chain, residues 1 to 118 of SEQ ID NO:8.

Complementarity determining regions (CDRs) of a given antibody may be identified using the system described by Kabat et al. in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991). Particular embodiments of antibodies of the present invention comprise, within the variable region of their light chain, at least one of the complementarity determining regions (CDRs), or hypervariable regions, found in the light chain of 6-2. CDRs of 6-2 are discussed in example 6. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the light chain variable region: amino acid residues 24-35 of SEQ ID NO:6; residues 51-57 of SEQ ID NO:6; and residues 90-97 of SEQ ID NO:6. Particular antibodies provided herein comprise, within the variable region of their heavy chain, at least one of the CDRs found in the heavy chain of 6-2. Thus, among

the antibodies provided herein are those comprising from one to all three of the following sequences in the heavy chain variable region: residues 31-35; residues 50-66; and residues 99-107 of SEQ ID NO:8.

Particular monoclonal antibodies of the invention are selected from the group consisting of MAb 12B5; a Mab that is cross-reactive with 12B5; a MAb that binds to the same epitope as 12B5; a MAb that competes with 12B5 for binding to a cell that expresses human IL-4R; a MAb that possesses a biological activity of 12B5; and an antigen-binding fragment of any of the foregoing antibodies. In one embodiment, the antibody has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of 12B5 for human IL-4R. MAb 12B5 is an IgG1 antibody. MAbs of other isotypes, derived from 12B5, also are encompassed by the present invention. In particular embodiments, the isotype of the MAb is IgG1, IgG4, or IgM. Hybridoma cell lines that produce any such monoclonal antibodies also are provided by the present invention.

One example of a biological activity of 12B5 is the ability to function as both an IL-4 antagonist and an IL-13 antagonist. In one embodiment, a MAb of the invention possesses IL-4-blocking activity substantially equivalent to that of 12B5, and possesses IL-13-blocking activity substantially equivalent to that of 12B5. Such activity may be measured in any suitable conventional assay (e.g., as measured in the CD23 expression assay described in example 5).

IgG4 monoclonal antibodies derived from 12B5 are provided herein. Another embodiment is directed to IgM monoclonal antibodies derived from 12B5. Procedures for switching (altering) the subclass or isotype of an antibody are known in the pertinent field. Such procedures may involve, for example, recombinant DNA technology, whereby DNA encoding antibody polypeptide chains that confer the desired subclass is substituted for DNA encoding the corresponding polypeptide chain of the parent antibody.

The DNA sequence of the variable region of the light chain of MAb 12B5 is presented in SEQ ID NO:9, and the encoded amino acid sequence is presented in SEQ ID NO:10. The DNA sequence for the variable region of the heavy chain of MAb 12B5 is presented as SEQ ID NO:11, and the encoded amino acid sequence is presented in SEQ ID NO:12. Antibodies of the present invention include, but are not limited to, monoclonal antibodies that comprise, in their light chain, residues 1 to 109 of SEQ ID NO:10; and antibodies that additionally or alternatively comprise, in their heavy chain, residues 1 to 115 of SEQ ID NO:12.

Particular embodiments of antibodies of the present invention comprise, within the variable region of their light chain, at least one of the complementarity determining regions (CDRs), or hypervariable regions, found in the light chain of 12B5. CDRs of 12B5 are discussed in example 8. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the light chain variable region: amino acid residues 24-35 of SEQ ID NO:10; residues 51-57 of SEQ ID NO:10; and residues 90-99 of SEQ ID NO:10. Particular antibodies provided herein comprise, within the variable region of their heavy chain, at least one of the CDRs found in the heavy chain of 12B5. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the heavy chain variable region: residues 31-35; residues 50-65; and residues 98-104 of SEQ ID NO:12.

Particular monoclonal antibodies of the invention are selected from the group consisting of MAb 27A1; a Mab that is cross-reactive with 27A1; a MAb that binds to the same epitope as 27A1; a MAb that competes with 27A1 for binding to a cell that expresses human IL-4R; a MAb that possesses a biological activity of 27A1; and an antigen-binding fragment of any of the foregoing antibodies. In one embodiment, the antibody has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of 27A1 for human IL-4R. 27A1 is an IgG1 antibody. MAbs of other isotypes, derived from 27A1, also are encompassed by the present invention. Hybridoma cell lines that produce any such monoclonal antibodies also are provided by the present invention.

One example of a biological activity of 27A1 is the ability to function as both an IL-4 antagonist and an IL-13 antagonist. In one embodiment, a MAb of the invention possesses IL-4-blocking activity substantially equivalent to that of 27A1; and possesses IL-13-blocking activity substantially equivalent to that of 27A1. Such activity may be measured in any suitable conventional assay (e.g., as measured in the CD23 expression assay described in example 5).

The DNA sequence of the variable region of the light chain of MAb 27A1 is presented in SEQ ID NO:13, and the encoded amino acid sequence is presented in SEQ ID NO:14. The DNA sequence for the variable region of the heavy chain of MAb 27A1 is presented as SEQ ID NO:15, and the encoded amino acid sequence is presented in SEQ ID NO:16. Antibodies of the present invention include, but are not limited to, monoclonal antibodies that comprise, in their light chain, residues 1 to 109 of SEQ ID NO:14; and antibodies that additionally or alternatively comprise, in their heavy chain, residues 1 to 116 of SEQ ID NO:16.

Particular embodiments of antibodies of the present invention comprise, within the variable region of their light chain, at least one of the complementarity determining regions (CDRs), or hypervariable regions, found in the light chain of 27A1. CDRs of 27A1 are discussed in example 9. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the light chain variable region: amino acid residues 24-35 of SEQ ID NO:14; residues 51-57 of SEQ ID NO:14; and residues 90-99 of SEQ ID NO:14. Particular antibodies provided herein comprise, within the variable region of their heavy chain, at least one of the CDRs found in the heavy chain of 27A1. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the heavy chain variable region: residues 31-35; residues 50-66; and residues 99-105 of SEQ ID NO:16.

Particular monoclonal antibodies of the invention are selected from the group consisting of MAb 5A1; a Mab that is cross-reactive with 5A1; a MAb that binds to the same epitope as 5A1; a MAb that competes with 5A1 for binding to a cell that expresses human IL-4R; a MAb that possesses a biological activity of 5A1; and an antigen-binding fragment of any of the foregoing antibodies. In one embodiment, the antibody has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of 5A1 for human IL-4R. 5A1 is an IgG1 antibody. MAbs of other isotypes, derived from 5A1, also are encompassed by the present invention. Hybridoma cell lines that produce any such monoclonal antibodies also are provided by the present invention.

One example of a biological activity of 5A1 is the ability to function as both an IL-4 antagonist and an IL-13 antagonist. In one embodiment, a MAb of the invention possesses IL-4-blocking activity substantially equivalent to that of 5A1; and possesses IL-13-blocking activity substantially equivalent to that of 5A1. Such activity may be measured in any suitable conventional assay (e.g., as measured in the CD23 expression assay described in example 5).

The DNA sequence of the variable region of the light chain of MAb 5A1 is presented in SEQ ID NO:17, and the encoded amino acid sequence is presented in SEQ ID NO:18. The DNA sequence for the variable region of the heavy chain of MAb 5A1 is presented as SEQ ID NO:19, and the encoded amino acid sequence is presented in SEQ ID NO:20. Antibodies of the present invention include, but are not limited to, monoclonal antibodies that comprise, in their light chain, residues 1 to 107 of SEQ ID NO:18; and antibodies that additionally or alternatively comprise, in their heavy chain, residues 1 to 123 of SEQ ID NO:20.

Particular embodiments of antibodies of the present invention comprise, within the variable region of their light chain, at least one of the complementarity determining regions (CDRs), or hypervariable regions, found in the light chain of 5A1. CDRs of 5A1 are discussed in example 9. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the light chain variable region: amino acid residues 24-34 of SEQ ID NO:18; residues 50-56 of SEQ ID NO:18; and residues 89-97 of SEQ ID NO:18. Particular antibodies provided herein comprise, within the variable region of their heavy chain, at least one of the CDRs found in the heavy chain of 5A1. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the heavy chain variable region: residues 31-35; residues 50-65; and residues 98-112 of SEQ ID NO:20.

Particular monoclonal antibodies of the invention are selected from the group consisting of MAb 63; a Mab that is cross-reactive with MAb 63; a MAb that binds to the same epitope as 63; a MAb that competes with 63 for binding to a cell that expresses human IL-4R; a MAb that possesses a biological activity of 63; and an antigen-binding fragment of any of the foregoing antibodies. In one embodiment, the antibody has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of 63 for human IL-4R. MAb 63 is an IgM antibody. MAbs of other isotypes, derived from 63, also are encompassed by the present invention. Hybridoma cell lines that produce any such monoclonal antibodies also are provided by the present invention.

One example of a biological activity of 63 is the ability to function as both an IL-4 antagonist and an IL-13 antagonist. In one embodiment, a MAb of the invention possesses IL-4-blocking activity substantially equivalent to that of 63; and possesses IL-13-blocking activity substantially equivalent to that of 63. Such activity may be measured in any suitable conventional assay (e.g., as measured in the CD23 expression assay described in example 5).

The DNA sequence of the variable region of the light chain of MAb 63 is presented in SEQ ID NO:21, and the encoded amino acid sequence is presented in SEQ ID NO:22. The DNA sequence for the variable region of the heavy chain of MAb 63 is presented as SEQ ID NO:23, and the encoded amino acid sequence is presented in SEQ ID NO:24. Antibodies of the present invention include, but are not limited to, monoclonal antibodies that comprise, in their light chain, residues 1 to 107 of SEQ ID NO:22; and antibodies that additionally or alternatively comprise, in their heavy chain, residues 1 to 117 of SEQ ID NO:24.

Particular embodiments of antibodies of the present invention comprise, within the variable region of their light chain, at least one of the complementarity determining regions (CDRs), or hypervariable regions, found in the light chain of 63. CDRs of 63 are discussed in example 9. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the light chain variable region: amino acid residues 24-34 of SEQ ID NO:22; residues 50-56 of SEQ ID NO:22; and residues 89-97 of SEQ ID NO:22. Particular antibodies provided herein comprise, within the variable region of their heavy chain, at least one of the CDRs found in the heavy chain of 63. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the heavy chain variable region: residues 31-35; residues 50-66; and residues 99-106 of SEQ ID NO:24.

Particular monoclonal antibodies of the invention are selected from the group consisting of MAb 1B7; a Mab that is cross-reactive with 1B7; a MAb that binds to the same epitope as 1B7; a MAb that competes with 1B7 for binding to a cell that expresses human IL-4R; a MAb that possesses a biological activity of 1B7; and an antigen-binding fragment of any of the foregoing antibodies. In one embodiment, the antibody has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of 1B7 for human IL-4R. MAbs of other isotypes, derived from 1B7, also are encompassed by the present invention. Hybridoma cell lines that produce any such monoclonal antibodies also are provided by the present invention.

One example of a biological activity of 1B7 is the ability to function as both an IL-4 antagonist and an IL-13 antagonist. In one embodiment, a MAb of the invention possesses IL-4-blocking activity substantially equivalent to that of 1B7; and possesses IL-13-blocking activity substantially equivalent to that of 1B7. Such activity may be measured in any suitable conventional assay (e.g., as measured in the CD23 expression assay described in example 5).

MAb 1B7 was derived from MAb 63. The amino acid sequence of the heavy chain of MAb 1B7 is identical to that of MAb 63. The only differences between the two antibodies are in the light chain. The DNA sequence of the variable region of the light chain of MAb 1B7 is presented in SEQ ID NO:25, and the encoded amino acid sequence is presented in SEQ ID NO:26. The DNA sequence for the variable region of the heavy chain of MAb 1B7 is presented as SEQ ID NO:23, and the encoded amino acid sequence is presented in SEQ ID NO:24 (same as for MAb 63). Antibodies of the present invention include, but are not limited to, monoclonal antibodies that comprise, in their light chain, residues 1 to 107 of SEQ

ID NO:26; and antibodies that additionally or alternatively comprise, in their heavy chain, residues 1 to 117 of SEQ ID NO:24.

Particular embodiments of antibodies of the present invention comprise, within the variable region of their light chain, at least one of the complementarity determining regions (CDRs), or hypervariable regions, found in the light chain of 1B7. CDRs of 1B7 are discussed in example 9. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the light chain variable region: amino acid residues 24-34 of SEQ ID NO:26; residues 50-56 of SEQ ID NO:26; and residues 89-97 of SEQ ID NO:26. Particular antibodies provided herein comprise, within the variable region of their heavy chain, at least one of the CDRs found in the heavy chain of 1B7. Thus, among the antibodies provided herein are those comprising from one to all three of the following sequences in the heavy chain variable region: residues 31-35; residues 50-66; and residues 99-106 of SEQ ID NO:24.

Derivatives of monoclonal antibodies directed against IL-4R may be prepared, and screened for desired properties, by any of a number of known techniques. Certain of the techniques involve isolating DNA encoding a polypeptide chain (or portion thereof) of a MAb of interest, and manipulating the DNA through recombinant DNA technology. The DNA may be fused to another DNA of interest, or altered (e.g., by mutagenesis or other conventional techniques) to add, delete, or substitute one or more amino acid residues, for example.

DNA encoding antibody polypeptides (e.g., heavy or light chain, variable region only or full length) may be isolated from B-cells of mice that have been immunized with IL-4R. The DNA may be isolated by conventional procedures such as polymerase chain reaction (PCR). Phage display is another example of a known technique whereby derivatives of antibodies may be prepared. In one approach, polypeptides that are components of an antibody of interest are expressed in any suitable recombinant expression system, and the expressed polypeptides are allowed to assemble to form antibody molecules.

Single chain antibodies may be formed by linking heavy and light chain variable region (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable region polypeptides (V_L and V_H). The resulting antibody fragments can form dimers or trimers, depending on the length of a flexible linker between the two variable domains (Kortt et al., *Protein Engineering* 10:423, 1997). Techniques developed for the production of single chain antibodies include those described in U.S. Patent No. 4,946,778; Bird (*Science* 242:423, 1988); Huston *et al.*

(*Proc. Natl. Acad. Sci. USA* 85:5879, 1988); and Ward *et al*. (*Nature* 334:544, 1989). Single chain antibodies derived from antibodies provided herein (including but not limited to scFvs derived from MAbs 6-2, 12B5, 63, 1B7, 5A1, and 27A1) are encompassed by the present invention.

Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, i.e., subclass switching. Thus, IgG1 or IgG4 monoclonal antibodies may be derived from an IgM monoclonal antibody, for example, and vice versa. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, e.g., DNA encoding the constant region of an antibody of the desired isotype.

In particular embodiments, antibodies raised against IL-4R have a binding affinity (Ka) for IL-4R of at least 1 x 10^8. In other embodiments, the antibodies exhibit a Ka of at least 1 x 10^9 or at least 1 x 10^{10}.

PEGylated derivatives of antibodies (modified with polyethylene glycol) also are contemplated, and may be prepared by conventional techniques. Also provided herein are conjugates comprising a detectable (e.g., diagnostic) or therapeutic agent, attached to an antibody directed against IL-4R. Examples of such agents are well known, and include but are not limited to diagnostic radionuclides, therapeutic radionuclides, and cytotoxic drugs. The conjugates find use in *in vitro* or *in vivo* procedures.

Particular embodiments of the invention are directed to novel nucleic acid molecules and polypeptides. DNA and amino acid sequence information has been determined for polypeptides that are components of certain antibodies of the present invention, as discussed in examples 6, 8, and 9 below. Among the nucleic acids of the present invention is isolated DNA comprising a nucleotide sequence selected from the group consisting of the nucleotide sequence presented in SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, and SEQ ID NO:25. Among the polypeptides of the present invention is a purified polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequence presented in SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, and SEQ ID NO:26. For *in vivo* use, the polypeptides advantageously are

purified. A polypeptide may be purified individually, or in the form of a purified antibody of which the polypeptide is a component.

Further examples of IL-4 antagonists are antibodies that bind IL-4 and inhibit the binding of IL-4 to cell surface receptors. Such antibodies may be prepared, and screened to identify those that are blocking antibodies, by conventional procedures. Antigen-binding fragments of such antibodies find use as antagonists, as do humanized or genetically engineered derivatives thereof.

Examples of procedures for preparing antibodies directed against human IL-4 (including monoclonal antibodies), assays by which blocking antibodies are identified, and techniques for generating humanized or genetically engineered derivatives of anti-IL-4 antibodies, are described in U.S. Patents 5,041,381, 5,863,537, 5,928,904, and 5,676,940, which are hereby incorporated by reference. Further examples of antibodies that may be employed as IL-4 antagonists are described in WO 91/09059, also incorporated by reference herein.

Other antagonists

Any compound that functions as an IL-4 antagonist and is suitable for administration in accordance with the methods of the present invention may be employed. Antagonists need not completely abolish IL-4-induced biological activity to be useful. Rather, a given antagonist may reduce a biological activity of IL-4.

Derivatives, mutants/muteins, and other variants of IL-4 that function as IL-4 antagonists may be employed. Peptides (which may or may not be muteins) derived from IL-4 that bind to an IL-4R without inducing transduction of a biological signal find use herein. Such peptides function as inert blockers, interfering with the binding of biologically active endogenous IL-4 to cell surface receptors. IL-4-induced signal transduction thereby is inhibited. Muteins or other antagonists that induce a biological response at a reduced level or to a lesser degree, compared to the response induced by native IL-4, also find use as IL-4 antagonists.

Further examples of IL-4 antagonists, including IL-4 muteins, and procedures for preparation thereof are described in Muller et al., *J. Mol. Biol*., 237:423-436, 1994; U.S. Patent 6,028,176, and U.S. Patent 5,723,118, which are each incorporated by reference herein.

Other options are antisense molecules (oligonucleotides) that inhibit expression of IL-4. Alternatively, the antisense molecule may suppress expression of other molecules involved in IL-4-induced signal transduction.

Any suitable assay, including *in vitro* assays, can be utilized to determine whether a given compound inhibits an IL-4-induced biological activity. An antagonist may be assayed for the ability to inhibit ^{3}H-thymidine incorporation in cells that normally proliferate in response to IL-4.

An alternative involves use of conventional binding assay techniques to test an antagonist for the ability to inhibit binding of IL-4 to cells expressing native or recombinant IL-4 receptors. For use in such assays, recombinant human IL-4 can be expressed and purified as described in U.S. Patent 5,017,691, hereby incorporated by reference herein, or in Park et al., *J. Exp. Med. 166*:476 (1987). The purified protein may be labeled with a detectable agent (e.g., radiolabeled) by any of a number of conventional techniques. A commercially available enzymobead radioiodination reagent (BioRad) may be employed in radiolabeling IL-4 with ^{125}I for example.

The ability of an IL-4 antagonist to inhibit IL-4-induced damage to epithelium, such as lung epithelium or intestinal epithelium (which may result in loss of barrier function), may be confirmed in any of a number of suitable assays. Among the suitable assay techniques are those described in example 7 below.

Therapeutic Methods and Administration of Antagonists

Methods provided herein comprise administering an IL-4 antagonist to a patient, thereby reducing an IL-4-induced biological response that plays a role in a particular condition. In particular embodiments, methods of the invention involve contacting endogenous IL-4 with an IL-4 antagonist, e.g., in an *ex vivo* procedure.

Treatment encompasses alleviation of at least one symptom of a disorder, or reduction of disease severity, and the like. An antagonist need not effect a complete “cure”, or eradicate every symptom or manifestation of a disease, to constitute a viable therapeutic agent. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. One embodiment of the invention is directed to a method comprising administering to a patient an IL-4 antagonist in an amount

and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

Antibodies that inhibit the binding of both IL-4 and IL-13 to cells are discussed herein. A method for suppressing IL-4-induced and IL-13-induced activities in humans comprises administering an effective amount of such an antibody. Conditions induced by IL-4 or by IL-13, or by both cytokines, thus may be treated.

As is understood in the pertinent field, antagonists are administered to a patient in a manner appropriate to the indication. Antagonists may be administered by any suitable technique, including but not limited to parenterally, topically, or by inhalation. If injected, the antagonist can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes, by bolus injection, or continuous infusion. Localized administration, e.g. at a site of disease or injury is contemplated, as are transdermal delivery and sustained release from implants. Delivery by inhalation includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments.

Use of IL-4 antagonists in *ex vivo* procedures is contemplated. For example, a patient's blood (bodily fluid containing IL-4) may be contacted with an antagonist that binds IL-4 *ex vivo*, thereby reducing the amount of IL-4 in the fluid when returned to the patient. The antagonist may be bound to a suitable insoluble matrix or solid support material.

Advantageously, antagonists are administered in the form of a composition comprising at least one IL-4 antagonist and one or more additional components such as a physiologically acceptable carrier, excipient or diluent. The present invention provides such compositions comprising an effective amount of an IL-4 antagonist, for use in the methods provided herein.

The compositions contain antagonist(s) in any of the forms described herein. The antagonist may be a whole antibody or an antigen-binding fragment or engineered derivative thereof, for example. For compositions containing an IL-4 receptor, the receptor may be any of the fragments, variants, or oligomers of the protein of SEQ ID NO:2 described herein, for example.

Compositions may, for example, comprise an antagonist together with a buffer, antioxidant such as ascorbic acid, low molecular weight polypeptide (such as those having fewer than 10 amino acids), protein, amino acid, carbohydrate such as glucose, sucrose or

dextrins, chelating agents such as EDTA, glutathione, and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are examples of appropriate diluents. In accordance with appropriate industry standards, preservatives such as benzyl alcohol may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in *Remington's Pharmaceutical Sciences*, 16th Ed., Mack Publishing Company, Easton, PA, 1980.

Kits for use by medical practitioners include an IL-4 antagonist and a label or other instructions for use in treating any of the conditions discussed herein. The kit preferably includes a sterile preparation of one or more IL-4 antagonists, which may be in the form of a composition as disclosed above, and may be in one or more vials.

Dosages and the frequency of administration may vary according to such factors as the route of administration, the particular antagonist employed, the nature and severity of the disease to be treated, whether the condition is acute or chronic, and the size and general condition of the patient. Appropriate dosages can be determined by procedures known in the pertinent art, e.g. in clinical trials that may involve dose escalation studies.

An antagonist may be administered once, or repeatedly. In particular embodiments, the antagonist is administered over a period of at least a month or more, e.g., for one, two, or three months or even indefinitely. For treating chronic conditions, long-term treatment is generally most effective. However, for treating acute conditions, administration for shorter periods, e.g. from one to six weeks, may be sufficient. In general, the antagonist is administered until the patient manifests a medically relevant degree of improvement over baseline for the chosen indicator or indicators.

Particular embodiments of the present invention involve administering an antagonist at a dosage of from about 1 ng/kg/day to about 10 mg/kg/day, more preferably from about 500 ng/kg/day to about 5 mg/kg/day, and most preferably from about 5 ug/kg/day to about 2 mg/kg/day, to a patient. In additional embodiments, an antagonist such as a soluble human IL-4R polypeptide is administered to adults one time per week, two times per week, or three or more times per week, to treat the medical disorders disclosed herein. If injected, the effective amount of antagonist per adult dose may range from 1-20 mg/m^2, and preferably is about 5-12 mg/m^2. Alternatively, a flat dose may be administered; the amount may range from 5-100 mg/dose. One range for a flat dose is about 20-30 mg per dose. In one

embodiment of the invention, a flat dose of 25 mg/dose is repeatedly administered by injection. If a route of administration other than injection is used, the dose is appropriately adjusted in accordance with standard medical practices. One example of a therapeutic regimen involves injecting a dose of about 20-30 mg of IL-4R or other antagonist one to three times per week over a period of at least three weeks, though treatment for longer periods may be necessary to induce the desired degree of improvement. For pediatric patients (age 4-17), one suitable regimen involves the subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of IL-4R, administered two or three times per week.

Particular embodiments of the methods provided herein involve subcutaneous injection of from 0.5 mg to 10 mg, preferably from 3 to 5 mg, of a soluble IL-4R, once or twice per week. Another embodiment is directed to pulmonary administration (e.g., by nebulizer) of 3 or more mg of a soluble IL-4R once a week.

Examples of therapeutic regimens provided herein comprise subcutaneous injection of a soluble human IL-4R once a week, at a dose of 1.5 to 3 mg, to treat pulmonary sarcoidosis, minimal change nephrosis, autoimmune uveitis, sickle cell crisis, Churg-Strauss syndrome, Sjogren's syndrome, autoimmune lymphoproliferative syndrome, pre-eclampsia, autoimmune hemolytic anemia, Barrett's esophagus, Grave's Disease, Kawasaki Disease, and cavitary buberculosis. Weekly administration of IL-4R is continued until symptoms subside. Treatment may resume as needed, or, alternatively, maintenance doses may be administered.

An antagonist is administered to the patient in an amount and for a time sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the patient's illness may be assessed for determining whether the amount and time of the treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease severity, symptoms, or manifestations of the disorder in question. In most instances, an improvement is considered to be sustained if the patient exhibits the improvement on at least two occasions separated by two to four weeks. The degree of improvement generally is determined by the patient's physician, who may make this determination based on signs or symptoms, and who may also employ questionnaires that are administered to the patient, such as quality-of-life questionnaires developed for a given disease.

As one example, in treating benign prostate hyperplasia, an IL-4 inhibitor is administered to the patient in an amount and for a time effective in scar regression or complete healing. Maintenance doses may be given or treatment resumed as needed.

Elevated levels of IL-4 are associated with a number of disorders, as discussed above. Patients with a given disorder may be screened, to identify those individuals who have elevated IL-4 levels, or to identify those with an elevated TH2-type immune response, thereby identifying the patients who may benefit most from treatment with an IL-4 antagonist. Thus, treatment methods provided herein optionally comprise a first step of measuring a patient's IL-4 level. An IL-4 antagonist may be administered to a patient in whom IL-4 levels are elevated above normal. Alternatively or additionally, a patient may be pre-screened to determine whether the patient has an elevated TH2-type immune response, prior to administration of antagonist(s) against one or more TH2-type cytokines.

A patient's levels of IL-4 (and, optionally, of other TH2-type cytokines) may be monitored during and/or after treatment with an IL-4 antagonist, to detect reduction in the levels of the cytokines. For some disorders, the incidence of elevated IL-4 levels, and the balance between TH1-type and TH2-type immune responses, may vary according to such factors as the stage of the disease or the particular form of the disease. Known techniques may be employed for measuring IL-4 levels, e.g., in a patient's serum, and for assessing TH2-type immune responses. Cytokine levels in blood samples may be measured by ELISA, for example.

Particular embodiments of methods and compositions of the invention involve the use of two or more different IL-4 antagonists. In further embodiments, IL-4 antagonist(s) are administered alone or in combination with other agents useful for treating the condition with which the patient is afflicted. Examples of such agents include both proteinaceous and non-proteinaceous drugs. When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art. "Co-administration" and combination therapy are not limited to simultaneous administration, but include treatment regimens in which an IL-4 antagonist is administered at least once during a course of treatment that involves administering at least one other therapeutic agent to the patient.

Examples of other agents that may be co-administered with IL-4 antagonists are other antibodies, cytokines, or cytokine receptors, which are chosen according to the particular condition to be treated. Alternatively, non-proteinaceous drugs that are useful in treating one of the particular conditions discussed above may be co-administered with an IL-4 antagonist.

For treating IgE-mediated conditions, an IL-4 antagonist may be co-administered with an IgE antagonist. One example is an anti-IgE antibody. Humanized anti-IgE monoclonal antibodies are described in Presta et al. (*J. Immunol*. 151(5):2623-2632, 1993) and Adelroth et al. (*J. Allergy Clin. Immunol*. 106(2):253-259, 2000), for example.

IL-4 antagonists may be co-administered with an IL-5 antagonist, which may be a molecule that interferes with the binding of IL-5 to an IL-5 receptor, such as an anti-IL-5 antibody (e.g., a human or humanized anti-IL-5 monoclonal antibody), or a receptor such as a soluble human IL-5 receptor polypeptide. IL-5 has been implicated as playing a role in mediating allergic responses. Thus, administration of antagonist(s) of IL-4 and IL-5 is contemplated for treatment of allergic reactions, including but not limited to allergic asthma.

IL-4 antagonists may be employed in conjunction with other agent(s) in treating the particular IL-4-induced conditions discussed above. For example, drugs currently employed in treating the conditions may be co-administered with one or more IL-4 antagonists.

For treating asthma, an IL-4 antagonist may be co-administered with other anti-asthma medications, such as inhaled corticosteroids, beta agonists, leukotriene antagonists, xanthines, fluticasone, salmeterol, albuterol, non-steroidal agents such as cromolyn, and the like. IL-4 antagonists may be co-administered with other anti-allergy medications to treat allergic reactions.

One embodiment of the present invention is directed to co-administration of an IL-4 antagonist (such as a soluble human IL-4R) and fluticasone and salmeterol to treat a disorder such as asthma. Compositions comprising an IL-4 inhibitor (e.g., soluble human IL-4R), fluticasone, and salmeterol are provided herein. Advair Diskus (Glaxo Wellcome) comprises fluticasone propionate and salmeterol xinafoate. For treating asthma, Advair Diskus and the IL-4 antagonist preferably are delivered by inhalation.

Another example of combination therapy comprises co-administration of an IL-4 antagonist and an IL-9 antagonist to a patient who has asthma. Any suitable IL-9 antagonist may be employed, such as an IL-9 receptor (preferably a soluble form thereof), an antibody that interferes with binding of IL-9 to a cell surface receptor (wherein the antibody may be raised against IL-9 or an IL-9 receptor polypeptide), or another compound that inhibits IL-9-induced biological activity. IL-9 receptors include those described in WO 93/18047 and U.S. Patents 5,789,237 and 5,962,269, which are hereby incorporated by reference herein.

In an additional embodiment of combination therapy, a method for treating ulcerative colitis comprises co-administration of at least one IL-4 antagonist and at least one IL-1 antagonist. Examples of IL-1 antagonists include type I IL-1 receptor, type II IL-1 receptor,

IL-1 receptor antagonist (IL-1Ra), antagonistic (blocking) antibodies directed against IL-1, and antagonistic antibodies directed against an IL-1 receptor. Various forms of the receptors may be employed, such as fragments, variants and fusions analogous to those described above for IL-4 receptor. A preferred IL-1 antagonist is a soluble form of type II IL-1 receptor, which is described in U.S. Patent 5,350,683, hereby incorporated by reference herein.

One method of the present invention comprises co-administering IL-4 antagonist(s) and IL-13 antagonist(s) to a patient who has minimal change nephrosis. Alternative embodiments involve administering IL-4 antagonist(s) alone, or IL-13 antagonist(s) alone, to a minimal change nephrosis patient. The IL-4 antagonists(s) and/or IL-13 antagonist(s) may be administered to reduce severity of the disease.

Another method provided herein is a method for treating various allergic inflammatory conditions, comprising co-administering IL-4 antagonist(s) and IL-13 antagonist(s). Conditions such as asthma, allergies, and chronic lung diseases such as cystic fibrosis and chronic obstructive pulmonary disease are treated by such a method.

Any suitable IL-13 antagonist may be employed, including but not limited to IL-13 receptors (preferably soluble forms thereof), IL-13 receptor antagonists, antibodies directed against IL-13 or an IL-13 receptor, other proteins that interfere with the binding of IL-13 to an IL-13 receptor, and compounds that inhibit IL-13-mediated signal transduction. IL-13 receptors and heterodimers comprising IL-13R polypeptides as components thereof are described above. Antibodies that are raised against IL-4R may be screened for the ability to also function as IL-13 antagonists, as discussed above.

A method for treating or preventing a condition characterized by reduced epithelial barrier function comprises co-administering IL-4 antagonist(s) and one or more IL-13 antagonists. Such conditions are discussed above. In one embodiment, the condition is asthma. Particular embodiments are directed to co-administering one or more IL-4 antagonists and one or more IL-13 antagonists to a patient having a condition involving reduction of lung epithelial barrier function or intestinal epithelial barrier function, wherein both IL-4 and IL-13 play a role in the reduced barrier function. The method thus inhibits both IL-4-induced reduction of barrier function and IL-13-induced reduction of barrier function. The adverse effect of IL-13 on lung and intestinal epithelial barrier function can be confirmed using assay techniques such as those described in example 7 below. (See also Zund et al., *J. Biol. Chem.* 271(13):7460-7464, 1996.)

Another method provided herein comprises co-administering IL-4 antagonist(s) and interferon-γ (IFN-γ) to a patient having a condition involving reduction of lung epithelial barrier function. Optionally, such a method further comprises co-administering one or more IL-13 antagonists to the patient (i.e., co-administering an IL-4 antagonist, IFN-γ, and an IL-13 antagonist). Other methods comprise administering IFN-γ as a single agent, or co-administering IFN-γ and an IL-13 antagonist, to a patient having a condition involving reduction of lung epithelial barrier function. In one embodiment, the patient has asthma. For treating asthma, the IL-4 antagonist, IFN-γ, and/or IL-13 antagonist preferably are administered by inhalation.

One method provided herein for treating asthma comprises administering an IL-4 antagonist and interferon-γ to a human who has asthma. Another method for treating asthma comprises co-administering an IL-4 antagonist, IFN-γ, and an IL-13 antagonist to a human who has asthma. In one embodiment, IFN-γ is co-administered to an asthmatic, together with an antibody that functions as an antagonist of both IL-4 and IL-13. Such antibodies are described elsewhere herein.

A single agent may function as an IL-4 antagonist and an IL-13 antagonist, as discussed above. As an example of such an agent, some antibodies raised against IL-4Rα may interfere with the binding of both IL-4 and IL-13 receptor complexes, due to the shared IL-4Rα component in such multi-subunit receptor complexes (discussed above). Thus, a single agent may be employed in a method for inhibiting reduction of barrier function.

Antagonists may be co-administered with one or more leukotriene receptor antagonists to treat disorders such as allergic inflammatory diseases, e.g., asthma and allergies. Examples of leukotriene receptor antagonists include but are not limited to montelukast, pranlukast, and zafirlukast. Drugs that function as 5-lipoxygenase inhibitors may be co-administered with an IL-4 antagonist to treat asthma.

Methods provided herein comprise administering one or more of the following to Churg-Strauss Syndrome patients: IL-4 antagonist(s), IL-5 antagonist(s), IL-13 antagonist(s) or IgE antagonist(s). One example of such a method involves co-administering IL-4 antagonist(s) and IL-5 antagonist(s) to a Churg-Strauss Syndrome patient. In another embodiment, IL-4 antagonist(s) and IgE antagonist(s) are co-administered to the patient. In yet another embodiment, IL-4 antagonist(s) and IL-13 antagonist(s) are co-administered to the patient.

The hormone relaxin may be co-administered with an IL-4 antagonist to treat scleroderma (systemic sclerosis), idiopathic pulmonary fibrosis, or any other disorder characterized by pulmonary fibrosis, such as the conditions involving fibrosis of the lung that are discussed above. Recombinant human relaxin is preferred for use in treating humans.

A method for treating benign prostate hyperplasia comprises co-administering IL-4 antagonist(s) and one or more additional anti-inflammatory agents. Examples of agents that inhibit inflammation include tumor necrosis factor (TNF) antagonists and IL-17 antagonists.

Any suitable IL-17 antagonist may be employed, including but not limited to an IL-17 receptor (preferably soluble forms thereof), IL-17 receptor antagonists, antibodies directed against IL-17 or an IL-17 receptor, other proteins that interfere with the binding of IL-17 to an IL-17 receptor, and compounds that inhibit IL-17-mediated signal transduction. An IL-17 receptor, including soluble forms thereof and oligomers thereof, is described in WO 96/29408, hereby incorporated by reference. An alternative method provided herein comprises administering an IL-17 antagonist to treat a patient with benign prostate hyperplasia.

Likewise, any suitable TNF antagonist may be employed, including but not limited to a TNF receptor (preferably soluble forms thereof), fusion proteins comprising a TNF receptor (or comprising the TNF-binding portion of a TNF receptor), TNF receptor antagonists, antibodies directed against TNF or a TNF receptor, other proteins that interfere with the binding of TNF to a TNF receptor, and compounds that inhibit TNF-mediated signal transduction. Further examples of TNF inhibitors are the drugs thalidomide and pentoxyfylline. The TNF receptor protein known as p75 or p80 TNF-R preferably is employed. A preferred TNF antagonist is a soluble human TNF receptor (sTNF-R) in dimeric form, such as dimers of sTNF-R/Fc fusion proteins. One such dimer is etanercept (Enbrel®, Immunex Corporation, Seattle, WA). p75/p80 TNF-R, including soluble fragments and other forms thereof, is described in WO 91/03553, hereby incorporated by reference herein.

In accordance with the present invention, an IL-4 antagonist is co-administered with a TNF antagonist to treat any condition in which undesirable IL-4-induced and TNF-induced immune responses play a role, such as inflammation. One method provided herein comprises co-administering an IL-4 antagonist and a TNF antagonist to a patient with inflammatory bowel disease, Crohn's disease, or ulcerative colitis. Other embodiments are directed to a method comprising co-administering an IL-4 antagonist and a TNF antagonist to a patient who has Kawasaki Disease, autoimmune hemolytic anemia, autoimmune

uveoretinitis, autoimmune lymphoproliferative syndrome, Sjogren's syndrome, chronic fatigue syndrome, or hepatotoxicity induced by a drug such as diclofenac.

Another method provided herein comprises co-administering an IL-4 antagonist and a TNF antagonist to a pregnant woman who has developed pre-eclampsia. Administration of the IL-4 antagonist and TNF-antagonist preferably continues for the duration of the pregnancy.

Suitable dosages of etanercept (Enbrel®, Immunex Corporation, Seattle, WA) will vary according to the nature of the disease to be treated, disease severity, the size of the patient (e.g., adult or child), and other factors, as is recognized in the pertinent field. In one embodiment of the methods provided herein, Enbrel® is administered twice a week by subcutaneous injection at a dose of from 1 to 25 mg. One embodiment of a pediatric dosage is 0.4 mg/kg. Particular methods provided herein comprise co-administration of an IL-4 antagonist and Enbrel® to a patient has autoimmune lymphoproliferative syndrome or Sjogren's syndrome, wherein Enbrel® is given by subcutaneous injection at a dose of from 1 to 25 mg.

For treating graft versus host disease, an IL-4 antagonist is co-administered with at least one of the following agents: a TNF antagonist, an IL-1 antagonist, steroids, or corticosteroids. The TNF inhibitor preferably is Enbrel®. A preferred IL-1 antagonist is a soluble form of type II IL-1 receptor, which is described in U.S. Patent 5,350,683. In one embodiment, the GVHD is associated with (e.g., develops subsequent to) bone marrow transplantation. An IL-4 antagonist may be employed in combination with at least one of the above-listed agents, in methods for suppressing an immune response directed against transplanted cells, tissue, and/or alloantigen.

A number of cytokine antagonists and other agents/drugs are disclosed herein as being useful for combination therapy (e.g., co-administration with an IL-4 antagonist) in treating particular diseases. It is to be understood that such antagonists, agents, or drugs also find use as single agents in treating those diseases. It also is to be understood that disclosure of methods involving administration of an antagonist to a particular cytokine, to treat a disease, encompasses administration of one type of antagonist, and also encompasses administration of two or more different antagonists for that cytokine, unless specified otherwise.

The following examples are offered by way of illustration, and not by way of limitation.

EXAMPLE 1: Preparation of Monoclonal Antibodies

IL-4 receptor polypeptides may be employed as immunogens in generating monoclonal antibodies by conventional techniques, e.g., techniques described in U.S. Patent 5,599,905, hereby incorporated by reference. It is recognized that polypeptides in various forms may be employed as immunogens, e.g., full length proteins, fragments thereof, fusion proteins thereof such as Fc fusions, cells expressing the recombinant protein on the cell surface, etc.

To summarize an example of such a procedure, an IL-4R immunogen emulsified in complete Freund's adjuvant is injected subcutaneously into Lewis rats, in amounts ranging from 10-100 µl. Three weeks later, the immunized animals are boosted with additional immunogen emulsified in incomplete Freund's adjuvant and boosted every three weeks thereafter. Serum samples are periodically taken by retro-orbital bleeding or tail-tip excision for testing by dot-blot assay, ELISA (enzyme-linked immunosorbent assay), or inhibition of binding of ^{125}I-IL-4 to extracts of IL-4R-expressing cells. Following detection of an appropriate antibody titer, positive animals were given a final intravenous injection of antigen in saline. Three to four days later, the animals are sacrificed, splenocytes harvested, and fused to the murine myeloma cell line AG8653. The resulting hybridoma cell lines are plated in multiple microtiter plates in a HAT selective medium (hypoxanthine, aminopterin, and thymidine) to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

Hybridoma clones thus generated are screened for reactivity with IL-4R. Initial screening of hybridoma supernatants utilizes an antibody capture and binding of partially purified ^{125}I-IL-4 receptor. Hybridomas that are positive in this screening method are tested by a modified antibody capture to detect hybridoma cells lines that are producing blocking antibody. Hybridomas that secrete a monoclonal antibody capable of inhibiting ^{125}I-IL-4 binding to cells expressing IL-4R are thus detected. Such hydridomas then are injected into the peritoneal cavities of nude mice to produce ascites containing high concentrations (>1 mg/ml) of anti-IL-4R monoclonal antibody. The resulting monoclonal antibodies may be purified by ammonium sulfate precipitation followed by gel exclusion chromatography, and/or affinity chromatography based on binding of antibody to Protein G.

EXAMPLE 2: Generation of Cmu targeted mice

This example describes procedures for generating transgenic mice. Additional procedures for generating transgenic mice, and the use of such mice for preparing human antibodies, are described in Examples 3 and 4.

Construction of a CMD targeting vector. The plasmid pICEmu contains an EcoRI/XhoI fragment of the murine Ig heavy chain locus, spanning the mu gene, that was obtained from a Balb/C genomic lambda phage library (Marcu et al. *Cell* 22: 187, 1980). This genomic fragment was subcloned into the XhoI/EcoRI sites of the plasmid pICEMI9H (Marsh et al; *Gene* 32, 481-485, 1984). The heavy chain sequences included in pICEmu extend downstream of the EcoRI site located just 3' of the mu intronic enhancer, to the XhoI site located approximately 1 kb downstream of the last transmembrane exon of the mu gene; however, much of the mu switch repeat region has been deleted by passage in *E. coli*.

The targeting vector was constructed as follows. (See Figures 2A-2C, which depict further details.) A 1.3 kb HindIII/SmaI fragment was excised from pICEmu and subcloned into HindIII/SmaI digested pBluescript (Stratagene, La Jolla, CA). This pICEmu fragment extends from the HindIII site located approximately 1 kb 5' of Cmu1 to the SmaI site located within Cmu1. The resulting plasmid was digested with SmaI/SpeI and the approximately 4 kb SmaI/XbaI fragment from pICEmu, extending from the Sma I site in Cmu1 3' to the XbaI site located just downstream of the last Cmu exon, was inserted. The resulting plasmid, pTAR1, was linearized at the SmaI site, and a neo expression cassette inserted. This cassette consists of the neo gene under the transcriptional control of the mouse phosphoglycerate kinase (pgk) promoter (XbaI/TaqI fragment; Adra et al. (1987) *Gene* 60: 65-74) and containing the pgk polyadenylation site (PvuII/HindIII fragment; Boer et al. (1990) *Biochemical Genetics* 28: 299-308). This cassette was obtained from the plasmid pKJ1 (described by Tybulewicz et al. (1991) *Cell* 65: 1153-1163) from which the neo cassette was excised as an EcoRI/HindIII fragment and subcloned into EcoRI/HindIII digested pGEM-7Zf (+) to generate pGEM-7 (KJ1). The neo cassette was excised from pGEM-7 (KJ1) by EcoRI/SalI digestion, blunt ended and subcloned into the SmaI site of the plasmid pTAR1, in the opposite orientation of the genomic Cmu sequences.

The resulting plasmid was linearized with Not I, and a herpes simplex virus thymidine kinase (tk) cassette was inserted to allow for enrichment of ES clones bearing homologous recombinants, as described by Mansour et al. (1988) *Nature* 336: 348-352. This cassette consists of the coding sequences of the tk gene bracketed by the mouse pgk promoter and polyadenylation site, as described by Tybulewicz et al. (1991) *Cell* 65:1153-1163.

The resulting CMD targeting vector contains a total of approximately 5.3 kb of homology to the heavy chain locus and is designed to generate a mutant mu gene into which has been inserted a neo expression cassette in the unique SmaI site of the first Cmu exon. The targeting vector was linearized with PvuI, which cuts within plasmid sequences, prior to electroporation into ES cells.

Generation and analysis of targeted ES cells. AB-1 ES cells (McMahon, A. P. and Bradley, A., (1990) *Cell* 62: 1073-1085) were grown on mitotically inactive SNL76/7 cell feeder layers (ibid.), essentially as described in *Teratocarcinomas and Embryonic Stem Cells: a Practical Approach,* E. J. Robertson, Ed., Oxford: IRL Press, 1987, pp. 71-112. The linearized CMD targeting vector was electroporated into AB-1 cells by the methods described in Hasty *et al.* (1991) *Nature* 350: 243-246. Electroporated cells were plated into 100 mm dishes at a density of 1-2 x 10^6 cells/dish. After 24 hours, G418 (200 micrograms/ml of active component) and FIAU (5 x 10^{-7} M) were added to the medium, and drug-resistant clones were allowed to develop over 8-9 days. Clones were picked, trypsinized, divided into two portions, and further expanded. Half of the cells derived from each clone were then frozen and the other half analyzed for homologous recombination between vector and target sequences.

DNA analysis was carried out by Southern blot hybridization. DNA was isolated from the clones as described by Laird *et al.*, (1991) *Nucleic Acids Res*. 19:4293). Isolated genomic DNA was digested with SpeI and probed with a 915 bp SacI fragment, probe A (Figure 2C), which hybridizes to a sequence between the mu intronic enhancer and the mu switch region. Probe A detects a 9.9 kb SpeI fragment from the wild type locus, and a diagnostic 7.6 kb band from a mu locus which has homologously recombined with the CMD targeting vector (the neo expression cassette contains a SpeI site).

Of 1132 G418 and FIAU resistant clones screened by Southern blot analysis, 3 displayed the 7.6 kb Spe I band indicative of homologous recombination at the mu locus. These 3 clones were further digested with the enzymes BglI, BstXI, and EcoRI to verify that the vector integrated homologously into the mu gene. When hybridized with probe A, Southern blots of wild type DNA digested with BglI, BstXI, or EcoRI produce fragments of 15.7, 7.3, and 12.5 kb, respectively, whereas the presence of a targeted mu allele is indicated by fragments of 7.7, 6.6, and 14.3 kb, respectively. All 3 positive clones detected by the SpeI digest showed the expected BglI, BstXI, and EcoRI restriction fragments diagnostic of insertion of the neo cassette into the Cmu1 exon.

Generation of mice bearing the mutated mu gene. The three targeted ES clones, designated number 264, 272, and 408, were thawed and injected into C57BL/6J blastocysts as described by A. Bradley in *Teratocarcinomas and Embryonic Stem Cells: a Practical Approach*, E. J. Robertson, Ed., Oxford: IRL Press, 1987, pp. 113-151. Injected blastocysts were transferred into the uteri of pseudopregnant females to generate chimeric mice representing a mixture of cells derived from the input ES cells and the host blastocyst. The extent of ES cell contribution to the chimera can be visually estimated by the amount of agouti coat coloration, derived from the ES cell line, on the black C57BL/6J background. Clones 272 and 408 produced only low percentage chimeras (i.e. low percentage of agouti pigmentation) but clone 264 produced high percentage male chimeras. These chimeras were bred with C57BL/6J females and agouti offspring were generated, indicative of germline transmission of the ES cell genome. Screening for the targeted mu gene was carried out by Southern blot analysis of BglI digested DNA from tail biopsies (as described above for analysis of ES cell DNA). Approximately 50% of the agouti offspring showed a hybridizing BglI band of 7.7 kb in addition to the wild type band of 15.7 kb, demonstrating a germline transmission of the targeted mu gene.

Analysis of transgenic mice for functional inactivation of mu gene. To determine whether the insertion of the neo cassette into Cmu1 has inactivated the Ig heavy chain gene, a clone 264 chimera was bred with a mouse homozygous for the JHD mutation, which inactivates heavy chain expression as a result of deletion of the JH gene segments (Chen et al, (1993) *Immunol.* 5: 647-656). Four agouti offspring were generated. Serum was obtained from these animals at the age of 1 month and assayed by ELISA for the presence of murine IgM. Two of the four offspring were completely lacking IgM (Table 1). Genotyping of the four animals by Southern blot analysis of DNA from tail biopsies by BglI digestion and hybridization with probe A (Figure 2C), and by StuI digestion and hybridization with a 475 bp EcoRI/StuI fragment (ibid.) demonstrated that the animals which fail to express serum IgM are those in which one allele of the heavy chain locus carries the JHD mutation, the other allele the Cmu1 mutation. Mice heterozygous for the JHD mutation display wild type levels of serum Ig. These data demonstrate that the Cmu1 mutation inactivates expression of the mu gene.

Table 1 presents the level of serum IgM, detected by ELISA, for mice carrying both the CMD and JHD mutations (CMD/JHD), for mice heterozygous for the JHD mutation

(+/JHD), for wild type (129Sv x C57BL/6J)F1 mice (+/+), and for B cell deficient mice homozygous for the JHD mutation (JHD/JHD).

TABLE 1

Mouse	Serum IgM (micrograms/ml)	Ig H chain genotype
42	<0.002	CMD/JHD
43	196	+/JHD
44	<0.002	CMD/JHD
45	174	+/JHD
129 x BL6 F1	153	+/+
JHD	<0.002	JHD/JHD

EXAMPLE 3: Generation of transgenic mice

The HCo12 human heavy chain transgene. The HCo12 transgene was generated by coinjection of the 80 kb insert of pHC2 (Taylor et al., 1994, *Int. Immunol.*, 6: 579-591) and the 25 kb insert of pVx6. The plasmid pVx6 was constructed as described below.

An 8.5 kb HindIII/SalI DNA fragment, comprising the germline human VH1-18 (DP-14) gene together with approximately 2.5 kb of 5' flanking, and 5 kb of 3' flanking genomic sequence was subcloned into the plasmid vector pSP72 (Promega, Madison, WI) to generate the plasmid p343.7.16. A 7 kb BamHI/HindIII DNA fragment, comprising the germline human VH5-51 (DP-73) gene together with approximately 5 kb of 5' flanking and 1 kb of 3' flanking genomic sequence, was cloned into the pBR322 based plasmid cloning vector pGP1f (Taylor et al. 1992, Nucleic Acids Res. 20: 6287-6295), to generate the plasmid p251f.

A new cloning vector derived from pGP1f, pGP1k (the sequence of which is presented in Figures 3A and 3B and SEQ ID NO:4), was digested with EcoRV/BamHI, and ligated to a 10 kb EcoRV/BamHI DNA fragment, comprising the germline human VH3-23 (DP47) gene together with approximately 4 kb of 5' flanking and 5 kb of 3' flanking genomic sequence. The resulting plasmid, p112.2RR.7, was digested with BamHI/SalI and ligated with the the 7 kb purified BamHI/SalI insert of p251f. The resulting plasmid, pVx4, was digested with XhoI and ligated with the 8.5 kb XhoI/SalI insert of p343.7.16. A clone was obtained with the VH1-18 gene in the same orientation as the other two V genes. This clone, designated pVx6, was then digested with NotI and the purified 26 kb insert coinjected, together with the purified 80 kb NotI insert of pHC2 at a 1:1 molar ratio, into the pronuclei of

one-half day (C57BL/6J x DBA/2J)F2 embryos as described by Hogan *et al.* (B. Hogan *et al.*, Manipulating the Mouse Embryo, A Laboratory Manual, 2nd edition, 1994, Cold Spring Harbor Laboratory Press, Plainview NY).

Three independent lines of transgenic mice comprising sequences from both Vx6 and HC2 were established from mice that developed from the injected embryos. These lines are designated (HCo12)14881, (HCo12)15083, and (HCo12)15087. Each of the three lines were then bred with mice comprising the CMD mutation described in Example 2, the JKD mutation (Chen *et al.* 1993, EMBO J. 12: 811-820), and the (KCo5)9272 transgene (Fishwild *et al.* 1996, Nature Biotechnology 14: 845-851). The resulting mice express human heavy and kappa light chain transgenes in a background homozygous for disruption of the endogenous mouse heavy and kappa light chain loci.

Additional transgenic mouse strains Particular strains of mice that may be used to generate IL-4R-reactive monoclonal antibodies are strain ((CMD)++; (JKD)++; (HCo7)11952+/++; (KCo5)9272+/++), and strain ((CMD)++; (JKD)++; (HCo12)15087+/++; (KCo5)9272+/++). Each of these transgenic strains is homozygous for disruptions of the endogenous heavy chain (CMD) and kappa light chain (JKD) loci. Both strains also comprise a human kappa light chain transgene (HCo7), with individual animals either hemizygous or homozygous for insertion #11952. The two strains differ in the human heavy chain transgene used. Mice were hemizygous or homozygous for either the HCo7 or the HCo12 transgene. The CMD mutation is described above in Example 2. The generation of (HCo12)15087 mice is described above (in this example). The JKD mutation (Chen *et al.* 1993, EMBO J. 12: 811-820) and the (KCo5)9272 (Fishwild *et al.* 1996, Nature Biotechnology 14: 845-851) and (HCo7)11952 mice, are described in U.S. Patent 5,770,429, which is hereby incorporated by reference.

EXAMPLE 4: Generation of Human Anti-IL-4R Monoclonal Antibodies

Transgenic mice Strain ((CMD)++; (JKD)++; (HCo7)11952+/++; (KCo5)9272+/++ which is homozygous for disruptions of the endogenous heavy chain (CMD) and kappa light chain (JKD) loci (see example 3), was used to generate IL-4R-reactive monoclonal antibodies. This strain also comprises a human kappa light chain transgene (HCo7) with individual animals either hemizygous or homozygous for insertion #11952. Mice were hemizygous or homozygous for the HCo7 transgene. The CMD mutation is described above in Example 2. The JKD mutation (Chen *et al.* 1993, EMBO J. 12: 811-820) and the

(KCo5)9272 (Fishwild *et al.* 1996, Nature Biotechnology 14: 845-851) and (HCo7)11952 mice, are described in U.S. Patent 5,770,429, which is hereby incorporated by reference.

Immunization. Transgenic mice were initially immunized i.p. with 25 ug IL-4R protein in adjuvant (Titermax, available from Cytrx Corporation, Norcross, GA). The immunogen was a human IL-4R polypeptide comprising the extracellular domain of the protein of SEQ ID NO:2. Immunized mice were subsequently boosted every 4 weeks i.p. with the IL-4R immunogen in incomplete freunds adjuvant. Animals were kept on protocol for 2 to 5 months. Prior to fusion, animals were boosted i.v. on days -4 and -3 with 5 to 8 ug immunogen.

Fusions. Spleen cells harvested from the immunized mice were fused to mouse myeloma cells NS-1 by standard procedures (Harlow and Lane, 1988, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor New York; Kennett et al. 1980, Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analysis. Plenum, New York; Oi and Hertzenberg, 1980, Immunoglobulin Producing Hybrid Cell Lines, in Selected Methods In Cellular Immunology, ed. Mishell and Shiigi, pp. 357-372. Freeman, San Francisco). Cells were cultured in DMEM, 10% FBS, OPI (Sigma O-5003), BME (Gibco 21985-023), 3% Origen Hybridoma Cloning Factor (Igen IG50-0615), and 5% P388d1 (ATCC TIB 63) conditioned media. HAT or HT supplement was added to the medium during initial growth and selection.

Hybridoma Screening. To identify hybridomas secreting human antibodies against the IL-4R, ELISA plates (Nunc MaxiSorp) were coated overnight at 4°C with 100 ul/well human IL-4R at 2.0 ug/ml in PBS. Plates were washed with 100 ul/well PBS-Tween (PBST) containing 1% BSA. Fifty ul cell culture supernatent was added followed by a 1.0 hour incubation. Plates were washed and then incubated for one hour with 100 ul/well goat anti-human IgG conjugated to horseradish peroxidase (Sigma #A-3813, or #A-7164). Plates were washed three times in PBS-Tween between each step.

Wells that read positive by ELISA were screened for their ability to block the binding of IL-4 to IL-4R. ELISA plates were coated overnight with a non-neutralizing mouse anti-human IL-4R antibody M10 at 2 ug/ml. Plates were washed 3X with PBST. 100 ul human IL-4R was added at 10 ng/ml in PBST and incubated for 1.0 hour. Plates were washed 4X with PBST and 100 ul supernatant samples were added and incubated for 1.0 hour. Wells were washed 4X with PBST. 5.0 ng/ml biotinylated IL-4 was added in PBST and incubated for 1.0 hour. 100 ul/well poly80 horseradish peroxidase (RDI) was added at 1:5000 in PBST and incubated for 45 minutes. Plates were washed 5X with PBST, and a colorimetric

reagent (3,3',5,5' tetramethylbenzidine, available from Kirkegaard and Perry) was added at 100 ul/well until color developed. Reaction was stopped with 100 ul phosphoric acid and plates were read at 450nm. Absent or reduced signal was interpreted as the antibody binding to receptor in a manner that blocked IL-4 from binding to receptor. Wells that appeared to block binding were expanded and tested for IL-4 and IL-13 blocking in a CD23 expression assay (see example 5).

EXAMPLE 5: Assay for assessing blocking activity

This assay is based on ability of both IL-4 and IL-13 to enhance the expression of the activation-associated surface antigen CD23 on human B cells. Antibodies are tested for the ability to inhibit CD23 expression induced by IL-4 and by IL-13.

Antibodies raised against human IL-4R (huIL-4R) were tested either in the form of hybridoma supernatants or purified protein. Prior to addition to cultures, the antibodies were buffer exchanged against culture medium (RPMI 1640 plus 10% heat-inactivated fetal bovine serum) by centrifugation, using Centricon filter devices (Amicon) with a 10kDa cutoff.

Human peripheral blood B cells were purified as described previously (Morris et al., *J. Biol. Chem.* 274:418-423, 1999). The B cells ($3x10^5$/well) in culture medium were placed in 96-well round-bottomed microtiter plates and preincubated at room temperature for 30 min with test antibodies at the final concentrations indicated. Recombinant human IL-4 or IL-13 was then added to the cultures at the concentrations indicated, and cells were cultured for 20-24 hours at 37°C in a humidified atmosphere of 5% CO_2. At the end of the culture period, cells were washed once in PBS + 0.02% NaN_3 in the 96-well culture plate and were resuspended in blocking buffer (2% normal rabbit serum + 1% normal goat serum in PBS + NaN_3). Phycoerythrin (PE)-conjugated CD23 monoclonal antibody (mAb) or PE-conjugated isotype control mAb (both from Pharmingen) was then added to cells at a final dilution of 1:10. Cells were incubated for 30 minutes at 4°C, washed x3 in PBS + NaN_3 and analyzed on a FacScan (Becton Dickinson) for CD23 expression.

In all experiments, negative controls were included which consisted of cells cultured with hybridoma growth medium or isotype-matched non-blocking human anti-hIL-4R antibody. An anti-huIL-4R murine mAb (R&D Systems), previously shown to block the binding and function of both hIL-4 and hIL-13, was used as a positive control for neutralization of CD23 induction by IL-4 and IL-13.

EXAMPLE 6: Hybridoma Cell Line

One hybridoma cell line generated by procedures described above (see example 4) is designated 6-2. The anti-IL-4R monoclonal antibody secreted by this hybridoma is a blocking antibody, as determined in a conventional plate binding assay, and thus functions as an IL-4 antagonist. The monoclonal antibody produced by 6-2 also exhibits the ability to reduce an IL-13-induced biological activity.

One embodiment of the invention is directed to a hybridoma cell line produced as described above, wherein the hybridoma secretes an isotype IgM MAb directed against human IL-4R. Also provided herein are IgG1 monoclonal antibodies derived from IgM monoclonal antibodies.

The DNA sequence of the variable region of the light chain of MAb 6-2 has been determined, and is presented in SEQ ID NO:5; the amino acid sequence encoded thereby is presented in SEQ ID NO:6. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 24-35, 51-57, and 90-97, of SEQ ID NO:6, respectively.

The DNA sequence of the variable region of the heavy chain of MAb 6-2 has been determined, and is presented in SEQ ID NO:7; the amino acid sequence encoded thereby is presented in SEQ ID NO:8. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 31-35, 50-66, and 99-107 of SEQ ID NO:8, respectively.

EXAMPLE 7: Assays for Measuring Loss of Barrier Function

A method provided herein involves use of IL-4 antagonists to inhibit IL-4-induced damage to epithelium, including but not limited to lung epithelium or intestinal epithelium. Damage to epithelium can result in loss of barrier function. A number of techniques are known for determining whether an epithelial layer is intact. The following are examples of techniques that may be employed in assessing the ability of an IL-4 antagonist to inhibit IL-4-induced damage to epithelium and loss of epithelial barrier function.

Cells that may be employed in preparing *in vitro* models of epithelium (epithelial barriers) are known. For example, Calu-3 human lung epithelial cells are suitable for use in barrier function studies. Another suitable cell line is the human intestinal epithelial cell line designated T84. T84 cells are cultured under conditions that result in formation of a monolayer of epithelial cells on a permeable support, as described in Madara, J. and K. Dharmsathaphorn (*J. Cell Biol.*, 101:2124-2133, 1985), Madara, J. and J. Stafford (*J. Clin. Invest.* 83:724-727, 1989), and Youakim, A. and M. Ahdieh (*Am. J. Physiol.* 276

(*Gastrointest. Liver Physiol*. 39):G1279-G1288, 1999). The cultured monolayers are tested for properties such as resistance to passive transepithelial ion flow (such resistance indicating an intact monolayer performing a barrier function). The thus-generated epithelial monolayer simulates the intestinal epithelial barrier.

One type of assay determines whether a particular radiolabeled compound is able to cross an epithelial monolayer (e.g., a monolayer generated as described above). Transport of the radiolabeled compound across the monolayer indicates that the barrier is permeable rather than intact. One such procedure is mannitol flux analysis, which assesses movement of radiolabeled mannitol (e.g., ^{3}H mannitol) across a monolayer (see Madara and Stafford, *supra*).

Methods for imaging a monolayer are identified in Madara and Stafford, *supra*. Such imaging methods are an alternative for assessing the condition of an epithelial layer, after exposure to IL-4 with or without an antagonist.

Youakim and Ahdieh, *supra,* discuss proteins that are part of "tight junction" complexes in intact intestinal epithelial barriers, and report studies of the effect of IFN-γ on proteins associated with tight junctions. Other techniques for studying the effect of a cytokine on barrier function are described. For example, the effect of a cytokine on monolayer permeability may be assessed by transepithelial electrical resistance measurements, using techniques described in the reference.

U.S. Patent 6,033,688 also describes procedures that may be employed in studies of barrier permeability; see especially examples 1 and 4 of the patent. Human tracheal epithelial cells were cultured under conditions that yielded a monolayer exhibiting transepithelial electrical resistance. Transepithelial resistance (indicating an intact barrier) was determined using a voltmeter. The effect of a particular reagent (HGH) on the epithelial monolayer was assessed by exposing the monolayer to HGH, and then measuring ion transport activities in Ussing chambers, by standard methods (column 8, lines 40-56). Similar studies were conducted on monolayers that were generated from bronchial epithelial cells from a human cystic fibrosis patient (example 4, column 11).

Using any of the above-described barrier function assay procedures, an epithelial monolayer is exposed to IL-4 alone, or exposed to IL-4 in the presence of an IL-4 antagonist. The antagonist's ability to inhibit the IL-4-induced reduction in barrier function thus is assessed.

In one such assay, a monolayer of T84 cells served as an *in vitro* model of an intestinal epithelial barrier, as discussed above. IL-4 added to the basolateral side of

polarized epithelial cells was found to reduce barrier function by 70% within 48-72 hours of treatment. When an IL-4 receptor polypeptide was added at the same time as IL-4, the reduction in barrier function was prevented, and the barrier was maintained at the same level as untreated (control) cells. A soluble human IL-4 receptor polypeptide, consisting of the extracellular domain, was employed in the assay.

The assay procedure also was conducted on a monolayer derived from lung epithelial cells, which served as an *in vitro* model of a lung epithelial barrier. IL-4 added to the basolateral side of polarized lung epithelial cells was found to reduce barrier function by 50% within 48-72 hours of treatment. When the IL-4 receptor polypeptide was added at the same time as IL-4, the reduction in barrier function was prevented, and the barrier was maintained at the same level as untreated (control) cells.

EXAMPLE 8: Monoclonal Antibody designated 12B5

A human monoclonal antibody directed against human IL-4 receptor was prepared by the following procedure. The monoclonal antibody, which is designated 12B5, is a blocking antibody that functions as an IL-4 antagonist and as an IL-13 antagonist.

The procedure began with immunization of a transgenic mouse with a soluble human IL-4 receptor polypeptide. Mouse strain ((CMD)++; (JKD)++; (HCo7)11952+/++; (KCo5)9272+/++), described in example 3 above, was employed. The antigen for immunization was purified soluble IL-4R, comprising the extracellular domain of human IL-4 receptor (500ug/ml). The mouse was initially immunized with 50 ug antigen emulsified in Complete Freund's Adjuvant, followed by two more immunizations with Incomplete Freund's Adjuvant at 50ug and then 25ug. Immunization was every two weeks by intraperitoneal injection. A specific human IgG anti-IL-4R titer from the serum was performed by ELISA, eight days after the last injection. A good titer against the target was detected, and the mouse then was IV/IP boosted 25ug each on day $^{-}3$ (i.e., 3 days before the mouse was sacrificed) and 15ug IV on day $^{-}2$.

The mouse was sacrificed, and spleen cells were extracted and fused with the murine myeloma cell line P3x63Ag8.653 (ATCC CRL 1580). A conventional PEG fusion protocol was followed. The fusion was screened for HuIgG and HuKappa, followed by a rescreen for human gamma and kappa specific to IL-4R. The positive clones were evaluated, and clone 12B5 was identified as a blocking antibody. The clone was subcloned; a hybridoma cell line that produces MAb 12B5 was isolated; and MAb 12B5 was purified from the supernatant.

12B5 was determined to be an IgG1 antibody, and to be fully human. Antibodies of other subclasses, such as IgG4 or IgM monoclonal antibodies, may be derived from 12B5. Techniques for altering (switching) the subclass/isotype of an antibody are known. The constant region of 12B5 may be replaced, for example, with a constant region derived from a human IgG4 antibody. Sequence information for a human IgG4 heavy chain is presented, for example, in Ellison et al. (*DNA* Vol. 1, no. 1, pp 11-18, 1981), which is hereby incorporated by reference herein.

DNA encoding the variable region of the light chain of MAb 12B5 was isolated, and the nucleotide sequence thereof was determined. The DNA sequence for the light chain variable region is presented as SEQ ID NO:9; the amino acid sequence encoded thereby is presented in SEQ ID NO:10. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 24-35, 51-57, and 90-99, of SEQ ID NO:10, respectively.

DNA encoding the variable region of the heavy chain of MAb 12B5 was isolated, and the nucleotide sequence thereof was determined. The DNA sequence for the heavy chain variable region is presented as SEQ ID NO:11; the amino acid sequence encoded thereby is presented in SEQ ID NO:12. CDR-1 of the heavy chain is believed to correspond to amino acids 31-35; CDR-2 to amino acids 50-65; and CDR-3 to amino acids 98-104 of SEQ ID NO:12.

EXAMPLE 9: Additional Monoclonal Antibodies that inhibit both IL-4 and IL-13

Additional human monoclonal antibodies were raised against human IL-4 receptor, by immunizing transgenic mice with a soluble human IL-4R polypeptide. The transgenic mice employed were selected from the transgenic mouse strains described in example 3.

Hybridoma cell lines secreting human monoclonal antibodies that specifically bind human IL-4R, and which are capable of functioning as IL-4 antagonists and IL-13 antagonists, were identified and isolated. The MAbs are designated 27A1, 5A1, and 63. Another MAb, designated 1B7, was derived from MAb 63, and differs from the parent antibody only in the light chain. 1B7 retains the ability to bind IL-4R and to function as an IL-4 antagonist and an IL-13 antagonist.

The DNA sequence of the variable region of the light chain of MAb 27A1 is presented in SEQ ID NO:13, and the encoded amino acid sequence is presented in SEQ ID NO:14. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 24-35, 51-57, and 90-99, of SEQ ID NO:14, respectively.

The DNA sequence for the variable region of the heavy chain of MAb 27A1 is presented as SEQ ID NO:15, and the encoded amino acid sequence is presented in SEQ ID NO:16. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 31-35, 50-66, and 99-105, of SEQ ID NO:16, respectively.

The DNA sequence of the variable region of the light chain of MAb 5A1 is presented in SEQ ID NO:17, and the encoded amino acid sequence is presented in SEQ ID NO:18. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 24-34, 50-56, and 89-97 of SEQ ID NO:18, respectively.

The DNA sequence for the variable region of the heavy chain of MAb 5A1 is presented as SEQ ID NO:19, and the encoded amino acid sequence is presented in SEQ ID NO:20. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 31-35, 50-65, and 98-112 of SEQ ID NO:20, respectively.

The DNA sequence of the variable region of the light chain of MAb 63 is presented in SEQ ID NO:21, and the encoded amino acid sequence is presented in SEQ ID NO:22. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 24-34, 50-56, and 89-97 of SEQ ID NO:22, respectively.

The DNA sequence for the variable region of the heavy chain of MAb 63 is presented as SEQ ID NO:23, and the encoded amino acid sequence is presented in SEQ ID NO:24. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 31-35, 50-66, and 99-106 of SEQ ID NO:24, respectively.

The DNA sequence of the variable region of the light chain of MAb 1B7 is presented in SEQ ID NO:25, and the encoded amino acid sequence is presented in SEQ ID NO:26. Complementarity determining regions 1 to 3 (CDR 1-3) are believed to correspond to amino acids 24-34, 50-56, and 89-97 of SEQ ID NO:26, respectively.

MAb 1B7 was derived from MAb 63, and the heavy chains of the two MAbs are identical. Thus, the DNA sequence for the variable region of the heavy chain of MAb 1B7 is presented as SEQ ID NO:23, and the encoded amino acid sequence is presented in SEQ ID NO:24. Complementarity determining regions 1 to 3 (CDRs 1-3) are believed to correspond to amino acids 31-35, 50-66, and 99-106 of SEQ ID NO:24, respectively.

CLAIMS

What is claimed is:

1. An isolated antibody that competes with a reference antibody for binding to human IL-4 receptor, wherein:

a. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12; or

b. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:14 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:16; or

c. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:18 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:20; or

d. the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:22 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:24.

2. The isolated antibody of Claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited.

3. The isolated antibody of Claim 1, wherein when said isolated antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited.

4. The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-4 to human IL-4 receptor.

5. The isolated antibody of Claim 1, wherein said isolated antibody inhibits the binding of human IL-13 to human IL-4 receptor.

6. The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-4 signaling through human IL-4 receptor.

7. The isolated antibody of Claim 1, wherein said isolated antibody inhibits human IL-13 signaling through human IL-4 receptor.

8. The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^8.

9. The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^9.

10. The isolated antibody of Claim 1, wherein said isolated antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1 x 10^{10}.

11. The isolated antibody of Claim 1, wherein said isolated antibody is a human, partially human, humanized, or chimeric antibody.

12. The isolated antibody of Claim 1, wherein said isolated antibody is a full-length antibody.

13. The isolated antibody of Claim 1, wherein said isolated antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody.

14. The isolated antibody of Claim 1, wherein said isolated antibody is a fragment of an antibody.

15. The isolated antibody of Claim 1, wherein said isolated antibody is a fusion protein.

16. The isolated antibody of Claim 1, wherein said isolated antibody is a single chain antibody (scFv).

17. The isolated antibody of Claim 1, wherein:

a. the light chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:14 and the heavy chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:16; or

b. the light chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:18 and the heavy chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:20; or

c. the light chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:22 and the heavy chain variable domain of said isolated antibody comprises the CDR1, 2, and 3 sequences of SEQ ID NO:24.

18. The isolated antibody of Claim 1, wherein:

a. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:14; or

b. the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:16; or

c. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:18; or

d. the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:20; or

e. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:22; or

f. the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:24.

19. The isolated antibody of Claim 1, wherein:

a. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:14 and the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:16; or

b. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:18 and the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:20; or

c. the light chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:22 and the heavy chain of said isolated antibody comprises the amino acid sequence of SEQ ID NO:24.

20. An isolated nucleic acid, wherein said isolated nucleic acid comprises a sequence encoding:

a. the light chain variable domain of said isolated antibody of Claim 1; or

b. the heavy chain variable domain of said isolated antibody of Claim 1; or

c. the light chain variable domain of said isolated antibody of Claim 1 and the heavy chain variable domain of said isolated antibody of Claim 1.

21. A vector, wherein said vector comprises said isolated nucleic acid of Claim 20.

22. The vector of Claim 21, wherein said vector is an expression vector.

23. An isolated cell, wherein said cell comprises said isolated nucleic acid of Claim 20.

24. The isolated cell of Claim 23, wherein said isolated cell expresses said isolated antibody.

25. A method of reducing IL-4 receptor-dependent signaling in a subject, comprising administering to said subject an effective amount of said isolated antibody of Claim 1.

26. The method of Claim 25, wherein said method suppresses a T_H2-type immune response.

27. The method of Claim 25, wherein said subject has, or is at risk of developing, a condition responsive to inhibition of IL-4R signaling.

28. The method of Claim 27, wherein said condition is an inflammatory condition.

29. The method of Claim 27, wherein said condition is an IgE mediated condition.

30. The method of Claim 27, wherein said condition is an allergic condition.

31. The method of Claim 27, wherein said condition is a condition in which IL-4 mediated epithelial barrier disruption plays a role.

32. The method of Claim 27, wherein said condition is asthma, COPD, pulmonary fibrosis, or septic arthritis.

33. A method of making an antibody, comprising incubating said cell of Claim 23 under conditions that allow it to express said isolated antibody.

34. A composition comprising said isolated antibody of Claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient.

35. A kit comprising said isolated antibody of Claim 1.

5

ABSTRACT OF THE DISCLOSURE

Methods for treating medical conditions induced by interleukin-4 involve administering an IL-4 antagonist to a patient afflicted with such a condition. Suitable IL-4 antagonists include, but are not limited to, IL-4 receptors (such as a soluble human IL-4 receptor), antibodies that bind IL-4, antibodies that bind IL-4R, IL-4 muteins that bind to IL-4R but do not induce a biological response, molecules that inhibit IL-4-induced signal transduction, and other compounds that inhibit a biological effect that results from the binding of IL-4 to a cell surface IL-4R. Particular antibodies provided herein include human monoclonal antibodies generated by procedures involving immunization of transgenic mice. Such human antibodies may be raised against human IL-4 receptor. Certain of the antibodies inhibit both IL-4-induced and IL-13-induced biological activities.

FIGURE 1A

```
ATG GGG TGG CTT TGC TCT GGG CTC CTG TTC CCT GTG AGC TGC CTG -31
Met Gly Trp Leu Cys Ser Gly Leu Leu Phe Pro Val Ser Cys Leu -11

GTC CTG CTG CAG GTG GCA AGC TCT GGG AAC ATG AAG GTC TTG CAG  15
Val Leu Leu Gln Val Ala Ser Ser Gly Asn Met Lys Val Leu Gln   5

GAG CCC ACC TGC GTC TCC GAC TAC ATG AGC ATC TCT ACT TGC GAG  60
Glu Pro Thr Cys Val Ser Asp Tyr Met Ser Ile Ser Thr Cys Glu  20

TGG AAG ATG AAT GGT CCC ACC AAT TGC AGC ACC GAG CTC CGC CTG 105
Trp Lys Met Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu  35

TTG TAC CAG CTG GTT TTT CTG CTC TCC GAA GCC CAC ACG TGT ATC 150
Leu Tyr Gln Leu Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile  50

CCT GAG AAC AAC GGA GGC GCG GGG TGC GTG TGC CAC CTG CTC ATG 195
Pro Glu Asn Asn Gly Gly Ala Gly Cys Val Cys His Leu Leu Met  65

GAT GAC GTG GTC AGT GCG GAT AAC TAT ACA CTG GAC CTG TGG GCT 240
Asp Asp Val Val Ser Ala Asp Asn Tyr Thr Leu Asp Leu Trp Ala  80

GGG CAG CAG CTG CTG TGG AAG GGC TCC TTC AAG CCC AGC GAG CAT 285
Gly Gln Gln Leu Leu Trp Lys Gly Ser Phe Lys Pro Ser Glu His  95

GTG AAA CCC AGG GCC CCA GGA AAC CTG ACA GTT CAC ACC AAT GTC 330
Val Lys Pro Arg Ala Pro Gly Asn Leu Thr Val His Thr Asn Val 110

TCC GAC ACT CTG CTG CTG ACC TGG AGC AAC CCG TAT CCC CCT GAC 375
Ser Asp Thr Leu Leu Leu Thr Trp Ser Asn Pro Tyr Pro Pro Asp 125

AAT TAC CTG TAT AAT CAT CTC ACC TAT GCA GTC AAC ATT TGG AGT 420
Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala Val Asn Ile Trp Ser 140

GAA AAC GAC CCG GCA GAT TTC AGA ATC TAT AAC GTG ACC TAC CTA 465
Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn Val Thr Tyr Leu 155

GAA CCC TCC CTC CGC ATC GCA GCC AGC ACC CTG AAG TCT GGG ATT 510
Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys Ser Gly Ile 170

TCC TAC AGG GCA CGG GTG AGG GCC TGG GCT CAG TGC TAT AAC ACC 555
Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr Asn Thr 185

ACC TGG AGT GAG TGG AGC CCC AGC ACC AAG TGG CAC AAC TCC TAC 600
Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser Tyr 200

AGG GAG CCC TTC GAG CAG CAC CTC CTG CTG GGC GTC AGC GTT TCC 645
Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser 215

TGC ATT GTC ATC CTG GCC GTC TGC CTG TTG TGC TAT GTC AGC ATC 690
Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile 230

ACC AAG ATT AAG AAA GAA TGG TGG GAT CAG ATT CCC AAC CCA GCC 735
Thr Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala 245
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FIGURE 1B

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CGC AGC CGC CTC GTG GCT ATA ATA ATC CAG GAT GCT CAG GGG TCA  780
Arg Ser Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser  260

CAG TGG GAG AAG CGG TCC CGA GGC CAG GAA CCA GCC AAG TGC CCA  825
Gln Trp Glu Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro  275

CAC TGG AAG AAT TGT CTT ACC AAG CTC TTG CCC TGT TTT CTG GAG  870
His Trp Lys Asn Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu  290

CAC AAC ATG AAA AGG GAT GAA GAT CCT CAC AAG GCT GCC AAA GAG  915
His Asn Met Lys Arg Asp Glu Asp Pro His Lys Ala Ala Lys Glu  305

ATG CCT TTC CAG GGC TCT GGA AAA TCA GCA TGG TGC CCA GTG GAG  960
Met Pro Phe Gln Gly Ser Gly Lys Ser Ala Trp Cys Pro Val Glu  320

ATC AGC AAG ACA GTC CTC TGG CCA GAG AGC ATC AGC GTG GTG CGA 1005
Ile Ser Lys Thr Val Leu Trp Pro Glu Ser Ile Ser Val Val Arg  335

TGT GTG GAG TTG TTT GAG GCC CCG GTG GAG TGT GAG GAG GAG GAG 1050
Cys Val Glu Leu Phe Glu Ala Pro Val Glu Cys Glu Glu Glu Glu  350

GAG GTA GAG GAA GAA AAA GGG AGC TTC TGT GCA TCG CCT GAG AGC 1095
Glu Val Glu Glu Glu Lys Gly Ser Phe Cys Ala Ser Pro Glu Ser  365

AGC AGG GAT GAC TTC CAG GAG GGA AGG GAG GGC ATT GTG GCC CGG 1140
Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu Gly Ile Val Ala Arg  380

CTA ACA GAG AGC CTG TTC CTG GAC CTG CTC GGA GAG GAG AAT GGG 1185
Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly Glu Glu Asn Gly  395

GGC TTT TGC CAG CAG GAC ATG GGG GAG TCA TGC CTT CTT CCA CCT 1230
Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu Leu Pro Pro  410

TCG GGA AGT ACG AGT GCT CAC ATG CCC TGG GAT GAG TTC CCA AGT 1275
Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe Pro Ser  425

GCA GGG CCC AAG GAG GCA CCT CCC TGG GGC AAG GAG CAG CCT CTC 1320
Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro Leu  440

CAC CTG GAG CCA AGT CCT CCT GCC AGC CCG ACC CAG AGT CCA GAC 1365
His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Asp  455

AAC CTG ACT TGC ACA GAG ACG CCC CTC GTC ATC GCA GGC AAC CCT 1410
Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro  470

GCT TAC CGC AGC TTC AGC AAC TCC CTG AGC CAG TCA CCG TGT CCC 1455
Ala Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro  485

AGA GAG CTG GGT CCA GAC CCA CTG CTG GCC AGA CAC CTG GAG GAA 1500
Arg Glu Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Glu  500

GTA GAA CCC GAG ATG CCC TGT GTC CCC CAG CTC TCT GAG CCA ACC 1545
Val Glu Pro Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr  515
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FIGURE 1C

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ACT GTG CCC CAA CCT GAG CCA GAA ACC TGG GAG CAG ATC CTC CGC 1590
Thr Val Pro Gln Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg  530

CGA AAT GTC CTC CAG CAT GGG GCA GCT GCA GCC CCC GTC TCG GCC 1635
Arg Asn Val Leu Gln His Gly Ala Ala Ala Ala Pro Val Ser Ala  545

CCC ACC AGT GGC TAT CAG GAG TTT GTA CAT GCG GTG GAG CAG GGT 1680
Pro Thr Ser Gly Tyr Gln Glu Phe Val His Ala Val Glu Gln Gly  560

GGC ACC CAG GCC AGT GCG GTG GTG GGC TTG GGT CCC CCA GGA GAG 1725
Gly Thr Gln Ala Ser Ala Val Val Gly Leu Gly Pro Pro Gly Glu  575

GCT GGT TAC AAG GCC TTC TCA AGC CTG CTT GCC AGC AGT GCT GTG 1770
Ala Gly Tyr Lys Ala Phe Ser Ser Leu Leu Ala Ser Ser Ala Val  590

TCC CCA GAG AAA TGT GGG TTT GGG GCT AGC AGT GGG GAA GAG GGG 1815
Ser Pro Glu Lys Cys Gly Phe Gly Ala Ser Ser Gly Glu Glu Gly  605

TAT AAG CCT TTC CAA GAC CTC ATT CCT GGC TGC CCT GGG GAC CCT 1860
Tyr Lys Pro Phe Gln Asp Leu Ile Pro Gly Cys Pro Gly Asp Pro  620

GCC CCA GTC CCT GTC CCC TTG TTC ACC TTT GGA CTG GAC AGG GAG 1905
Ala Pro Val Pro Val Pro Leu Phe Thr Phe Gly Leu Asp Arg Glu  635

CCA CCT CGC AGT CCG CAG AGC TCA CAT CTC CCA AGC AGC TCC CCA 1950
Pro Pro Arg Ser Pro Gln Ser Ser His Leu Pro Ser Ser Ser Pro  650

GAG CAC CTG GGT CTG GAG CCG GGG GAA AAG GTA GAG GAC ATG CCA 1995
Glu His Leu Gly Leu Glu Pro Gly Glu Lys Val Glu Asp Met Pro  665

AAG CCC CCA CTT CCC CAG GAG CAG GCC ACA GAC CCC CTT GTG GAC 2040
Lys Pro Pro Leu Pro Gln Glu Gln Ala Thr Asp Pro Leu Val Asp  680

AGC CTG GGC AGT GGC ATT GTC TAC TCA GCC CTT ACC TGC CAC CTG 2085
Ser Leu Gly Ser Gly Ile Val Tyr Ser Ala Leu Thr Cys His Leu  695

TGC GGC CAC CTG AAA CAG TGT CAT GGC CAG GAG GAT GGT GGC CAG 2130
Cys Gly His Leu Lys Gln Cys His Gly Gln Glu Asp Gly Gly Gln  710

ACC CCT GTC ATG GCC AGT CCT TGC TGT GGC TGC TGC TGT GGA GAC 2175
Thr Pro Val Met Ala Ser Pro Cys Cys Gly Cys Cys Cys Gly Asp  725

AGG TCC TCG CCC CCT ACA ACC CCC CTG AGG GCC CCA GAC CCC TCT 2220
Arg Ser Ser Pro Pro Thr Thr Pro Leu Arg Ala Pro Asp Pro Ser  740

CCA GGT GGG GTT CCA CTG GAG GCC AGT CTG TGT CCG GCC TCC CTG 2265
Pro Gly Gly Val Pro Leu Glu Ala Ser Leu Cys Pro Ala Ser Leu  755

GCA CCC TCG GGC ATC TCA GAG AAG AGT AAA TCC TCA TCA TCC TTC 2310
Ala Pro Ser Gly Ile Ser Glu Lys Ser Lys Ser Ser Ser Ser Phe  770

CAT CCT GCC CCT GGC AAT GCT CAG AGC TCA AGC CAG ACC CCC AAA 2355
His Pro Ala Pro Gly Asn Ala Gln Ser Ser Ser Gln Thr Pro Lys  785

ATC GTG AAC TTT GTC TCC GTG GGA CCC ACA TAC ATG AGG GTC TCT 2400
Ile Val Asn Phe Val Ser Val Gly Pro Thr Tyr Met Arg Val Ser  800
```

FIGURE 2A

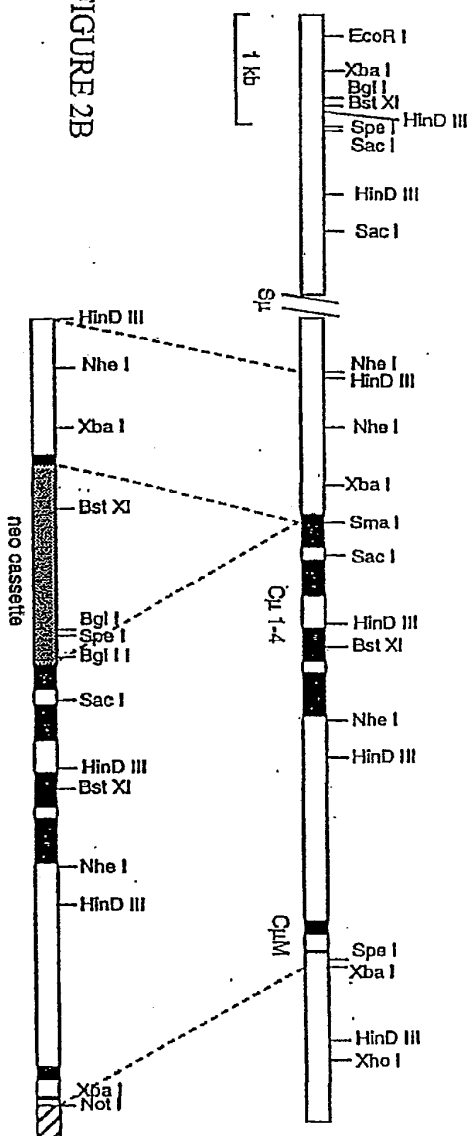

FIGURE 2B

FIGURE 2C

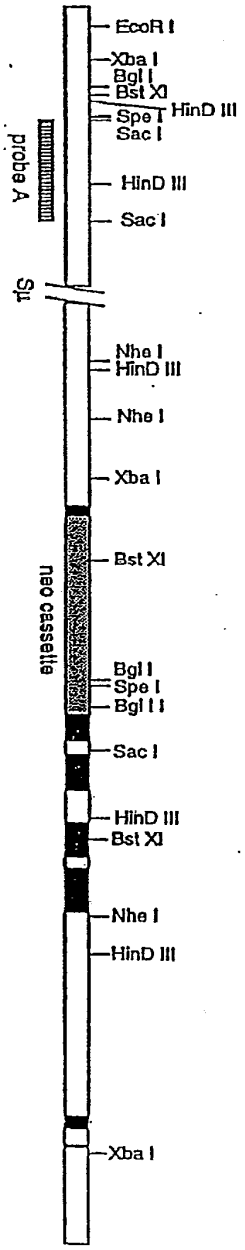

FIGURE 3A

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AATTAGCGGC CGCTGTCGAC AAGCTTCGAA TTCAGTATCG ATGTGGGGTA   50
CCTACTGTCC CGGGATTGCG GATCCGCGAT GATATCGTTG ATCCTCGAGT  100
GCGGCCGCAG TATGCAAAAA AAAGCCCGCT CATTAGGCGG GCTCTTGGCA  150
GAACATATCC ATCGCGTCCG CCATCTCCAG CAGCCGCACG CGGCGCATCT  200
CGGGCAGCGT TGGGTCCTGG CCACGGGTGC GCATGATCGT GCTCCTGTCG  250
TTGAGGACCC GGCTAGGCTG GCGGGGTTGC CTTACTGGTT AGCAGAATGA  300
ATCACCGATA CGCGAGCGAA CGTGAAGCGA CTGCTGCTGC AAAACGTCTG  350
CGACCTGAGC AACAACATGA ATGGTCTTCG GTTTCCGTGT TTCGTAAAGT  400
CTGGAAACGC GGAAGTCAGC GCCCTGCACC ATTATGTTCC GGATCTGCAT  450
CGCAGGATGC TGCTGGCTAC CCTGTGGAAC ACCTACATCT GTATTAACGA  500
AGCGCTGGCA TTGACCCTGA GTGATTTTTC TCTGGTCCCG CCGCATCCAT  550
ACCGCCAGTT GTTTACCCTC ACAACGTTCC AGTAACCGGG CATGTTCATC  600
ATCAGTAACC CGTATCGTGA GCATCCTCTC TCGTTTCATC GGTATCATTA  650
CCCCCATGAA CAGAAATTCC CCCTTACACG GAGGCATCAA GTGACCAAAC  700
AGGAAAAAAC CGCCCTTAAC ATGGCCCGCT TTATCAGAAG CCAGACATTA  750
ACGCTTCTGG AGAAACTCAA CGAGCTGGAC GCGGATGAAC AGGCAGACAT  800
CTGTGAATCG CTTCACGACC ACGCTGATGA GCTTTACCGC AGCTGCCTCG  850
CGCGTTTCGG TGATGACGGT GAAAACCTCT GACACATGCA GCTCCCGGAG  900
ACGGTCACAG CTTGTCTGTA AGCGGATGCC GGGAGCAGAC AAGCCCGTCA  950
GGGCGCGTCA GCGGGTGTTG GCGGGTGTCG GGGCGCAGCC ATGACCCAGT 1000
CACGTAGCGA TAGCGGAGTG TATACTGGCT TAACTATGCG GCATCAGAG  1050
AGATTGTACT GAGAGTGCAC CATATGCGGT GTGAAATACC GCACAGATGC 1100
GTAAGGAGAA AATACCGCAT CAGGCGCTCT TCCGCTTCCT CGCTCACTGA 1150
CTCGCTGCGC TCGGTCGTTC GGCTGCGGCG AGCGGTATCA GCTCACTCAA 1200
AGGCGGTAAT ACGGTTATCC ACAGAATCAG GGGATAACGC AGGAAAGAAC 1250
ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG AACCGTAAAA AGGCCGCGTT 1300
GCTGGCGTTT TTCCATAGGC TCCGCCCCCC TGACGAGCAT CACAAAAATC 1350
GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAG 1400
GCGTTTCCCC CTGGAAGCTC CCTCGTGCGC TCTCCTGTTC CGACCCTGCC 1450
GCTTACCGGA TACCTGTCCG CCTTTCTCCC TTCGGGAAGC GTGGCGCTTT 1500
CTCATAGCTC ACGCTGTAGG TATCTCAGTT CGGTGTAGGT CGTTCGCTCC 1550
AAGCTGGGCT GTGTGCACGA ACCCCCCGTT CAGCCCGACC GCTGCGCCTT 1600
ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC GACTTATCGC 1650
CACTGGCAGC AGCCAGGCGC GCCTTGGCCT AAGAGGCCAC TGGTAACAGG 1700
ATTAGCAGAG CGAGGTATGT AGGCGGTGCT ACAGAGTTCT TGAAGTGGTG 1750
GCCTAACTAC GGCTACACTA GAAGGACAGT ATTTGGTATC TGCGCTCTGC 1800
TGAAGCCAGT TACCTTCGGA AAAAGAGTTG GTAGCTCTTG ATCCGGCAAA 1850
CAAACCACCG CTGGTAGCGG TGGTTTTTTT GTTTGCAAGC AGCAGATTAC 1900
GCGCAGAAAA AAAGGATCTC AAGAAGATCC TTTGATCTTT TCTACGGGGT 1950
CTGACGCTCA GTGGAACGAA AACTCACGTT AAGGGATTTT GGTCATGAGA 2000
TTATCAAAAA GGATCTTCAC CTAGATCCTT TTAAATTAAA AATGAAGTTT 2050
TAAATCAATC TAAAGTATAT ATGAGTAAAC TTGGTCTGAC AGTTACCAAT 2100
GCTTAATCAG TGAGGCACCT ATCTCAGCGA TCTGTCTATT TCGTTCATCC 2150
ATAGTTGCCT GACTCCCCGT CGTGTAGATA ACTACGATAC GGGAGGGCTT 2200
ACCATCTGGC CCCAGTGCTG CAATGATACC GCGAGACCCA CGCTCACCGG 2250
CTCCAGATTT ATCAGCAATA AACCAGCCAG CCGGAAGGGC CGAGCGCAGA 2300
AGTGGTCCTG CAACTTTATC CGCCTCCATC CAGTCTATTA ATTGTTGCCG 2350
GGAAGCTAGA GTAAGTAGTT CGCCAGTTAA TAGTTTGCGC AACGTTGTTG 2400
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FIGURE 3B

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CCATTGCTGC AGGCATCGTG GTGTCACGCT CGTCGTTTGG TATGGCTTCA 2450
TTCAGCTCCG GTTCCCAACG ATCAAGGCGA GTTACATGAT CCCCCATGTT 2500
GTGCAAAAAA GCGGTTAGCT CCTTCGGTCC TCCGATCGTT GTCAGAAGTA 2550
AGTTGGCCGC AGTGTTATCA CTCATGGTTA TGGCAGCACT GCATAATTCT 2600
CTTACTGTCA TGCCATCCGT AAGATGCTTT TCTGTGACTG GTGAGTACTC 2650
AACCAAGTCA TTCTGAGAAT AGTGTATGCG GCGACCGAGT TGCTCTTGCC 2700
CGGCGTCAAC ACGGGATAAT ACCGCGCCAC ATAGCAGAAC TTTAAAAGTG 2750
CTCATCATTG GAAAACGTTC TTCGGGGCGA AAACTCTCAA GGATCTTACC 2800
GCTGTTGAGA TCCAGTTCGA TGTAACCCAC TCGTGCACCC AACTGATCTT 2850
CAGCATCTTT TACTTTCACC AGCGTTTCTG GGTGAGCAAA AACAGGAAGG 2900
CAAAATGCCG CAAAAAAGGG AATAAGGGCG ACACGGAAAT GTTGAATACT 2950
CATACTCTTC CTTTTTCAAT ATTATTGAAG CATTTATCAG GGTTATTGTC 3000
TCATGAGCGG ATACATATTT GAATGTATTT AGAAAAATAA ACAAATAGGG 3050
GTTCCGCGCA CATTTCCCCG AAAAGTGCCA CCTGACGTCT AAGAAACCAT 3100
TATTATCATG ACATTAACCT ATAAAAATAG GCGTATCACG AGGCCCTTTC 3150
GTCTTCAAG                                             3159
```

Via EFS-Web
July 1, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Richard J. Armitage, Jose Carlos Escobar, Arvia E. Morris and John D. Pluenneke
Serial No.:	-- to be assigned --
Filed:	July 1, 2010
For:	USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF
Docket No.:	3005-US-CNT3

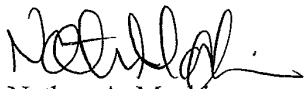
ATTORNEY'S STATEMENT PURSUANT TO 37 CFR § 1.821(f)

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

Sir:

I hereby state that the Sequence Listing submitted herewith does not include any new matter that goes beyond the disclosure of the application as filed.

Respectfully submitted,



Nathan A. Machin
Attorney for Applicants
Registration No.: 47,763
Phone: (206) 265-8779
Date: July 1, 2010

Please send all future correspondence to:

22932

IMMUNEX CORPORATION
Law Department
1201 Amgen Court West
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(206) 265-7000

CERTIFICATE OF EFS-Web TRANSMISSION

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/	July 1, 2010
Jae Cho	Date

Via EFS-Web
July 1, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Richard J. Armitage, Jose Carlos Escobar, Arvia E. Morris and John D. Pluenneke

Serial No.: --to be assigned-- Group Art Unit No.: Unknown

Filed: July 1, 2010 Examiner: Unknown

For: USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF

Docket No.: 3005-US-CNT3

INFORMATION DISCLOSURE STATEMENT

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

Sir:

As a means of complying with the duty of disclosure under 37 CFR 1.97 and 1.98, applicant(s) submit(s) a "List of References Cited by Applicant" on a modified PTO-1449 form.

Applicants make no determination of relevancy with respect to the reference(s) submitted herewith and request the Examiner to make an independent determination of the relevance and/or materiality of the reference(s).

In accordance with 37 CFR 1.98(d), copies of the patents, publications, pending U.S. applications or other information listed in this information disclosure statement are not required to be provided and are not enclosed because they were previously cited by or submitted to the Office in prior application Serial No. **12/291,702**, filed **November 13, 2008**. The present application is a continuation of this prior application which is relied upon for an earlier filing date under 35 USC 120 and the information disclosure statement submitted in the earlier application complies with 37 CFR 1.98(a)-(c).

The information disclosure statement submitted herewith is being filed within three months of the filing date of the application or date of entry into the national stage of an international application or before the mailing date of a first Office action on the merits, or before the mailing of a first Office action after the filing of a request for continued examination under section 1.114, whichever event occurs last. 37 CFR 1.97(b).

Applicant(s) request(s) consideration of this information and passage of the application to issue.

CERTIFICATE OF EFS-Web TRANSMISSION
I hereby certify that this paper (along with any referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office via EFS-Web on the date indicated below:

/Jae Cho/	July 1, 2010
Jae Cho	Date

The Commissioner is hereby authorized to charge any filing fees which may be required or credit any overpayment to Deposit Account No. 09-0089 in the name of Immunex Corporation.

Respectfully submitted,

Nathan A. Machin
Attorney for Applicants
Registration No.: 47,763
Phone: (206) 265-8779
Date: July 1, 2010

Please send all future correspondence to:
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Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, WA 98119-3105
(206) 265-7000

Via EFS-Web
July 1, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of:		Docket No.:	3005-C
	John Pluenneke		
Serial No	09/847,816	Art Unit:	1645
Filed:	May 1, 2001	Examiner:	Not assigned
Title:	USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF		

STATEMENT UNDER 37 C.F.R. 3.73(b) AND POWER OF ATTORNEY BY ASSIGNEE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

IMMUNEX CORPORATION (hereinafter "IMMUNEX"), a corporation of the State of Washington having a place of business at 51 University Street, Seattle, Washington 98101, is the assignee of the entire right, title, and interest in the above-identified U.S. patent application. Documentary evidence of a chain of title from the original owner(s) to Immunex is demonstrated by:

☒ the enclosed copy of an Assignment, the original of which is being filed for recordation by the United States Patent and Trademark Office.

☐ the assignment recorded in the United States Patent and Trademark Office at Reel , Frame.

The undersigned, whose title is supplied below, is empowered to sign this statement on behalf of IMMUNEX.

IMMUNEX hereby appoints the registered practitioners at the following Customer Number to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

22932

Immunex Corporation
Statement Under 37 CFR 3.73(b) and Power of Attorney by Assignee
USSN 09/847,816

Please send all correspondence and direct telephone calls to the above-identified Customer Number.

Respectfully submitted,

Date August 20, 2001

By _____
Michael K. Kirschner
Vice President, Intellectual Property

Enclosure: Copy of Assignment

bl082604 7/18/01

Express Mail Label No. EV 947188008 US

Immunex Corporation

ASSIGNMENT

WHEREAS, I, John D. Pluenneke, residing at Parkville, Missouri, have made an invention entitled "USE OF INTERLEUKIN-4 ANTAGONISTS AND COMPOSITIONS THEREOF," for which U.S. Patent Application Serial No. 09/847,816 was filed on May 1, 2001;

AND, WHEREAS, IMMUNEX CORPORATION, a corporation of the State of Washington, having a principal place of business at 51 University Street, Seattle, Washington 98101 (hereinafter referred to as ASSIGNEE) is desirous of acquiring the entire right and title to and interest in the invention disclosed in said application;

NOW, THEREFORE, for sufficient, good and valuable consideration, the receipt of which is hereby acknowledged, I do hereby sell, assign, and transfer unto said ASSIGNEE my entire right and title to and interest in said application and said invention(s) and all U.S. and foreign applications and patents on said invention(s) to be held and enjoyed by ASSIGNEE as entirely as the same would have been held and enjoyed by me had this sale, assignment, and transfer not been made, and I do hereby further agree and promise to execute all instruments and render all such assistance as ASSIGNEE may request in order to make and prosecute any and all applications on said invention(s), to enforce any and all patents on said invention(s), and to confirm in ASSIGNEE legal title to said invention(s) and all applications and patents on said invention(s), all without charge to ASSIGNEE but at no expense to me.

Executed at Kansas City, MO, this 7 day of August, 2001.

John D. Pluenneke

STATE OF Missouri)
) ss.
COUNTY OF Platte)

On this 7 day of August, 2001, personally appeared before me John D. Pluenneke, to me known to be the individual named above who executed the within and foregoing instrument, and acknowledged that he signed the same as his free and voluntary act and deed, for the uses and purposes therein mentioned.

LORENE A. BUCHMAN NOTARY SEAL NOTARY PUBLIC STATE OF MISSOURI

Signature
Print Name: Lorene A Buchman
Notary Public in and for the State of Missouri
My appointment expires Oct 19 2001

cf053103 7/18/01

LORENE A. BUCHMAN
Notary Public - State of Missouri
PLATTE COUNTY
My Commission Expires Oct. 19, 2001