UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/100,088	04/09/2008	Gerard T. Hardiman	DX0724XK1D	5423

24265 7590 07/23/2009

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

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

MAIL DATE	DELIVERY MODE
07/23/2009	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)	
	12/100,088	HARDIMAN 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 *22 April 2009*.

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) *4,23 and 24* 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4a) Of the above claim(s) _____ is/are withdrawn from consideration.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) *4,23 and 24* 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 _____ 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: *sequence compliance, PTO-90C*.

DETAILED ACTION

1a. Receipt of Applicants' amendment and arguments, filed on 22 April 2009 is acknowledged.

Status of Claims:

1b. Claims 1-3 and 5-22 have been cancelled. Thus claims 4 and 23-24 are pending and under consideration.

Sequence Compliance:

2a. A paper copy of a new sequence listing and a statement that the paper copy and the computer readable form, (CRF) are the same were submitted in the amendment filed on 22 April 2009. However, Applicants failed to file a CRF for the new sequence listing. Accordingly, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). See the attached sequence compliance form. The basis for this issue was set forth at page 2 in the previous Office Action of 26 January 2009.

Specification:

2b. The amendment filed on 22 April 2009 provides sequence identifiers for the sequences recited in figures 2A and 2B ands the sequences recited on pages 50-51. No new matter has been added.

Response to Applicants' arguments:

3. The following objection and rejections are withdrawn in light of Applicants' arguments:

I. The objection to the specification is withdrawn. The title of the invention has been amended and Applicants indicate that the embedded hyperlink and/or other form of browser-executable code is intended as active links, (See MPEP § 608.01 VIII).

II. Relevant sequence identifiers have been provided for sequences disclosed in figures 2A-2B and pages 50-51. Thus, the current Application complies with the requirements of 37 CFR §1.821-1.825. The substitute sequence listing, providing sequence identifiers for the sequences disclosed in figures 2a-A-2B and pages 50-51, is acknowledged. No new matter is added.

Maintenance pf previous Rejections:

Claim Rejections - 35 U.S.C. §112:

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

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

4. Claims 4 and 23-24 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

Claims 4 and 23-24 encompass a method of treating a patient having sepsis or septic shock comprising administering to said patient an antibody or an antigen fragment thereof that specifically binds to an isolated or recombinant polypeptide

comprising the amino acid sequence SEQ ID NO:8, wherein said antibody is administered intravenously or subcutaneously.

The specification describes the polypeptide of SEQ ID NO:8 as being the mature form of human toll like receptor 4, (TLR4), (see page 7, line 13). The instant specification contemplates the use of anti-TLR4 antibodies or soluble TLR4 for treating disease conditions such as sepsis, (see page 78, lines 1-20). The specification discloses that LPS is a ligand for TLR4, and that LPS stimulates TNF-α and IL-6 in $CD4^{+}CD3^{-}C^{+}$ immature dendritic cells that were shown to express moderate levels of TLR4, (see page 76, lines 1-7 and lines 22-25). However, the instant specification does not disclose the administration of an antibody or binding fragment of an antibody that binds to the polypeptide of SEQ ID NO:8 to a patient suffering from sepsis or septic shock to treat said condition.

Applicants argue that at the time the subject application was filed, it was well known in the art that LPS challenge initiates intracellular signaling that results in the expression of cytokines and other inflammatory molecules, resulting in a potentially lethal systemic host inflammatory response, i.e., sepsis/septic shock. Applicants also submit that it was also recognized in the art that the binding of LPS to TLR4 was a key step in this process. Applicants point out that the subject invention refers to inhibition of the LPS signal-transducing function of TLR4 and that one skilled in the art would recognize that the LPS signal transducing function of a complex comprising TLR4 and MD-2 may be blocked by inhibiting a key component of that complex (e.g., TLR4). Applicants argue that Qureshi et al., J. Exp. Med. 189(4):615-625, 1999, demonstrates

that mice with altered TLR4 function are hyporesponsive to LPS challenge and exhibit natural tolerance to the lethal effects of LPS. Thus, Applicants conclude that the skilled artisan would thus have predicted that inhibiting the effects of LPS by blocking TLR4 activity, e.g., by using an antibody, would provide a protective effect against sepsis. Regarding Dabeuf et al. (J. Immunol. 179:6107-6114 (2007), cited by the Examiner, Applicants argue that the antibody exemplified by Dabeuf et al. should have no bearing on the patentability of the subject claims. Applicants further submit that at the time the application was filed, the preparation and characterization of antibodies was well known, as were assays by which TLR4 downstream function could be measured, the skilled worker would have been in possession of the amino acid sequence of the mature TLR4 protein (SEQ ID NO: 8), the skilled worker would thus have been able to raise antibodies against the TLR4 sequence, and to test such antibodies for inhibition of downstream TLR4 function, e.g., cytokine expression, without undue experimentation.

These arguments have been considered, but are not deemed persuasive. It is acknowledged that it was recognized in the art at the time the current invention was filed that TLR4 is the receptor for LPS and that LPS is involved in sepsis. It is also acknowledged that the preparation and characterization of antibodies were well known in the art and that antibodies against the polypeptide of SEQ ID NO:8 could be raised and tested against TLR4 activities. However, the etiology of sepsis or septic shock is very complex. Although LPS can induce the sepsis syndrome when injected into animals and humans, agents that block LPS do not lessen the manifestations or improve the outcome of sepsis, (Brunn et al, Trends in Molecular Medicine, 2006, Vol.

12, No.1, pages 10-16, especially abstract). Brunn et al teach that the classical model of Gram-negative sepsis places TLR4 in a pivotal position, because when stimulated by LPS or other PAMPs from microorganisms, TLR4 causes fever, shock and death in sepsis, (see page 11, columns 1 and 2). However, Brunn et al also teach that TLR4 appears to protect rather than cause shock in sepsis and that TLR4 paradoxically protects humans from Gram-negative infection, (page 12, bottom of column 1 and top of column 2). With respect to the Debeuf et al reference, the Examiner agrees with the Applicants that the antibody exemplified by Dabeuf et al. should have no bearing on the patentability of the subject claims. However, since the role of TLR4 in sepsis is complex, and because it is now known that TLR4 can have protective as well as detrimental effects in sepsis, the method of treating sepsis or septic shock, as required by the instant claims, requires more than a mere prophetic suggestion that antibodies against the polypeptide of SEQ ID NO:8 can be used in said treatment method.

Conclusion:

5. 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, Manjunath N. Rao can be reached on (571) 272-0939. 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
06 July 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647