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

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
HAMUD, FOZIA M	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
01/26/2009	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 *16 October 2008*.

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4a) Of the above claim(s) _____ is/are withdrawn from consideration.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 *04/09/08* 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 *04/09/08, 04/29/08, 10/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Sequence compliance form, PTO-90C.

DETAILED ACTION

1a. The preliminary amendment filed on 09 April 2008 has been entered.

Status of Claims

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

Specification:

The disclosure is objected to because of the following informalities:

2a. 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.

2b. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, on page 56. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Sequence Compliance

2b. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, 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). Specifically, the sequences disclosed in page 50-51 and sequence in figure 2A and 2B are not accompanied by the required reference to the relevant sequence identifiers. See attached sequence compliance form.

Information Disclosure Statement:

3. The information disclosure statements submitted on 09 April 2008, 29 April 2008 and 16 October 2008 have been received and comply with the provisions of 37 CFR §1.97 and §1.98. All of the cited reference have considered as to the merits. Some of the references were in parent U.S. Application 09/950,041 or 10/975,909.

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 this application is supported by the disclosure in application serial no. 09/950,041 filed on 10 September 2001, because it establishes a link between TLR4 (SEQ ID NO:8) and septic shock, (see Example XVII on page 78). Accordingly, the subject matter defined in claims 4 and 23-24 is afforded an effective filing date of 10 September 2001, which is the filing date of the U.S. application No. 09/950,041.

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 09/10/01, 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 09/10/01.

Claim rejections-35 USC § 112: First Paragraph

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.

5. Claims 4 and 23-24 are 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.

Claim 4 encompasses 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 or an antigen fragment thereof, while claims 23-24, add further limitation that said antibody is administered intravenously or subcutaneously.

However, the specification fails to disclose any such method. 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 stimulated 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 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. It is known in the art that LPS is involved in septic shock and that TLR4 functions as the primary receptor for endotoxins.

However, identifying TLR receptors that are involved in the recognition of important microbial products is the first step in formulating TLR pharmaceuticals to be used for the treatments of individuals who suffer from TLR mediated diseases, such as septic shock, (see Golenbock et al, Nature Immunology, April 2001. Vol.2, No.4, pages 286-288, page 286, column 2 and page 288, column 2). Golenbock et al also teach that for TLR4 to function efficiently as an LPS signal transducer, it requires MD-2 protein, (see page 287, bottom of column 1). Daubeuf et al, (The Journal of Immunology, 2007, Vol. 179, pages 6107-6114) teach a monoclonal antibody, (5E3) against TLR4/MD2 that binds to amino acids 292-371 of TLR4 complex that protects a mouse experimental model from septic shock, (see abstract, page 6110, column 2). Daubeuf et al state that to their knowledge, theirs is the first antagonistic antibody against TLR4/MD2 that is capable of exerting an LPS-TLR4 neutralizing effect in vivo in acute gram-negative infections, (see page 6112, bottom of column 2). Thus, although it was known that TLR4 plays a role in gram-negative septic shock at the time the instant invention was made and although the instant contemplates an antibody that binds the polypeptide of SEQ ID NO:8 or that bind antigenic fragments thereof, to be used to treat septic shock, the instant specification did not provide an enabling disclosure of said antibody to be used to treat septic shock. There is no disclosure of the administration of antagonistic or agonistic antibodies against the polypeptide of SEQ ID NO:8 to a septic shock patient, and no disclosure of a regimen or dosage or duration for treatment.

With respect to the recitation of "an antigenic fragment thereof" in claim 4, there is insufficient guidance and direction as to make and use antibodies that bind an

antigenic fragment of SEQ ID NO:8 to be administered to a septic shock patient. The instant claims encompass administration of a genus of antibodies that bind an antigenic fragment of SEQ ID NO:8, regardless of how small said antigenic fragments are. The specification does not teach antigenic fragments of SEQ ID NO: 8. Thus, the encompassed antibodies could bind polypeptides that have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes. However, the present specification fails to provide sufficient disclosure of such infinite number of antibodies that bind to bind any antigenic fragment of SEQ ID NO:8 that maintain the desired structural and functional properties. For example, Lederman et al. (Mol Immunol 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al. (Proc Natl Acad Sci USA 77: 3211-3214, 1980) also disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Because of this lack of guidance, the extended experimentation that would be required to determine antigenic fragments of SEQ ID NO: 8 and then which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require an undue amount of experimentation for one of skill in the art to arrive at the antibodies that bind an antigenic fragment of SEQ ID NO:8 as encompassed by the claimed invention.

The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant case, it is unpredictable that an antibody to the polypeptide of SEQ ID NO: 8 would be effective in treating sepsis or septic shock, because of the complexity of the bacterial-host interaction. The therapeutic role of TLR4 in sepsis was in its early stages of research at the time the instant invention was made, and there were a lot of challenges and problems to be elucidated. The mere prophetic assertions disclosed in the current specification that anti-TLR4 antibody could be used to treat sepsis or septic shock does not satisfy the enablement requirement under 35 USC § 112, first paragraph.

Conclusion:

6 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, 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
08 January 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647