REMARKS

Amendments to the Specification

The title of the specification has been amended to more clearly and distinctly point out the subject matter of the application.

Further, the specification has been amended to identify by SEQ ID NO the sequences in the description of Figures 2A and 2B (p. 4, line 21 to p. 5, line 10) and in Table 1 (pp. 50-51).

Finally, the specification has been amended to insert the Substitute Sequence Listing (pages 1-193) after the Abstract.

These amendments do not add new matter. Their entry is respectfully requested.

Amendments to the Claims

Claim 4 has been amended to delete the reference to an antigenic fragment of an isolated or recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 8.

No new matter is added by this amendment. Its entry is respectfully requested. Upon entry of this amendment, claims 4, 23 and 24 will be pending in this application.

Objections to the Specification

The Examiner objects to the title of the application, contending that the title is "not descriptive." Without conceding the correctness of this objection, applicants have amended the title of the application to recite "HUMAN DNAX TOLL-LIKE RECEPTOR 4 PROTEINS, RELATED REAGENTS AND METHODS," thereby obviating this objection.

Further, the Examiner objects to the specification for containing "an embedded hyperlink and/or other form of browser-executable code, on page 56." Applicants direct the Examiner's attention to MPEP § 608.01VII, which states:

> Where the hyperlinks and/or other forms of browser-executable codes themselves rather than the contents of the site to which the hyperlinks are directed are part of applicant's invention and it is necessary to have them included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, examiners should not object to these hyperlinks.

In the subject case, hyperlinks are referenced to identify a consensus program used by the inventors to discern conserved sequence alignment pattern (p. 56, lines 5-7) and to describe a library of protein fingerprints used by the inventors to identify particular patterns (p. 56, lines 7-11). These links are part of applicants' enablement disclosure and are not intended to act as active hyperlinks. Applicants respectfully request reconsideration and withdrawal of this objection.

Sequence Compliance

The Examiner objects to the sequences disclosed in Table 1 (pp. 50-51) and in Figures 2A and 2B of the specification. According to the Examiner, these sequences are not identified by SEQ ID NO. Applicants have amended the specification to identify by SEQ ID NO the sequences in Table 1 and in Figures 2A and 2B. Further, applicants submit herewith paper and computer readable form (CRF) copies of a Substitute Sequence Listing comprising the sequences in Table 1 and in Figures 2A and 2B. Finally, applicants have amended the application to insert the Substitute Sequence Listing (pages 1-193) at the end of the specification, after the Abstract. Applicants' amendments obviate this objection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 4, 23 and 24 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement. The Examiner acknowledges that TLR4 was known to play a role in gram-negative septic shock at the time the subject application was filed. However, the Examiner contends that the specification does not enable one skilled in the art to practice the claimed invention. According to the Examiner:

> 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. (Office Action, p. 7.)

The Examiner concludes that claim 4, and claims 23 and 24 dependent therefrom, are not enabled by the specification. Applicants traverse.

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. It was also recognized in the art that the binding of LPS to TLR4 was a key step in this process. The Examiner asserts, "for TLR4 to function efficiently as an LPS signal transducer, it requires MD-2 protein" (Office Action, p. 5). Applicants point out that the subject invention refers to inhibition of the LPS signal-transducing function of TLR4. 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). Indeed, Exhibit A (Qureshi et al., *J. Exp. Med.* **189(4)**:615-625 (1999); enclosed herewith), demonstrates that mice with altered TLR4 function are hyporesponsive to LPS challenge and *exhibit natural tolerance to the lethal effects of LPS.* See, e.g., Abstract. 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.

The Examiner further cites Dabeuf et al. (*J. Immunol.* 179:6107-6114 (2007) as stating 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" (Office Action, p. 5). Even if this is the case, the antibody exemplified by Dabeuf et al. should have no bearing on the patentability of the subject claims. Pursuant to MPEP § 2164.02, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." 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 (e.g., cytokine expression; see, e.g., p. 51, lines 26-29). With the subject application in hand, 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.

Claim 4 stands further rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement for the recited "antigenic fragment thereof." According to the

Examiner, "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." Office Action, pp. 5-6.

Without conceding the correctness of this rejection, but merely to expedite prosecution, applicants have amended claim 4 to delete the phrase "or an antigenic fragment thereof," thereby obviating this rejection.

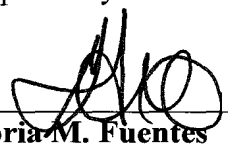
For all of the above reasons, claims 4, 23 and 24 are enabled. Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

Applicants believe that no fees are necessary for the filing of this response. However, should any fee become necessary to render this response timely filed, the Commissioner is authorized to draw the required amount from Applicants' Deposit Account No. 19-0365.

If the undersigned can be of assistance in advancing the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,



Gloria M. Fuentes
Attorney for Applicants
Reg. No. 47,580

Schering-Plough Corporation
2000 Galloping Hill Road
Patent Department, K-6-1,1990
Kenilworth, NJ 07033
Tel: (908) 298-2266
Fax: (908) 298-5388