REMARKS

Sequence Compliance

A CRF copy of the sequence listing submitted with the amendment of April 22, 2009 is submitted concurrently herewith. Please contact the Undersigned if further action is required to overcome the outstanding 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: 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; and antibodies against the polypeptide of SEQ ID NO:8 could be raised and tested against TLR4 activities. However, the Examiner argues that the etiology of sepsis or septic shock is very complex and that, therefore, in order to meet the enablement requirement more information was required. To support his rejection, the Examiner points to Brunn et al., *TRENDS in Molecular Medicine* 12(1):10-17 (2006), a paper published many years after the Applicant's original filing date, that allegedly states that: "agents that block LPS do not lessen the manifestations or improve the outcome of sepsis" and "TLR4 appears to protect rather than cause shock in sepsis and that TLR4 paradoxically protects humans from Gram-negative infection". The Examiner concludes that "[s]ince 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."

Applicants respectfully traverse. As an initial matter, Applicants submit that the Examiner cannot rely on this post-filing publication to show non-enablement. MPEP 2164.05(a) states that "[t]he state of the art ***existing at the filing date*** of the application is used to determine whether a particular disclosure is enabling as of the filing date". (emphasis added) This section further states that ***Examiners should not use post-filing date references to demonstrate non-enablement***, with only once exception: "if a later-dated reference provides evidence of what one skilled in the art would ***have known on or before the effective filing date*** of the patent application." *Id.* (citing *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977))." Applicants respectfully submit that the cited reference cannot be used since it does not fall within

the cited exception – it does not provide evidence of what one skilled in the art would have known on as of the filing date of the patent application.

Further, Applicants note that the cited reference does not establish that anti-TLR4 antibodies cannot be used to treat sepsis or septic shock. In fact, the reference concludes that "focusing on endogenous ***agonists*** **(*or inhibitors*) of TLR4, *rather than on LPS***, might enable more widely useful therapies to be devised ..." (emphasis added). The cited reference merely provides an alternative hypothesis to explain the development of sepsis. This alternative hypothesis has not been generally accepted since multiple researchers continue to pursue the development of LPS and TLR4 antagonist for the treatment of sepsis. *See, e.g.,*

- Roger et al., "Protection from lethal gram-negative bacterial by targeting Toll- like receptor 4", PNAS 106(7):234852 (2009) (Exhibit A)
- Takashima et al., "Analysis of binding site for the novel small-molecule TLR4 signal transduction inhibitor TASK-242 and its therapeutic effect on mouse sepsis model", *British Journal of Pharmacology* 157:1250-1262 (2009) (Exhibit B)
- O'Neill et al., "Therapeutic Targeting of Toll-Like Receptors for Infectious and Inflammatory Diseases and Cancer", *Pharmacological Reviews* 61(2):177-197, at pages 183-184 (2009) (Exhibit C, particularly pages 183-184)
- Leon et al., "Discovery and Development of Toll-Like Receptor 4 (TLR4) Antagonist: A New Paradigm for Treating Sepsis and Other Diseases", *Pharmaceutical Research* 25(8):1452-1761 (2008) (Exhibit D, particularly Table III)
- Debeuf et al., "TLR4/MD-2 monoclonal antibody therapy affords protection in experimental models of septic shock", *J. Immunol.* 179(9):6107-14 (2007) (cited by the Examiner in the Office Action mailed January 29, 2009)

Thus, Applicants respectfully request reconsideration and withdrawal of this rejection. Applicants respectfully submit that the pending claims were enabled as of the filing date of the instant application

CONCLUSION

Applicants believe that no fees, other than the RCE fee, 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,

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