Reviewer’s report

Title: Identification of tuberculosis-associated proteins in whole blood supernatant

Version: 1 Date: 7 December 2010

Reviewer: Robert Wallis

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This manuscript describes a study of differentially expressed proteins in stimulated and unstimulated whole blood cultures of TB patients and matched healthy controls. The authors used the QFN system to do the cultures. Proteins were separated by 2D gel electrophoresis, measured by phospholuminescense, and identified by MS. 2 proteins were identified as low in unstimulated cultures of TB patients compared to controls. These were confirmed by ELISA. 1 protein was high (I believe) in TB-stimulated cultures of TB patients. None of these proteins have previously been studied in the context of TB. For this reason the study is potentially of interest.

My main concern is that as presently written the paper will be confusing to many BMC ID readers. This includes, for example, MASCOT scores, and the numbering system of the imaging system. It was difficult for me to tell under which pair of conditions each of the proteins were identified. The text does not adequately refer to and discuss the tables and figures.

A second important issue arises due to lack of understanding of the QFN IGRA. The test is not a diagnostic test for tuberculosis, nor is it intended to serve as an in vitro model of Mtb infection. It consists of 3 protein antigens with limited distribution in nature aside from Mtb, and measures mainly a CD4 T cell recall response. It does not distinguish active from latent Mtb infection. The signals generated during interactions of Mtb with cells of the host immune system are much broader than those represented in the QFN assay. These are generated by other cells (monocytes, CD8 cells, etc.) by other mycobacterial constituents (glycolipids, lipoproteins, etc.). For this reason, I am less certain of the significance of the clusterin finding. If my understanding is correct that this was identified in stimulated cultures, it might be best to confirm this observation in another system and report it separately. This would also resolve another related issue, as to why the stimulated cultures did not identify other proteins known to be induced in short term antigen-stimulated mononuclear or whole blood cultures, such as IP-10, for which levels can be quite high.

Lastly, the introduction could be shortened substantially. Much of the discussion of IFNg is not really relevant.

Level of interest: An article of importance in its field
**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no competing interests.