Reviewer’s report

**Title:** IP-10 response to RD1 antigens can be a useful biomarker for monitoring tuberculosis therapy

**Version:** 1  **Date:** 10 December 2010

**Reviewer:** Morten Ruhwald

**Reviewer’s report:**

The paper by Kabeer et al explores the use of IP-10 and selected RD-1 peptides as a tool to monitor treatment effect in patients with active TB. The results are compared to standard QFT test which also is analysed for IP-10. The paper builds on another paper published by the same group as it (seems to) apply cut offs determined on another material. IP-10 and QFT responses to selected RD-1 peptides decline with effective treatment; there is no apparent difference between the two markers. Previous studies have suggested that nil IP-10 measurements contain the same treatment efficacy information as the responses to RD-1 selected peptides – these data are available and should be included in the paper.

The paper reads well, but the numbers are small. There are some methodological issues that need major revision (especially the statistics) before the data can be appreciated in full.

**Major compulsory revisions**

There is little information on the treatment effect, we only know they are AFB smear negative (29.6% were AFB neg at start of Tx). Were all patients healthy after treatment, were there any drug resistance? I wonder if the increase in IP-10/IFN-g seen in some of the patients is explained by insufficient treatment? If possible please describe the patients who have an increase in IP-10/IFN-g in more detail.

P10-13, fig 1 and fig 2 and elsewhere. IP-10 and IFN-g responses are not normal distributed; it does not make sense to use a parametric test. The p-values cannot be interpreted.

Azurri et al have described a decline in plasma levels of IP-10 with successful treatment and previous observations in patients with active TB have demonstrated that TB patients have high levels of nil IP-10 - controls do not. Assuming that successful treatment reverts a patient to a control, there will be a decline in nil IP-10. Would it be possible to use changes in the Nil IP-10 response (e.g. 1 or 2 fold reduction or a cut off set on your previous cases and controls) instead of a change in the response in selected peptides. Although important information arise from the findings in this paper, it would be much easier just to follow patients with a “nil” sample compared to a “selected peptides IGRA”. Please present the nil values from both QFT and selected RD-1 assays e.g. in a figure or table and discuss the potential of this simpler approach.
Does “the same Indian population” mean that the patients are the same? If not suggest to use “same Indian setting” or similar.

What is the effect of DMSO? You set up parallel cultures of QFT nil and selected peptides nil, did you find a difference?

You see no apparent difference in the diagnostic ability of IP-10 and IFN-g, please discuss if there is any real impact of IP-10 compared to IFN-g other than a >20 fold difference in magnitude of response?

Minor Essential Revisions
The term “overtime” is the amount of time someone works beyond normal working hours, suggest to rephrase.

TB7.7 is encoded in RD-11 not RD-1

Do IFN-# responses to antigens change with Tx? On P4l20 it is conflicting, in the abstract l7 it appears that there is no doubt. Please be consistent.

P8l4 Duo Set?

P14 Last paragraph this is a limitation and should be moved to this section

Discretionary Revision

P5l9 what is ment by in-house, should in-house not relate to the selected RD-1 peptides used in the stimulation step and not the ELISA (which was done according to manufactures’ instructions?)

P7l1 the word “measure” is confusing. Suggest rephrasing, as you are describing the generation of antigen-specific signals.

P7l7 what is ment by “assayed”

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I am registered as inventor on pending and issued patents relating to IP-10 as a diagnostic biomarker for infection with M.t.b. I have received travel grants by Cellestis in 2008 and 2007.