Reviewer's report

Title: Network analysis identifies a putative role for the PPAR and type 1 interferon pathways in glucocorticoid actions in asthmatics

Version: 1 Date: 26 March 2012

Reviewer: Charles Auffray

Reviewer's report:

The paper by Diez et al. reports the results of integrated statistical, interactome and promoter analyses of a gene expression dataset in asthmatic patients treated with glucocorticoids or a placebo. It is based on state-of-the-art methods associated with comprehensive documentation in Figures and supplementary material, as well as relevant references.

The main finding reported is the identification of a putative relation between the PPAR and type-1 interferon pathways supporting the anti-inflammatory action of the glucocorticoid Flovent, in line with previous reports in the literature.

Major compulsory revisions

1) The authors have not designed and performed any new experiments to support or challenge the working hypothesis generated.

2) The paper lacks substantial novelty, as 'a link between glucocorticoids and the interferon pathways has been previously reported' (refs 5, 38-40, cited on page 15), and 'shifts in PPAR/TLR pathways that correlate with GC responsiveness' have been 'previously described for the current dataset' by the authors themselves (refs 45-46, page 16).

3) The fact that the reported analyses are a follow up of the initial study performed by the authors and published in 2007 (ref 19) is not mentioned explicitly in the abstract, background or results sections, cited in passing on page 11 at the beginning of the discussion, and introduced explicitly at the beginning of Material and Methods on page 17.

4) The analysis workflow of Figure 1 is not in line with the Results section, which makes it difficult to follow the authors arguments. The order and labels should be the same: (I) Statistical analysis; (II) Co-expression network; (III) Interactome.

Minor essential revisions

5) The authors have chosen to focus attention on common pathways, leaving out a number of potentially interesting genes, pathways and biological functions, e.g. the proteasome highlighted in Figure 2 as detected in RAW, FDR and BIONET; module M5 which contains 'the greatest number of DEGs' (page 8) is insufficiently highlighted (see next point); the 94/114 genes in the FDR list not regulated by interferons (page 11) could be investigated for other types of
regulatory elements.

6) Figures S7+S8 are more informative and easy to read than Figure 2; same for Figures S4+S5 compared to Figure 3 or Figure 4.

7) The authors attribute 'the reduced statistical power' to 'the use of multiple testing correction methods' without referring to sample size effects, nor discussing the problem of false negatives (page 11).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests