Reviewer's report

Title: Targeting of human interleukin-12B by small hairpin RNAs in xenografted psoriatic skin

Version: 1 Date: 14 May 2010

Reviewer: Frank Nestle

Reviewer's report:

General Comments.

1. Although the generation of shRNA lentiviral constructs, and the stable expression of IL-12B, should be applauded and the efforts made in developing this technology acknowledged. However, the study fails to achieve its goal in targeting IL-12B for the treatment of psoriasis. In other words, the manuscript presents mostly negative data.

2. The authors should discuss the suitability of using lentiviral constructs for the treatment of humans.

3. The authors present ‘clinical psoriasis scores’ as a measure of shRNA efficacy. Two problems: i) this type of scoring systems is subjective, ii) the psoriatic skin transplantation score decreased even in the negative control group (why did the psoriasis not progress)?

4. Why is there no histology presented. KC proliferation/acanthosis and lymphocyte expansion are key characteristics of this type of animal model.

5. In order to evaluate the efficacy of an anti-IL-12B treatment, the expression of IL-12 and of IL-23 should have first been evaluated at the mRNA and protein level within the chosen xenotransplant model. It may be that the authors are trying to target a molecule that has no consequence in the disease phenotype.

6. The combining of two control groups into one group (figure 4) is difficult to justify. No justification for this was clearly made (only clinical scores) and therefore no justification can be made regarding similarities in other unknown biological readouts (these may very well differ between the groups).

7. It would be nice to have the lentiviral vector targeting TNFalpha in the same experimental set as a comparator.

Minor comments:

1. The use of only two MOI units in the study does not constitute a proper dose response experiment. It is also unclear why approximate values were used throughout.

2. During the initial whole mouse luc experiments (figure 3) it is unclear whether
normal or psoriatic skin was used. There is no mention in the text of figure 3a being separate from figure 3b)

3. Figure 4b. The authors suggest a ‘tendency’. This phraseology is too ambiguous and data should be interpreted on face value.

4. Epidermal thickness based on histology. This may very well depend on the angle of sectioning and not reflect the actually skin thickness at all. What about calliper measurements?

5. Figure 4b. Betnovat appears to reduce clinical score at day 14. Is this significant?

6. There is no mention of figure 5 in the results section.

7. Have the authors attempted to analyse shRNA KD of IL-12 or IL-23 in primary KCs or DCs?

8. As a result of the points made above, the discussion section over-interprets the results.

9. What effect do the shRNAs have on endogenous levels of IL-12 and IL-23?

10. No legends on any of the multi-barred graphs. No error bars on figure 2b.

11. What time point was used for figure 4d (3 weeks?). Could the authors measure IL-12 over a time course?

**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.