Reviewer's report

Title: Genetic and biochemical markers of hydroxyurea therapeutic response in sickle cell anemia

Version: 2 Date: 1 June 2012

Reviewer: Philippe JOLY

Reviewer's report:

Introduction:
In this article, the authors have tried to correlate the bêta-globin gene cluster haplotype of SCA patients with their steady-state oxydative stress (OS) and their amplitude of response to HU.

The results led the authors to hypothesize that the Bantu haplotype is associated with a better response to HU because of an important steady-state OS.

Major Compulsory Revisions
The initial idea to correlate the beta-globine haplotype and the level of OS in SCA is interesting as it has well been proved that SCA patients present a very important OS compare to normal patients. I take the occasion to recommand the authors to read an excellent review on biochemical markers of SCD that has recently been published (British Journal of Haematology 2011, 156, 433–445).

My major concern is about the statistics. I think that the size of the SCD cohort and of the groups of patients are too weak to drive any conclusion. I am not an expert in statistics but I would say that, even for non-parametric tests such as U-test or ANOVA, conclusions can hardly been made with groups of less than 10 patients as it is the case in this study ? So, I think that this point should absolutely be checked by a competent biostatistician.

As a consequence, I can hardly believe to the conclusion of the authors even if they propose an apparently logical 'pathophysiological' explanation. Indeed, in a very recent work relative to the pharmacogenetics of HU (Blood 2011, 118(8): 4985-91), Ware et al have shown that the best predictor of HU efficacy was the base-line HbF level and not the steady-state level of OS. But I admit that this point has surely not been tested by Ware et al.

To drive any conclusion with such a protocol, I think that the authors need groups of at least 30 patients homozygous for the considered haplotype (ex: Bantu / Bantu ; Benin / Benin ; Senegal / Senegal). Moreover, do all patients receiving HU have reached the maximal tolerated dose (MTD) ? It was not precised in the text and it would be necessary for standardization.

Minor Essential Revisions
- The texte should be reviewed by a native english speaker to avoid some
mistakes (ex: severest... in place of the most severe ; efficacious in place of efficiency, etc...)  
- The terms TBARS and TEAC shuld be explained when they are employed for the first time  
- Table VI: what mean the "a" and the "b" in asterix ?  

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

**Quality of written English:** Needs some language corrections before being published  

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.  

**Declaration of competing interests:**  
'I declare that I have no competing interests'