Reviewer’s report

Title: LY294002 may overcome 5-FU resistance via down-regulation of activated p-Akt in EBV-positive gastric cancer cells

Version: 1 Date: 7 May 2010

Reviewer: Emmanuel Drouet

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This manuscript presents results from in vitro experiments designed to determine the effect of drugs, separately and in association with each other on gastric cancer (GC) cell lines (EBV-negative and EBV-positive). These drugs are the (i) 5-Fluorouracil (5-FU), a commonly used drug, and (ii) a new one, called LY294002, targeting the phosphatidylinositol 3-kinase. This enzyme plays a critical role in cancer cells, because it provides a survival signal and chemoresistance to cytotoxic anti-cancer drugs. The authors pointed out this enzyme because it is able to be activated by the latent membrane protein LMP-2A in EBV associated GC. The experiments are pretty well conducted and the document is well structured. The text is roughly correct but further editing would significantly strengthen the paper. As a general comment, the writing of the manuscript could be acceptable for publication at this time, but there are a number of instances where data are unclear:

- In the whole manuscript (abstract, full text, legends and figures), the acronym “Akt” is not homogeneously written (“Akt” versus “AKT”)
- In the introduction, a reference must be put at the end of the sentence: “EBV+ gastric carcinomas tend to express much higher amounts of p53 than do EBV-negative carcinomas”
- The authors didn’t mention the origin (manufacturer) of the compounds used (5-FU and LY29002).
- Figure 1 should be split in fig 1A and 1B
- In the results and especially in figure 3B, the doses of 5-FU and LY294002 are not mentioned. They have got to be.
- “Scrambled siRNA” (also called “Scramble II duplex”) is mentioned in M&M. However in the results (§5 and fig 6A), the authors wrote “scramble LMP2A siRNA”, which doesn’t sounds correct.
- Regarding the knockdown of LMP2A expression (§5 results), a control must be performed: i.e., is LMP2A is truly expressed in SNU-719 before the knockdown? What is its expression after knockdown?

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.