Reviewer's report

Title: Cidofovir selectivity is based on the different response of normal and cancer cells to DNA damage

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Reviewer: Hiroyuki Sakai

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Tim De Schutter et al. described the effect of cidofovir (CDV) on the gene expression profiles of HPV-positive and –negative cells. CDV is applied for the treatment of recurrent respiratory papillomatosis (RRP). It is also expected to be applicable for the HPV-positive cancers. Therefore, the detailed analysis of CDV effect is important for the development of anti-viral and –tumor reagents.

Major Compulsory Revisions:
1. Authors employed HaCaT cells as the HPV-negative tumor cells. HaCaT is originally isolated as a naturally immortalized normal keratinocyte. It had been maintained in low-Ca culture medium and possessed a potential for cell differentiation. In several papers, HaCaT was used as a “normal keratinocyte”. This reviewer considers the description of HaCaT as tumor cell makes the readers confused. C33A or several SSC cell lines should be replaced HaCaT as the “HPV-negative tumor cell”. It could make it clear whether the effect of CDV is HPV-positive tumor cell specific or not. (When SCC cell lines, such as SCC4, SCC13, SCC14, are used, it is necessary to carefully check the HPV DNA existence in those cell lines. This reviewer is not confident whether the HPV DNA status has been definitely analyzed in those cell lines.)

2. CDV functions as DNA-damaging reagent for the cells. It is necessary to analyze other DNA-damaging reagents that are used for anti-tumor treatment, which clarifies the specificity of CDV effect on the HPV-positive cells.

3. The results of CDV effects on cell growth, cell division cycle (G1, S, G2/M), apoptosis induction should be incorporated.

Minor Essential Revisions:
4. Authors mentioned the CDV treatment did not alter the E6 and E7 expression level (p16, line 455). It is essential to present the data as the result (in Figure 2).

5. The data shown in the additional files are difficult for comprehension. Please summarize them more concisely.

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.