Author’s response to reviews

Title: Heparin (GAG-hed) inhibits LCR activity of Human Papillomavirus type 18 by decreasing AP1 binding

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Author's response to reviews: see over
August 24th, 2006

Iratxe Puebla
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Dear Prof. Puebla,

Please find enclosed the revised version of the manuscript entitled “Heparin (GAG-hed) inhibits LCR activity of Human Papillomavirus type 18 by decreasing AP1 binding”.

In the new revised version, we have taken into consideration the valuable comments of the reviewer and have made the pertinent experiments and modifications to the original manuscript. Our answer to the referee is listed below:

**Reviewer 1: eun hwang**

**Major points**

The authors probably did not understand what I and the third reviewer asked to be more specific to their description of the effect of GAG-hed on cell viability. What I pointed was that, for a possible cancer therapeutic, understanding the nature of its effect on cancer cells is a critical factor. Whether the cancer cells die of apoptosis or they just stop proliferation would be an important information that determines the treatment strategy. Therefore, I asked the authors if the chemical induces apoptotic death of HeLa cells or it just causes growth arrest. However, the authors kept using the term 'cell viability'. What do they mean by this? By definition, cell viability should mean cell survival. Do they know that the reason why the MTT value did not increase? Was it due to the death of certain portion of cells or due to arrest in cell proliferation? I hope the authors understand how these two cases are different and how important it is to distinguish these two outcomes.

**Answer:**

We tried our very best to address the reviewer point and as the reviewer asked, besides to determine the cell viability and proliferation rates under GAG-hed treatment, we also found that this heparinoid did not induce apoptosis (Figure 5, new version). Under our experimental conditions, we observed that cell cycle may be arrested most
likely in G2M phase (Figure 5). Concordantly, we found a diminution in the percentage of cells in G1 and S phases. Mechanisms for this arrest are a good pathway for further exploration, which constitutes now part of our current work and future goals.

In the matter of further language revisions, I tried to contact with University of Aberdeen, but page link directed us to a wrong address. Even contacting directly with the University directory service, we got no answer. However, to take care of English editing, we hired the service from American Journal Experts (https://www.journalexperts.com/). We incorporated all manuscript corrections pointed out for them.

We hopefully wish that all the performed changes in the manuscript account adequately referee suggestions and our work can be now suitable for publication in BMC Cancer.

Sincerely,

Professor Esther López-Bayghen, PhD