Reviewers report

Title: Small lytic peptides escape the inhibitory effect of heparan sulfate on the surface of cancer cells

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Reviewer: David Bedell B. Alexander

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This paper addresses the issue of cancer therapy. The major focus of the paper is a description of the properties of three small lytic peptides and their interaction with heparan sulfate and chondroitin sulfate. Several points need to be addressed before the paper is acceptable for publication.

Major revisions

1. The authors show that the three lytic peptides are more active against three cancer cell lines than they are against HUVEC cells. However, the cytotoxic effects of these peptides can vary significantly depending on the cell line tested. Therefore, at least two additional normal-like human cell lines need to be tested before the authors can assume that the lytic peptides display selective anticancer activity.

2. An experiment which delineates the cytotoxic effect of these peptides against cancer cells at concentrations at which normal-like cells are mostly unaffected needs to be performed.

3. The authors need to demonstrate the significance of this paper. One of the 9mers described in this paper, LTX-302, has already been reported to have antitumor effects in vivo. Why are the findings reported here significant? Without convincing evidence that the 9mers described in this paper display selective anticancer activity (comments 1 and 2), it would appear that the only new finding concerns interaction with HS and CS. Does this make these peptides a better therapy in some situations than previously reported CAPs? If so, this needs to be demonstrated. How does the activity of these peptides compare with other CAPs, such as lactoferricin and the 15mer reported on by Shai’s group? Do these 9mers have improved activity or specificity? Again, if this is the case, it needs to be demonstrated.

Minor revisions

1. The authors need to recheck their results. Several of the activities appear to be exaggerated. For example, the authors state that LTX-302 and LTX-3318 display a 5-fold to 6-fold higher activity against the neuroblastoma cell line compared to HUVEC cells. However, the results in Table 2 indicate that the ratio of IC-50 values are 123/28 (4.4) and 383/78 (4.9).
2. The tables are not numbered correctly in the text.

3. Figure 2 is not needed.

4. There a number of typographical errors in the text. A few examples are (1) "The influence of HS and CS in their cytotoxic activity...." should be "The influence of HS and CS on their cytotoxic activity...."; (2) "the present study show that...." should be "the present study shows that...."; (3) chondriotin is spelled chondroitin in the vast majority of cases.

**Level of interest:** An article of limited interest

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

**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.