Reviewer's report

Title: The anticancer activity of lytic peptides is inhibited by heparan sulfate on the surface of the tumor cells

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Reviewer: David A Phoenix

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Minor Essential Revisions

The paper is of interest and takes an approach I have not seen before. The data adds to the literature and is of interest to a wide readership. It should be published. Overall I support the authors views but the paper could benefit from some minor changes to show the balanced consideration of the options early on in the work. For example:

a) They compare FEMX and HT29 and based on higher toxicity levels for FEMX the cell line with higher HS levels assume this is the key factor effecting activity. They are in fact using two cell lines hence there will be a number of variables generating different membrane compositions (eg lipid variations). There is no analysis of the overall membrane composition making it impossible to say for sure if HS is the key factor from this data. Indeed much work has been done showing the effect of a range of other membrane based factors which may also have altered between the two cell lines

b) They then used chlorate to reduce the GAGS and see an increase in toxicity (ie opposite result predicated by their hypothesis at the start). This could mean the hypothesis is wrong or that the GAGS do increase peptide targeting by increased binding but that if the binding is too great they inhibit cell death by sequestering the peptides away from the phospholipids as reported for other molecules. Indeed this is the conclusion they come to at the end. They seem though to report this inconsistency in the middle of the paper but then move past it with no discussion or linkage.

c) The expt where activity against CHO cells and the null mutant are in my mind central to the paper as here they are looking at variation of GAGS in a more controlled manner and in a system that has been widely reported. This confirms the result from (b) implying that GAGs may well bind lytic peptides but inhibit activity. They then go on to support this hypothesis with other work

Overall therefore it would increase the impact in my view if the introduction indicated that the authors felt GAGs could either

a) have no effect on toxicity,

b) increase binding of peptides but due to sequestration inhibit activity as seen in terms of GAG impact for some other bio-systems or

c) increase binding and therefore in line with work on other anionic membrane
components increase access to the membrane and therefore activity.
The paper can then go on to look at these three options.
Finally in the introduction and elsewhere the authors need to note that not all peptides reported as anticancer show high levels of anticancer selectivity. Indeed in many cases they simply turn out to be lytic and non-specific. There are though specific examples as reported by the authors.
Overall though a nice piece of work

**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' below