Reviewer's report

Title: Novel treatment option for MUC16-positive malignancies with the targeted TRAIL-based fusion protein Meso-TR3

Version: 2
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Reviewer: Chris Scarlett

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Major Compulsory Revisions

The authors describe a very interesting study whereby they have generated a novel TRAIL-based drug platform (TR3), to target MUC16 expressing cancers. It is an interesting approach exploiting a mechanism known to drive tumor invasion and metasatasis in MUC16 positive cells to use as a modality for the delivery of a novel therapeutic agent. TR3 has been engineered to fuse with mesothelin to assist in the delivery to MUC16 positive cells via the known high affinity that mesothelin has with MUC16. They authors demonstrate impressive binding of meso-TR3 to MUC16 positive cells, accumulation of meso-TR3 on the MUC16 positive cells, as well as increased cell death in vitro and in vivo of MUC16 expressing ovarian cancer cells.

MUC16 overexpression is a hallmark of numerous cancer types, especially for the aggressive cancers of the ovary and pancreas. Investigations into new therapeutic strategies are very important to combat these diseases, which have very few effective therapies.

They manuscript is very well written, however I have a few queries that will need to be addressed prior to publication in BMC cancer:

1. The title describes a novel treatment option for MUC-16 positive malignancies, yet you only show data for the ovarian cancer cell line OVCAR-3. Do you have any data on other cancer types that overexpress MUC16 (such as pancreatic cancer cells) to strengthen your argument? Particularly as pancreatic cancer is eluded to throughout the manuscript?

2. Mesothelin is known to interact with MUC16 to drive invasion and metastasis. How efficient (%) is meso-TR3 in delivering TR3 to the TR3 cells? By this I mean is there any chance that meso-TR3 can be dissociated resulting in only mesothelin alone being introduced to MUC16 expressing cells and accelerating tumor progression?

3. How is the meso-TR3 administered to mice? IP? IV? Oral gavage?

4. Do the authors have further data that may outline the exact cellular death mechanisms initiated by meso-TR3?
Level of interest: An article of importance in its field

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.