Reviewer's report

Title: Adenoviral Delivery of Pan-Caspase Inhibitor p35 Enhances P450 Gene-directed Enzyme Prodrug Therapy using Cyclophosphamide

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Reviewer: Matthias Renner

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The manuscript by Doloff et al. presents proof-of-principle of adenoviral delivery of the pan-caspase inhibitor p35 to enhance P450 GDEPT using the prodrug CPA. This concept has been already evaluated and published by this group using cells transduced with p35-gene carrying retroviral vectors. Here, the authors show that p35 and Cyp450/reductase gene delivery using a replication-deficient adenoviral vector and expression of these genes is enhancing cell killing of non-infected bystander cells and that this effect is also evident when using a conditionally-replicating adenoviral vector system using a replicating helper vector to deliver the p35 and P450/reductase gene.

The experimental data are sound and the manuscript is well written, albeit a few issues have to be clarified.

Major points:

1. Abstract: The first sentence of the conclusion should be rephrased as this concept has not been proven to be functional with other anti-apoptotic factors and other prodrug-activation gene therapies in this manuscript and in literature.

2. Figure 1c: In contrast to the proposed mode of action that the p35-mediated delay in death of P450-expressing cells should allow generation of an increased amount of cytotoxic metabolites by these cells, similar amounts of 4-OH-CPA of Ad-2B6- and Ad2B6/p35-transduced cells have been detected. The authors should clarify.

3. Although effects of p35 on CPA-converting cells have been determined by measuring caspase activity, the manuscript would benefit from quantifying the actual protective effect on p35/P450/reductase expressing cells. For example, survival rates of Ad2B6/p35- and Ad-2B6-infected and CPA-treated cells could be determined.

4. Discussion: Balancing p35-mediated protection of cancer cells and gain in therapeutic efficacy by prolonged prodrug conversion in infected cells, however, might be critical for clinical application of this approach, in particular when adenoviral vector spread is envisaged. The authors should address this point in the discussion section.
Minor points:

1. p12 line 2: should be read ….."Adeno-2B6/p35-infected cells" instead of 
...."Adeno-2B6-infected cells".

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.