Reviewer's report

**Title:** Adeno-associated Virus-mediated Doxycycline-regulatable TRAIL Expression Suppresses Growth of Human Breast Carcinoma in Nude Mice

**Version:** 2  **Date:** 10 January 2012

**Reviewer:** Xiangbing Meng

**Reviewer's report:**

The manuscript by Zheng et al reports establishment of an inducible expression of soluble TRAIL based on Tet-On system in both normal and cancer cells. This study is novel and well designed and the authors demonstrate that transduction of human cancer cell lines with rAAV-TRE-TRAIL&rAAV-Tet-On under the presence of inducer doxycycline resulted a considerable cell death by apoptosis and intravenous injection of the recombinant virus efficiently suppressed the growth of human breast carcinoma in nude mice. However, there are several questions that need to be addressed.

1. In figure 5, the resistance of HepG2 to AAV-TRE-TRAIL&AAV-Tet-On might be a result of inefficient of rAAV transduction or intracellular distinguishable events with TRAIL and its receptors in the cells.

   Does efficiency of rAAV transduction in HepG2 is very low compared to other cell lines detected by rAAV-TRE-EGFP&AAV-Tet-On or AAV-CAG-EGFP infection?

   Are the expression of TRAIL receptors in HepG2 cells different from other cell lines sensitive to sTRAIL?

2. As shown in figure 8, cell death induction by sTRAIL is below 30%. Other treatments should be consider to combine with sTRAIL induced cell death. There are reports about the restoring TRAIL sensitivity by co-treatment with sTRAIL and HDAC inhibitors combination.

   Do HDAC inhibitors increase the cell death induction by inducible adenovirus mediated sTRAIL expression in your in vitro study if HDAC inhibitors are combined with sTRAIL expression?

**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.