Reviewer's report

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

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Reviewer: Donald J Buchsbaum

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This manuscript reports on the generation and testing of an adeno-associated virus (AAV) expressing TRAIL which was regulated by doxycycline. The AAV was shown to be cytotoxic to human cancer cells in vitro and to inhibit growth of human breast cancer xenografts following systemic injection. The fact that the virus was effective at inhibiting tumor growth after systemic injection and did not produce toxicity is a feature of this article. In addition, caspase activation was measured in treated tumors. A limitation of the approach is that two AAV vectors were used as a mixture. One contained TRAIL regulated by the tetracycline responsive element, and the second contained the Tet-On element activated by doxycycline. If the two AAV do not co-localize equally in tumors, then TRAIL mediated killing would not be optimized.

Minor Essential Revisions:

Page 2, para 3, line 3, resulted in; line 5, in nude mice when activated by doxycycline; page 4, para 1, line 5, delete have; para 2, line 1, because of; page 5, para 2, line 7, for cancer; page 6, para 2, line 1, most safe vector with less pathogenic effects and mediating; page 7, para 2, line 4, in complete; para 3, line 3, protocol and performed; para 4, last line, instructions; page 8, para 2, line 3, instructions; line 5, representative of the; page 10, para 1, line 2, first transduced; line 5, 70 fold; page 11, line 1, while there was no detectable; para 2, line 7, in presence of; line 9, in absence; line 12, correlated with the; para 3, line 4, occurred; page 12, para 2, line 2, establish a xenograft ... subcutaneous transplantation; line 5, were administered; line 7, for a total of; line 3 from bottom, system-controlled; page 13, line 1, hallmark; line 5, Dox in the water, ... controlled sTRAIL; page 14, para 1, line 2, because of its; line 5, a clinical point of view; para 2, line 1, we introduced the; line 8, of inefficiency; clarify the last line; para 3, line 2, conditions; page 15, para 2, line 2, with the Tet-On; line 4, Data in our; para 3, line 2, as an antibiotic; line 3, the clinical; line 7, recognizes; para 4, line 1, attempted; page 16, Conclusions, line 6, for cancer; page 21, Fig. 3 legend, line 1, controlled; Fig. 4 legend, line 1, controlled; line 2, subcutaneous; lines 5 and 7, administered; line 11, PCR; page 22, Fig. 5 legend, line 1, controlled; line 2, administered, line 3, lysed, label figures as Figure 1A, Figure 1B, Figure 1C, Figure 1D, Figure 2A, Figure 2B, Figure 3A, Figure 3B, Figure 4A, Figure 4B, Figure 5.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

The reviewer has a non-financial competing interest which involves intellectual property interests related to an agonistic DR5 antibody.