Reviewer's report

Title: Methylthioadenosine (MTA) inhibits melanoma cell proliferation and in vivo tumor growth.

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Reviewer: Barry Nelkin

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Andreu-Perez et al present data indicating that high concentrations of methylthioadenosine (MTA) can inhibit melanoma cell growth, both in vitro and in vivo. Similar findings have been reported for other cancer types. This interesting finding suggests that MTA potentially may be considered as a component of a treatment strategy for melanoma. One may speculate that this could be especially effective in melanomas that have lost MTAP; since they cannot degrade MTA, they may more readily accumulate toxic levels of MTA.

Major compulsory revisions.

1. On page 7, GI50 estimates are presented for 4 of the 6 cell lines examined in Figure 1. GI50s for the other two cell lines – the BRAF V600E mutant cell lines UACC903 and Colo 829 – must be presented.

2. The clonogenic assays in Fig. 2 are not interpretable in their present form. Quantitative data must be shown. This is especially important, since at least one of the cell lines (37-31E) is said to exhibit increased growth in low concentrations of MTA. Also, the BRAF V600E mutant cell lines do not appear to be much more sensitive than the other cell lines in the clonogenic assay. If this is so, then the authors must explain why there is a difference between the results in Fig. 1 and Fig. 2.

3. The authors show that treatment of mice with 96 nmol/kg MTA inhibits the growth of melanoma xenografts. However, much higher concentrations were required for any growth inhibition in tissue culture. The authors must explain the reason for this difference. Alternatively, they may show that such a similar concentration is effective for blocking growth of a second melanoma cell line xenograft.

Minor essential revisions

1. The authors should note, when they identify the cell lines, that the 37-31E cell line is murine, and the others are human.

2. There are several spelling and syntax errors.

3. The correct terminology for human genes should be used – capitalized italics.

Discretionary revisions

1. Since the authors present data suggesting that MTA may inhibit angiogenesis, they could strengthen their manuscript by a direct assay for microvessel density
in xenografts, e.g., immunohistochemical staining for PECAM.

2. The GI50 values for MTA might be best presented within the panels of Fig. 1, where they would be most convenient for the reader.

3. If the status of the MTAP gene is known in these cells, it would useful to present it.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**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.