Reviewer’s report

Title: Threonyl-tRNA Synthetase Overexpression Correlates with Angiogenesis and Progression of Human Ovarian Cancer

Version: 2  Date: 26 June 2014

Reviewer: John Hays

Reviewer’s report:

I think this is an interesting paper and the authors do a good job demonstrating evidence of a correlation between stage and TARS level as well as an interesting trend towards improved survival. I also think they have demonstrated a plausible mechanism for TARS secretion from ovarian cancer cells in response to hypoxia or stress. I believe the evidence for a link to the immunology of the tumor microenvironment and angiogenesis is not as strong but very interesting nonetheless.

Major Compulsory Revisions:
1. Please explain in more detail the method for detection of overexpressed TARS vs background levels. My concern is that if you are detecting a level of protein that is only slightly greater than background, are you really only measuring noise on top of a large peak?
2. On the IHC analysis, is the intensity a function of number of cells stained or intensity within a few cells? Why not use a validated method that takes into account both number of cells and intensity?
3. In figure 2, what is the rational for inclusion of 2C? I do not understand the staging being used in this legend, e.g. what is stage 3.75?
4. Also in figure 2, why group 1-2 and 3-4 in 3B? It would be more compelling to have all four stages individually listed with a correlation to TARS level.
5. One of the hypothesis is the correlation of TARS with angiogenesis, however I do not believe there is convincing evidence of this presented in the paper. Co-localization with VEGF may only be indicative of tumor staining and the images for co-localization with PECAM are not compelling. There may be a correlation between intensity of CD31 staining and TARS staining, but I would need to see this information and controlled for tumor grade and stage (both of which have previously been shown to correlate with angiogenesis)
6. Please change the heading on the section “Serum levels of TARS correlate with tumor TARS and markers of angiogenesis” as angiogenesis is not addressed in this section unless one assumes that TNFa is a direct link to angiogenesis

Discretionary Revisions:
Please discuss the weaknesses that are inherent in some of the experiments and
conclusions that you have drawn during the discussion section.

**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