Reviewer’s report

Title: Interaction of a traditional Chinese Medicine (PHY906) and CPT-11 on the inflammatory process in the tumor microenvironment

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Reviewer: Benjamin Rodriguez

Reviewer’s report:

The authors have investigated how a traditional Chinese medicine (PHY906) exerts antitumor effects during chemotherapy in an established clinical model through microarray expression profiling. This study is novel and may draw wide readership because PHY906 demonstrates anti-inflammatory effects when administered alone in vivo. The author’s principle finding is that co-administration of PHY906 with a chemotherapeutic agent exerts a pro-inflammatory, pro-apoptotic effect in a cancer cell-specific manner.

The microarray study is well designed and the abstract clearly conveys the author’s findings and their wider implications, but the presentation of the actual results and the explanation/justification of the analytical strategies employed are often confusing to the point of frustration. Even if one is to assume the analytical strategy is sound, the results as presented, in the reviewer’s opinion, could be easily interpreted by a limited number of readers. Furthermore, interpretation of the results is problematic as the authors have performed no experimental validation of the microarray data. The authors have, however, experimentally validated an immunologic effect suggested by pathway analysis, immune cell infiltration in tumors.

Major Compulsory Revisions

1. The order of and manner in which gene expression data and pathway analyses are presented requires the reader to constantly refer back and forth between multiple results sections and figures. As the study and data are complex (effects of three factors on three tissues with cross-comparisons), the authors should make a thorough revision of the results section. Starting at section two, a more effective and coherent order of presentation would be “Comparison between the tumor, spleen, and liver”, “Tumor”, “Effect of CPT-11”, “Effect of PHY906”, “Effect of PHY906 when combined with CPT-11”, “PHY906-specific effects during CPT-11 therapy”, and “validation of immune cell infiltration in tumor by immunohistochemistry”.

2. The data analysis packages BRBArray Tools and Ingenuity Pathway Analysis were both designed, in part, to allow experimental scientists to perform sophisticated computational analyses typically done by biostatisticians and bioinformaticians. Given that (a) the authors used these tools, (2) none are affiliated with a statistics or computational science department, and (3) there is no acknowledgement of their having consulted a statistician or biomedical informatics core facility at their respective institutions, the authors should do so
now and include such an acknowledgment in the manuscript or provide justification as to why they conclude this is not necessary.

3. The authors should experimentally validate some of the gene expression data by an independent method, such as qRT-PCR. This should include expression of Mcp-1 and Irf1. Simply plotting microarray data for a gene (as in Figure 5E) is insufficient.

Minor Essential Revisions

1. The first page of the manuscript lists supplementary data as being available at Cancer Research Online.

2. On page 7 Results paragraph 2, the authors describe “7,856 transcripts differentially expressed by tumors compared to the two normal tissues”. To be clear, does this mean both or either normal tissues? If expression patterns are distinct in tumors versus the normal tissues, between the normal tissues themselves, and drug responses are also different among tissues, why combine liver and spleen (Figure 2, legend)?

3. The syntax of citing of p-values for Fisher’s exact test is inconsistent. See page 9 Results paragraph 4.

4. The powerpoint file containing Figure S1A does not have a file extension, at least on the BMC web site.

5. The axis values on Figure 2 are illegible. This makes data interpretation difficult. The authors should export the file at a higher resolution; 300 dpi, compressed tiff may be appropriate. They may also consider checking whether IPA allows one to increase font sizes.

6. I somehow doubt this is the first study in which the effect of chemotherapy was assessed at the global transcript level. See page 14, Discussion paragraph 1.

7. Why are data being introduced in the Discussion section? See page 16 Discussion paragraph 4, Data S2.

8. There are several grammatical errors in the manuscript.

Discretionary Revisions

1. The second sentence of Discussion paragraph 6 on page 17, “the study … documentable effects” is rather general.

2. The headings of the Results section are not very descriptive. For example, “Tumor” or “Effect of CPT-11”.

3. CPT-11 is referred to as Irinotocan in legend of Figure 4D and nowhere else in the manuscript.

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:

I declare I have no competing interests