Reviewer's report

Title: A microRNA Molecular Modeling Extension for Therapeutic Prediction of Colorectal Cancer Treatment

Version: 2
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Reviewer: Yajun Yi

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I. MAJOR COMPULSORY REVISIONS

1. Data presented in the study is not sufficient to support the conclusion as indicated in the manuscript, e.g.,
   "miRNA expression data contribute to making clinical decisions, including identification of the optimal drug with regard to individual patients".

2. In the study, miRNA results of CRC cell lines seems independent of the miRNA data in CRC patients
   For example,
   Author claimed in the study that "certain miRNAs (such as mir-181b, -21, -30a, -95, -135a, -145, -224 and -320) might be the key factors contributing to the clinical outcome of CRC patients".
   Are the similar miRNA profiles also observed in CRC cell lines?

   If there are similar miRNA profiles between CRC cell line and CRC patients, the miRNA profiles may serve as a translational link of drug sensitivity from CRC cell lines to patient treatment. Otherwise, the tight correlation between experimental GI50 and predicted proliferation scores in CRC cell lines does not support the prediction model used in CRC patients.

3. Most drug agents used in CRC cell lines are tyrosine inhibitors, and there are only two out of 10 drug agents in CRC cell line model (Everolimus and Temsirolimus) targeting to mTor protein that are the same type of chemotherapy agents for CRC patients.
   Can authors further calculate the specificity and sensitivity of prediction in CRC cell line model for these two related agents (Everolimus and Temsirolimus) by comparing predicted sensitivity with actual experimental response (GI50 cutoff at 1)?

3. According to the study, there are about 9~10 out of 22 patients (41%) can be predicted as responders to Sirolimus and LY294002 because of their hallmark proliferation < 1 (Fig. 5).
   However, CRC Patient clinic outcomes such as pCR/RCB and long-term survival events after Sirolimus and LY294002 treatment are not available in the study.
Proliferation’ hallmark is not commonly used in clinical settings for justification of chemotherapy response. Thus, there is no easy way to prove that the prediction in CRC patients.

II. MINOR ESSENTIAL REVISIONS

1. Abbreviation for Colorectal cancer (CRC) should be explained when used in the first time (abstract).

2. What miRNA gene records are used in prediction model of CRC cell lines and CRC patients?
   Are they derived from a common set?

III. Discretionary Revisions

1. The manuscript could be improved by paragraph of discussion of the limitations of the method.

2. The conclusion section is too long which can be more succinct.

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: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I have no competing interests in relation to this paper I am reviewing.