Reviewer's report

Title: MicroRNA signature associated with outcome of gastric cancer patients following chemotherapy

Version: 2 Date: 26 July 2011

Reviewer: Emmanuel Beillard

Reviewer's report:

General
The manuscript by Kim et al. reports the identification and validation of a microRNA signature to predict Gastric Cancer patients outcome following chemotherapy.

The prediction of disease outcome following chemotherapy is important for both patients and clinicians. With this regard, the manuscript provides new information that could be used for patient stratification and personalized medicine. While the statistical approach in this paper seems to be correct, several points have to be addressed before further consideration of the manuscript.

Major Compulsory Revisions
1. The GC signature

“Most of the differentially expressed miRs in the Gastric Cancer (GC) signature were previously reported”. This GC signature does not provide more much more information than what has already been published so far. The authors do not seem to make good use of GC signature data and should clearly state why this signature is important and how it is connected to the “chemoresistance” signature.

2. The chemoresistance signature

The authors have to describe more clearly their findings, including the presence of several star (*) and clustered microRNAs (on chromosome 19) in their “chemoresistance” signature (Table 2). The proof-of-principle test set and Table 3 should be part of the results. The authors have to provide quantitative PCR data for miR-122a and -195, which are the miRs with the most significant p value for disease progression prediction.

3. Assays validation

The authors have to indicate how their assays were validated in the Materials and Methods or Results sections. Required information, which can be supported by the manufacturer’s data includes: 1. Sensitivity of the detection of known over-expressed miRs (e.g. miR-372 in AGS cells), 2. Specificity of the detection of miRs from the same family (e.g. let-7, miR-146), 3. Quantitative PCR validation of their microarray findings (e.g. miR-195, -122a, and -486).
4. miR-486 over-expression

It is required that the authors check the miR-486 expression in their sample sets (as in Figure 2) with the TaqMan MicroRNA Assay kit for miR-486 quantitation (preferred), as reported in Oh et al. Clin Cancer Res (2011). It is also required that the authors comment on their finding as the loss of miR-486 expression in the Oh et al. paper was supported by CGH data.


I have noticed that several miRs in Table 2 have been renamed since the release 9 of miRbase (2006). miR-526c does not exist anymore, and seems to be miR-519c-5p (see MI0003148 in miRbase). Similarly, miR-524* has been renamed (miR-524-3p?). miR-486 has 2 arms but there is no indication in this table. miR-146 appears in the “underexpressed in cancer” category while miR-146a and –b are listed in the “chemoresistance”-related miRs. I strongly recommend the authors to contact the vendor(s) to get an updated version of the miR annotation.

6. Discordance regarding miR-25 between figure 2 and Table 2

The authors have to comment on the fact that miR-25 appears in their “overexpressed” list while miR-25 amount does not significantly differ between normal and tumors in Table 2.

7. miR star sequences = deficient pri-miR processing?

One important finding in Table 2 is the presence of several star (*) miRs: “Chemoresistance” list: 8/28 – “Chemosensitive” list: 0/30. A possible explanation is that the processing of the primary miR transcript is impaired (See Tchernitsa et al., J Pathol, 2010). The authors have to discuss this result.

Minor Essential Revisions

1. Part of the results (published biological activity of the candidate miRs) has to be moved to the Discussion while Results (hypothesis testing with 8 sample pairs) in the Discussion should appear in the Results section.

2. It is not unexpected that over-expressed or under-expressed miRs from the same cluster are found in Table 2. It is recommended that the authors comment on the fact that the information provided by these miRs might be redundant. The authors should comment on having a shorter list, supported by previous publication(s) (Yu, Cancer Cell, 2008 as an exemple). Would a list of 2-5 miRs instead of 58 be as informative? Or is the tumor type too heterogeneous?

3. The authors should not make too much emphasis on putative targets of their miR signature outside of the Gastric Cancer field but rather cite their own work or related work on Gastric Cancer. As an exemple:

- Tchernitsa et al. Systematic evaluation of the miRNA-ome and its downstream

4. “Prediction accuracy” should be defined in the text.

Minor issues not for publication
1. Transcriptional degradation is not correct
2. There is a repeat in the Results paragraph “58 miRs correlated with TTP …”.
3. References #7, 12, 15 do not have the YEAR. This has to be corrected.
4. In table 2 “listed in the order of increasing p value” should appear in the legend.

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

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.