Reviewer’s report

Title: MicroRNA-433 negatively regulates the expression of thymidylate synthase (TYMS) responsible for 5-fluorouracil sensitivity in HeLa cells

Version: 1 Date: 9 May 2013

Reviewer: manuela garibaldi

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The authors did an in silico search of miRNAs targeting TYMS gene and rise above resistance to 5-FU-based chemotherapy induced by high levels of TYMS. They identified miR-433 which has a binding site close to the rs16430 polymorphism of TYMS, a 6-bp deletion associated with decreased mRNA stability and lower gene expression. Functional validation of miR-433 confirmed the binding of the miRNA to TYMS and its independence from the 6-bp deletion. Probably this region has a regulatory activity on the gene, operated through different mechanisms. They also showed that transfection of miR-433 in HeLa cells reduces TYMS levels and sensitizes cells to 5-FU treatment by decreasing proliferation. This is the first report of a miRNA that targets TYMS, reducing its expression, and renders cells sensitive to 5-FU, suggesting that miR-433 could be used to bypass drug resistance.

Methods used are appropriate and sufficiently described, discussion and conclusions are well balanced and adequately supported by the data.

Minor essential revisions
Add p-values for results of overexpression of mir-433 in the section “results” of the abstract
Page 4 lane 3: increased, substitute d with s
Page 10 lane 17 and 19, change reacted with hybridized
Page 11 lane 1, add information on City and State for GE Healthcare
Page 12 lane 7, specify that the 6-bp deletion is polymorphism rs16430
Page 15, lane 6, specify that the 6-bp deletion is polymorphism rs16430

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