April 22, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2940-edited_CG.doc).
Title: MicroRNAs and liver cancer associated with iron overload: therapeutic targets unraveled.
Authors: Catherine M. Greene, Robert B. Varley, Matthew W. Lawless
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 2940

The manuscript has been improved according to the suggestions of reviewers:
1 The format has been updated – author contributions and 100 word core tip were inserted.

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 00053451, no changes recommended
(2) Reviewer 00068586, no changes recommended
(3) Reviewer 00007076

The only problem is that HCC is considered mainly as the consequence of iron overload. Though hemochromatosis is indeed associated with and increased risk of HCC, iron is not the major player of HCC development in viral- or alcohol-related liver disease where is a co-player. This needs to be better emphasized or the title should be changed in "MicroRNAs and the liver cancer associated with iron overload: therapeutic targets unraveled". Alternatively the issue of iron should be tuned down ion the text. I personally favor the second option

As requested we have altered the title

(4) Reviewer 02521203

The authors should perhaps want to include the use of miR-124 in reducing HCC as a potential therapeutic agent in the "miRNAs AS THERAPEUTICS FOR HCC" section. An HNF4α-miRNA Inflammatory Feedback Circuit Regulates Hepatocellular Oncogenesis doi:10.1016/j.cell.2011.10.043

As requested we have inserted this reference and refer to it in the text as follows:

Recently it was demonstrated that HNF4a, a key regulator of hepatocellular carcinogenesis, becomes stably inhibited during hepatocellular transformation. Perturbation of this event through miR-124 systemic administration, can prevent and suppress HCC development in a murine liver cancer model by inducing tumour-specific apoptosis without toxic side effects [163]. This miR-124 has therapeutic potential for treating liver cancer.

3 References and typesetting were corrected.

4. We added in the following sentences on page 23 and added the references

Findings have also pointed towards long non-coding RNAs (lncRNA) as important tumorigenic candidates actively involved in gene regulation, with lncRNAs suggested as a link in carcinogenesis. Morover, lncRNAs can act as negative regulators of microRNAs and therefore may become important factors to consider when developing miRNA therapeutics. Several reports demonstrate an association of lncRNA with the development, progression, metastasis and poor prognosis in HCC patients [164-168].

164 ***Gutschner T***, *Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. RNA Biology 2012;* ***9****: 703-719 [PMID: 22664915 DOI: 10.4161/rna.20481]*
165 ***Yuan SX***, *Yang F, Yang Y, Tao QF, Zhang J, Huang G, Yang Y, Wang RY, Yang S, Huo XS, Zhang L, Wang F, Sun SH, Zhou WP. Long noncoding RNA associated with microvascular invasion in hepatocellular carcinoma promotes angiogenesis and serves as a predictor for hepatocellular carcinoma patients' poor recurrence-free survival after hepatectomy. Hepatology 2012;* ***56****: 2231-2241 [PMID: 22706893 DOI: 10.1002/hep.25895]*
166 ***Liu Y***, *Pan S, Liu L, Zhai X, Liu J, Wen J, Zhang Y, Chen J, Shen H, Hu Z. A genetic variant in long non-coding RNA HULC contributes to risk of HBV-related hepatocellular carcinoma in a Chinese population. PLoS One 2012;* ***7****: e35145 [PMID: 22493738 DOI: 10.1371/journal.pone.0035145]*
167 ***Yang F***, *Zhang L, Huo XS, Yuan JH, Xu D, Yuan SX, Zhu N, Zhou WP, Yang GS, Wang YZ, Shang JL, Gao CF, Zhang FR, Wang F, Sun SH. Long noncoding RNA high expression in hepatocellular carcinoma facilitates tumour growth through enhancer of zeste homolog 2 in humans. Hepatology 2011;* ***54****: 1679-1689 [PMID: 21769904 DOI: 10.1002/hep.24563]*
168 ***Hauptman N***, *Glavac D. Long Non-Coding RNA in Cancer. Int J Mol Sci 2013;* ***14****: 4655-4669. [PMID: 23443164 DOI: 10.3390/ijms14034655]*

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

C Greene

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