Author’s response to reviews

Title: Combination of hepatocyte specific delivery and transformation dependent expression of shRNA inducing transcriptional gene silencing of c-Myc promoter in hepatocellular carcinoma cells

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Author’s response to reviews:

To
The Editor-in-Chief,
BMC Cancer.

Subject: Submission of a manuscript titled “Combination of hepatocyte specific delivery and transformation dependent expression of shRNA inducing transcriptional gene silencing of c-Myc promoter in hepatocellular carcinoma cells” for consideration for publication in BMC Cancer.

Dear Sir,

We are submitting the manuscript titled “Combination of hepatocyte specific delivery and transformation dependent expression of shRNA inducing transcriptional gene silencing of c-Myc promoter in hepatocellular carcinoma cells” by Zakaria et al. for your kind consideration for publication in BMC Cancer. This manuscript has not been published or is under consideration for publication anywhere else.

Potential gene targeting approaches are hindered by the lack of tumour specificity and efficacy. In this work, we have attempted to impart various hierarchical levels of specificity for efficient killing of hepatoma cells. Firstly, we have targeted the cargo to liver cells by Sendai virosomal delivery system. The fusion (F) protein on the virosome ensured its delivery to hepatocyte via asialoglycoprotein receptors (ASGPR). As the delivery was to both normal and neoplastic cells, we used alpha-fetoprotein (AFP) promoter, in combination with various tumour specific enhancers, to ensure specific expression of shRNA for long term suppression via transcriptional gene silencing (TGS) of c-Myc in transformed cells. It has been shown by one of our group (D.P.S) earlier that F
protein mediated delivery ensures the cytoplasmic delivery of the cargo, which in turn decreases the possibility of degradation by endosomal pathway, and reduces immunogenicity.

Many reports have already demonstrated the effects of reduction in transcripts of various oncogenes by Post-transcriptional Gene Silencing (PTGS). However, suppression of transcription itself by TGS in mammalian system is comparatively novel and offers a different and potentially long acting approach for silencing oncogenes as it generates heritable epigenetic marks. In this study the suppression of gene expression was demonstrated to be mediated by both heterochromatization and CpG methylation of the c-Myc P2 promoter.

The combination of cell type specific delivery system with neoplasia induced activation of TGS has a better possibility of targeting malignant hepatocytes. In situations where c-Myc is deregulated, it could be of particular use in tackling recalcitrant cancer cells. Furthermore, such approaches may also be considered for introducing specific genes for expression in the embryonic liver where AFP expression is high.

We request you to kindly consider the manuscript for publication in BMC Cancer.

With regards,

Yours sincerely,

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