Reviewer's report

Title: Cyproheptadine, an Antihistaminic Drug, Inhibits Proliferation of Hepatocellular Carcinoma Cells by Blocking Cell Cycle Progression through the Activation of P38 MAP Kinase

Version: 2 Date: 28 July 2014

Reviewer: Chiun Hsu

Reviewer's report:

Major compulsory revisions

1. The IC50 of the HCC cells tested in this study was above 40 microM. This is far above the concentration achievable in human (< 1 microM) (Gunja N et al. J Toxicol 2004). Therefore, the clinical relevance of the pre-clinical findings in this study is questionable. Since the authors reported potential clinical efficacy of cyproheptadine in patients with advanced HCC, the authors should try experiments using clinically achievable concentrations of cyproheptadine.

2. The authors observed clinical efficacy in patients with advanced HCC who were treated with cyproheptadine plus thalidomide. In vitro and in vivo studies of this drug combination will greatly improve the scientific merit of this study.

3. The authors showed association between cyproheptadine efficacy and changes in cell cycle regulatory proteins and activities of cellular signaling pathways. The authors should try to establish the causal relationship by using small-molecule kinase inhibitors or siRNA.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

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.