Reviewer's report

Title: Novel c-Met inhibitor suppresses the growth of c-Met-addicted gastric cancer cells.

Version: 4  Date: 19 November 2015

Reviewer: Flavio Maina

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Major Compulsory Revisions

The authors have improved the quality of the text and the discussion is better structured in the revised version of the manuscript. There are still several sentences that are not correct (either in English or as a concept). Five examples, among others:

- Introduction: “Oncogene addiction refers to the phenomenon which the tumorigenesis results from the abrogation of specific one or two normal signalling pathway”. Oncogene addiction refers to the dependency of cancer cells to a specific signal (cells are addicted to this signal), and it is not a phenomenon by which tumorigenesis results from the abrogation of pathways.

- Introduction: “In adults, the expression of these two proteins are normally very low and confined to the epithelial or mesenchymal origin cells”. Expression of Met is restricted to some epithelial cell types whereas the expression of HGF is predominantly confined to some mesenchymal-like cells.

- Results: “Hs746T cell line has constitutively activated c-Met signaling by the amplified c-Met gene and the truncated form of c-Met protein”. In Hs746T cells, a splice site mutation in c-Met causes deletion of a specific exon located in the juxtamembrane domain, leading to a form of Met protein that lack only this exon (and it is not a truncated form). This can be also appreciated in Figure 2A of the present manuscript.

- Results: “Doxorubicin, …, was treated with 18 cancer cell lines for 72 hrs”. It is rather the cells that are treated with doxorubicin for 72 hrs.

- Discussion: First sentence in the discussion section. Experimentally, the authors did not address any concern I previously highlighted, which, in my opinion, were meant to improve the quality of their study and strengthen the outcomes.

- 1° point: The fact that “PF04217903 is suspended at phase I clinical trial” is not a reason for not using it as a reference compound; the authors may gather further evidences that KRC compounds permit overcoming limits of PF04217903, thus supporting the relevance to further explore them in clinics. The issue of patent conflicts is irrelevant for the point I underlined.

- 2° point: Additional in vivo studies together with histological analyses would further clarify the benefit (and limitations) of KRC compounds. The “lack of
scientific resources” is not a scientific reason for not doing studies that would improve the quality of a research work (beside the fact that it is not clear what the authors intend to state with “lack of scientific resources”).

- 3° point: In vivo side effects should be explored through a series of basic parameters related to: a) tolerance of a drug overtime; b) effects on different organs, c) dose effects (using increasing compound doses). The authors have only explored KRC-00715 toxicity by following body weight, which is a first indication and could be sufficient for this type of reports. However, based on 10 days of treatment, the authors cannot state that KRC-00715 is very safe in mice (considering also that mice treated with KRC-00509 die after 3-4 days of treatment). It is therefore not an issue that “I have to worry” or not about KRC-00715 regarding safety.

Although I maintain my overall positive evaluation on the discovery of these compounds and on the results reported in the present manuscript, I leave the editor to take an editorial decision concerning these experimental issues.

Minor Essential Revisions:

- Results: How was the reduction on Met phosphorylation quantified (number of experiments performed, statistics, …)?

- Results: “This means that the inhibition of the c-Met activity is the direct reason for the suppression of the Hs746T cell proliferation”. The authors should reformulate this sentence as such strong statement must be supported by rescue experiments.

- The authors claim that SNU5 cells treated with KRC drugs were arrested at G1/S phase. Whereas I can see an increase in the percentage of cells in G phase, I rather see a decrease in the percentage of cells in S phase (Results and Figure 4). In Figure 4A and B, M1, M2, M3, and M4 must be replaced with subG1, G1, S, G2/M (I suppose).