Reviewer's report

Title: Constitutively active c-Met kinase in PC-3 cells is autocrine-independent and can be blocked by the Met kinase inhibitor BMS-777607

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Reviewer: Anthony Joshua

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In the article, Dai and Siemann present a series of experiments exploring the mechanics of MET signaling in PC-3 cells in vitro. These series of experiments have clinical relevance with the recent activity of XL184 (dual MET/ VEGFR2) in patients with prostate cancer, although pure MET inhibition (ARQ197) appeared considerably less active so although the authors speak highly of MET inhibition in prostate cancer, to date there is little evidence that pure MET inhibition will achieve clinically meaningful responses. The applicability of the paper to the clinical setting is also somewhat limited by the neuro-endocrine like limitations of using PC3 as a prostate adenocarcinoma model. Thus the whole paper, in particular given the lack of in vivo modeling is more relevant to MET signaling biologists than prostate cancer and herein likes the problem with the paper - in trying to be both, it has successfully achieved neither. The authors need to commit to this paper being about prostate cancer (in which case some in vivo experiments are needed) or being about MET signaling in which case further experimentation is needed to clarify the abnormal characterized protein they found, for a start.

Major Compulsory Revisions

As mentioned above, the authors need to characterize the abnormal HGF AND/OR carry out some in vivo experiments to confirm their in vitro findings.

For example, The authors bring up some reasonable suggestions for exploring MET signaling in the discussion, which should really be acted on in the paper to improve the science therein.

Minor Essential Revisions

The effect on cell proliferation with BMS 777607 would be better off depicted as an IC50 curve. It seems that effects at 3 or 10 um actually indicate that the drug is not that potent - wouldn't an siRNA approach be a good confirmatory experiment?

The first paragraph contains some errors - I would suggest that references 4,5 imply that HGF has been identified as an independent prognostic factor FOR advanced disease NOT of advanced disease. I failed to find a reported figure of 100% in references 6,7 - can the authors suggest where that figure is exactly in those references?
Is it unclear what the 2 control lanes in Figure 2B represent, these should be better described in the legend; the rationale for the anti-HGF is not explained in the text or the legend and why this was also not added to the 10% FBS experiment; Finally whether the CM (PC-3) bar should have extended over the HGF column too?

The relevance of an aniokis experiment is unusual in the usual panel of tests of a malignant phenotype, whilst I have no objection to its inclusion, it would be better placed if the authors justified its importance to a greater extent.

Figure 1A - NT as an abbreviation for Not determined is peculiar. Was it in fact, non detectable?

The clinical relevance of Fig 6 would be better supported if some measure of apoptosis was also included or at least the scientific justification for the experiment was bette explained. Why is characterizing these changes important? Do they differ in other cell lines? Is apoptosis possible what accounts for the decreased proliferation seen?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interests