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: Gary Edward Gallick

Reviewer’s report:

The manuscript of Dai and Siemann first attempts to determine if constitutive activation of c-Met in PC3 prostate cancer (PCa) cells is due to autocrine stimulation by the c-Met ligand, HGF/SF. As active HGF secretion has been known to be very low or non-existent in these cells, the conclusion that an autocrine loop does not exist is not surprising. Thus, it is expected that anti-HGF antibodies will not block the partial activation of c-Met and the biologic properties affected by this partial activation. The strength of the data in the manuscript is the demonstration that the c-Met inhibitor (BMS777607) does affect constitutive c-Met signaling, important because multi-targeted inhibitors with c-Met as one of the targets are promise in treatment of prostate cancer bone metastases. The weakness of the manuscript is that no data are presented that suggest a mechanism for the partial activation of c-Met in PC-3 cells. In addition, prostate cancer bone metastases have a rich source of HGF from stromal cells, thus the significance of in vitro results are uncertain. Nevertheless, the well-performed experiments could lead to future mechanistic based studies. Minor concerns with the manuscript include:

Major Compulsory Revisions: none

Minor Essential revisions:

(1) In the Background section, most reports indicate 85% of prostate cancer bone metastases are positive for c-Met expression, not 100%.

Discretionary Revisions:

(2) A positive control using cells that secrete HGF would be important for the analyses in Figure 1.

(3) While the culture medium (CM) was not functional in activating c-Met or inducing c-Met functions, e.g. migration, a true test would be to determine if the CM can activate purified c-Met.

(4) The experiments that show an anti-HGF neutralizing antibody did not block constitutive c-Met signaling are among the most interesting in this manuscript. However, they would be greatly strengthened using a cell line that does produce and respond to HGF, and demonstrating in this instance, c-Met phosphorylation decreases in the presence of the neutralizing antibody.

(5) The expected downstream c-Met targets are affected; this adds little to the
manuscript unless the authors determine which are important for the effects they see.

(6) The authors note in the discussion (as this reviewer did above) that the prostate is a rich source of HGF. Thus, an in vivo experiment in an appropriate mouse model would be important and should be feasible, although the reviewer recognizes mouse HGF does not strongly activate human c-Met.

**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:**

I declare that I have no competing interests