A novel and selective c-Met inhibitor against subcutaneous xenograft and orthotopic brain tumor models

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INTRODUCTION

c-Met (Heiengchymal Giaothelial Transition factor) de-regulation has been recognized in multiple types of cancer, including gastric, lung, colorectal, breast, prostate, pancreatic, head and neck, liver, ovarian, renal, glioma, melanoma, and a number of sarcomas. c-Met is aberrantly activated through gene amplification and/or overexpression, mutation, and cross talk to other kinases involved in tumor cell growth and metastasis. c-Met gene amplification is identified in ~10% of stomach and head & neck cancers, and 20% of breast tumors. c-Met overexpression and activation is observed in 67% of lung cancer, 33% of ovarian cancer, and 80% of multiple myeloma, respectively. With no doubt, c-Met is a promising target for human cancer. Considering the observation of small toxicity for SXI 525 in its phase I clinical trial, HM504 (also coded as HMPL 504) was designed away from protein unstable metabolites. Here, the preclinical data of this novel and selective c-Met inhibitor is reported.

RESULTS AND DISCUSSION

- HM5016504 is a reversible ATP-competitive c-Met inhibitor, and is highly selective over 274 kinase by >1000-fold.
- HM5016504 demonstrates potent inhibitory activity on multiple target-related cellular functions, e.g. tumor cell growth and angiogenesis including proliferation of endothelial cells and VEGF secretion from tumor cells.
- The tumor cells with c-Met gene amplification are highly sensitive to HM5016504, suggesting that subcutaneous activity of HM5016504 on c-Met plays a dominant role in these tumor cells.

Key pharmacological properties of HM5016504

Inhibition of HM5016504 on tumor cell growth

<table>
<thead>
<tr>
<th>Genotype</th>
<th>KIC50 (µM)</th>
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</thead>
<tbody>
<tr>
<td>K-Ras</td>
<td>0.12 µM</td>
</tr>
<tr>
<td>V600E</td>
<td>0.11 µM</td>
</tr>
<tr>
<td>V600E/G13D</td>
<td>0.037 µM</td>
</tr>
<tr>
<td>PTEN</td>
<td>0.012 µM</td>
</tr>
<tr>
<td>HM5016504</td>
<td>0.002 µM</td>
</tr>
</tbody>
</table>

Functions of c-Met in cellular signaling cascades vary with tumor cells

In in vitro effcacy studies of HM5016504

- In SNU-5, a human gastric cancer cell with c-Met amplification, c-Met dominantly controls the key signaling cascades, such as p-AKT and p-ERK, in the case of with or without EGF. Differently, both c-Met and EGF play roles in H441 cell signaling. These data gives an explanation on the different responses of two cell lines to HM5016504.

- HM5016504 demonstrated high potency on various types of human tumor xenografts, particularly, those with c-Met gene amplification.
- EGFR overexpression or Rb/Raf mutation may cause constitutive activation of EGFR-Ras/Raf signaling pathways, which can compensate cell survival signals in the presence of HM5016504.
- U87MG, the glioblastoma with high expression level, showed high sensitivity to HM5016504 in both in vivo and orthotopic models, suggesting the potentiality for HM5016504 to achieve c-Met dominant brain tumor and therefore be beneficial to patients with brain tumors or brain metastasis.

CONCLUSIONS

- HM5016504 is a potent, reversible and ATP-competitive c-Met inhibitor with high selectivity over a 274 kinase panel. It demonstrates good efficacy on multiple human tumor xenografts in a target related manner.
- HM5016504 is favorable PK profiles, including good oral pharmacokinetic property and potentiality of penetrating brain blood barrier.
- In preclinical studies, no HEGR inhibition and gene toxicity were observed. Significant safety margins were obtained from both rodent and non-rodent animals, which make HM5016504 a favorable drug candidate targeting c-Met. The compound is in the prior position in HMPL development pipeline.