Abstract #3612

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

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INTRODUCTION

c-Met (Mesenchymal Epithelial Transition factor) dysregulation 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 brain 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 renal toxicity for SGX 523 in its phase I clinical trail, HMPL-504 (also coded as HM5016504 or 16504) was designed away from of producing insoluble 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 kinases by >200 folds.
- HM5016504 demonstrates potent inhibitory activities 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 inhibitory activity of HM5016504 on c-Met plays a dominant role in those tumor cells.

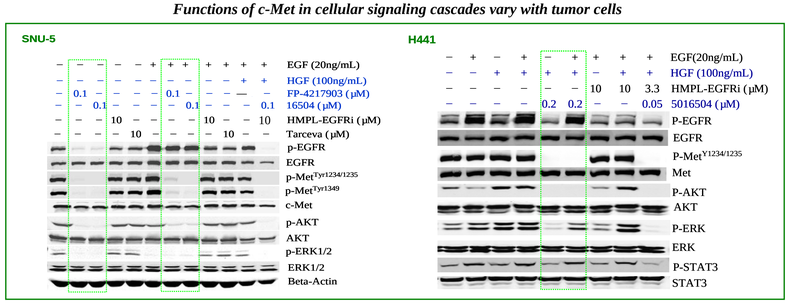
Key pharmacological properties of HM5016504

Assay	IC_{50} (μM)
c-Met kinase	0.005
c-Met autophosphorylation (H441)	0.003
HGF stimulated c-Met phosphorylation (H69)	0.002
HGF dependent tumor cell function	
Proliferation (H441/H69)	0.006/0.009
Scattering (MDCK)	<0.012
Migration (H441)	0.02
Invasion (H441)	89% @ 0.02 μM
Angiogenesis related	
HGF dependent proliferation (HUVEC)	0.005
HGF dependent tube formation (HUVEC)	0.012
VEGF secretion (H441)	0.024

Inhibition of HM5016504 on tumor cell growth

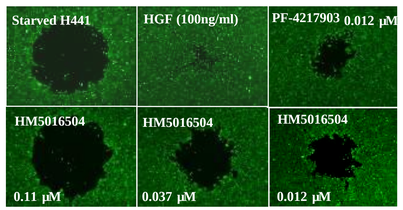
Cell line	c-Met Gene Ampli.	c-Met Protein overexp.	c-Met Constitutive activation	Genotype of related kinases	IC_{50} (μM) MTT
HUVEC	–	+	–	/	>30
H1650	–	LOW	–	$PTEN^{-}$	>30
SNU-16	–	LOW	–	/	>30
H1993	+	+	+	/	0.010
EBC-1	+	+	+	/	0.002
SNU-5	+	+	+	/	0.003
Hs174T	+	+	+	/	0.005
MKN-45	+	+	+	/	0.004
H1975	–	+	+	$EGFR^{T790M/L858R}$	>30
H441	–	+	+	$K\text{-}Ras^{G12V}$	>30
HCT116	–	+	+	$K\text{-}Ras^{G13D}$	>30
HT29	–	+	+	Raf^{V600E}	>30

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

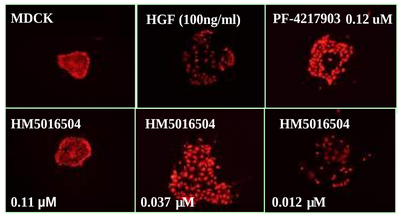


In SNU-5, a human gastric cancer cell with c-Met amplification, c-Met dominantly controlls the key signaling cascades, such as p-AKT and p-ERK, in the case of with or without EGF. Differently, both c-Met and EGFR play roles in H441 cell signaling. These data gives an explanation on the different responses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

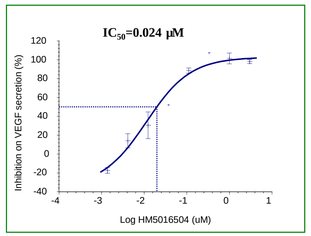
Inhibition of H441 migration



Inhibition of MDCK scattering

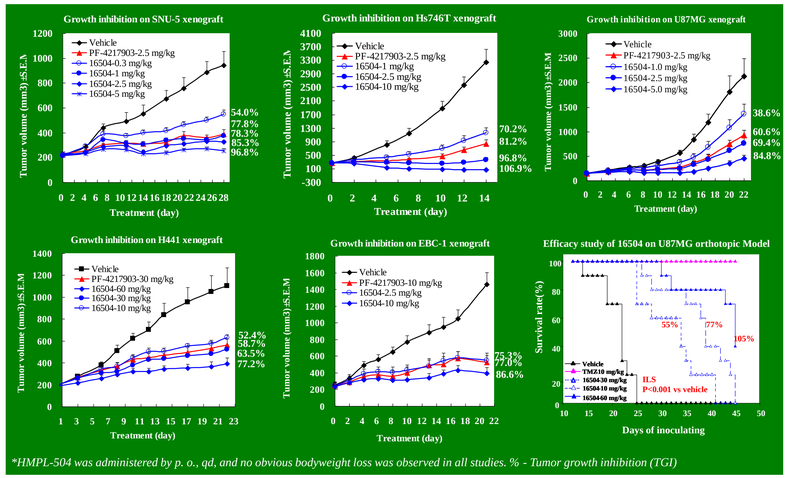


Inhibition of VEGF secretion of H441 cells

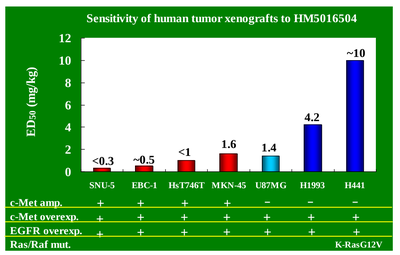


- HGF-dependent migration of human lung cancer cell H441 is inhibited by 16504 in a dose-dependent manner.
- c-Met, also named as a scattering factor receptor, plays key roles in cell scattering. MDCK scattering induced by 100 ng/mL of HGF is effectively and dose-dependently inhibited by 16504.
- VEGF expression and secretion is a common feature for tumor cells to stimulate angiogenesis and obtain nutrition. 16504, the selective c-Met inhibitor, blocks VEGF secretion effectively.

In vivo efficacy studies of HM5016504

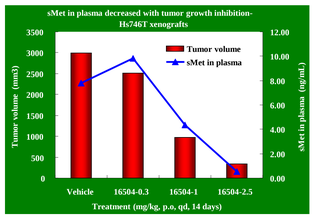


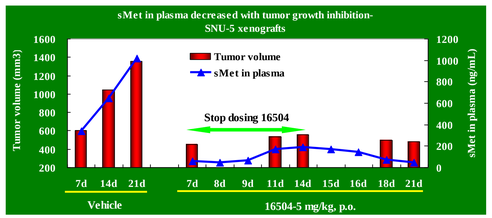
**HMPL-504 was administered by p. o., qd, and no obvious bodyweight loss was observed in all studies. % - Tumor growth inhibition (TGI)*

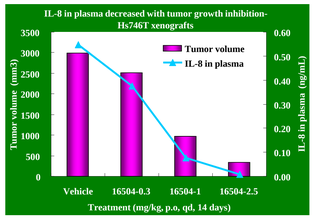


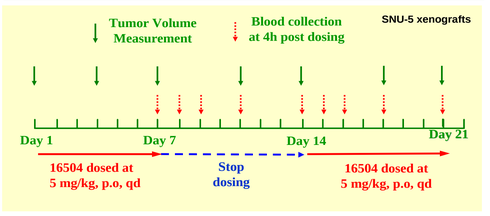
- HM5016504 demonstrated high potency on various types of human tumor xengorafts, particularly, those with c-Met gene amplification.
- EGFR overexpression or KRas/Raf mutation may cause constitutively activation of EGFR-Ras/Raf singling pathways, which can compensate cell survival signals in the presence of HM5016504.
- U87MG, the glioblastoma with HGF autocrine loop, showed high sensitivity to HM5016504 in both s.c. and orthotopic models, suggesting the potentiality for HM5016504 to penetrate into the blood barrier and therefore be beneficial to patients with brain tumors or brain metastasis.

Biomarker study on human gastric tumor xenograft models









- The concentrations of human IL-8 and soluble c-Met (sMet) in mouse plasma demonstrated good correlation to the tumor volumes on both Hs746T and SNU-5 xenograft models.
- On SNU-5 xenograft model, the sMet concentration in mouse plasma showed the same trend with the tumor re-growth upon stopping dosing 16504, suggesting that sMet could be a predictive marker for tumor shrinkage.

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 has favorable PK profiles, including good oral pharmacokinetic property and potentiality of penetrating brain blood barrier.
- In preclincal studies, no hERG 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.