Abstract #3719
Poster #1321

TPX-0022, a polypharmacology inhibitor of MET/CSF1R/SRC for treatment of cancers with abnormal HGF/MET signaling

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Introduction

Aberrant activation of the HGF/MET pathway has frequently been observed in human cancers including MET mutation, gene amplification and translocation, as well as paracrine or autocrine HGF upregulation. The abnormal HGF/MET signaling not only acts as an oncogenic driver but also confers resistance to many cancer therapies, such as EGFR targeted therapy in NSCLC.[1,2] One key downstream effector of activated MET is SRC, which is also involved in malignancy formation, tumor metastasis and drug resistance.[3] In the tumor microenvironment, CSF1R plays an important role in regulation of tumor associated macrophages, which promote tumor progression and angiogenesis.[4] Therefore, the polypharmacological inhibition of MET/CSF1R/SRC has great potential to target cancers with abnormal HGF/MET signaling more effectively by simultaneously targeting tumor intrinsic signaling and the tumor microenvironment.

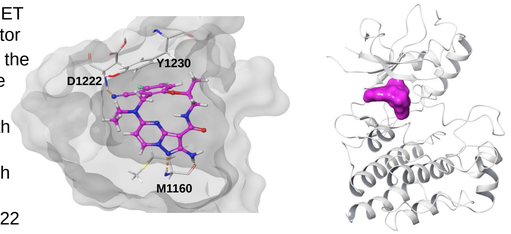
TPX-0022, a novel macrocyclic compound, has been designed based on the unique autoinhibitory crystal structure of MET and optimized to inhibit MET/CSF1R/SRC with enzymatic kinase inhibition IC_{50}s of 0.14, 0.71 and 0.12 nM, respectively. TPX-0022 potently inhibited cell proliferation of the *MET*-amplified MKN-45 and SNU-5 gastric cancer cells, with IC_{50}s <0.2 nM, which ranks it as one of the most potent MET inhibitors. TPX-0022 suppressed MET auto-phosphorylation at an IC_{50} of approximately 0.3 nM in the MKN-45 cell line. TPX-0022 also potently inhibited the phosphorylation of MET downstream signaling effectors, including AKT, ERK, STAT3 and PLCγ2 in a dose-dependent manner. In the cancer cell line- and patient-derived xenograft tumor models from gastric, lung and liver cancers harboring *MET* amplification or *MET* exon14 skipping (Δex14) mutations, TPX-0022 treatment resulted in marked tumor regression and tumor growth inhibition (up to 85.3% tumor regression), without overt abnormality and body weight loss in treated mice.

Overall, TPX-0022 is a novel and potent MET inhibitor with desirable drug-like properties, a good preclinical safety profile, that warrants further clinical development and an IND submission is currently planned.

The activity of TPX-0022 against CSF1R *in vitro* and *in vivo* will be presented at Poster # 1325 (Abstract #3749)

TPX-0022 potently inhibited MET/CSF1R/SRC kinases

- Novel structure as first MET macrocyclic kinase inhibitor
- Modeling of TPX-0022 in the complex with MET kinase domain (PDB ID 2WGJ)
- Hinge hydrogen bond with M1160
- Strong π-π interaction with Y1230
- Hydrogen bond with D1222



Kinase inhibition IC_{50}s of TPX-0022 on MET, CSF1R and SRC at 10 μM of ATP[a]

	Enzyme IC_{50} (nM)		
Inhibitor	MET	SRC	CSF1R
TPX-0022	0.14	0.12	0.71
Capmatinib[b]	0.20	ND	ND
Crizotinib[b]	4.0	ND	ND

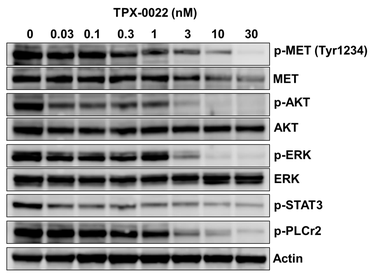
[a] Kinase activity was determined at Reaction Biology, Inc. [b] Data based on evaluation of comparable proxy chemical reagent purchased from commercial sources. ND: not determined

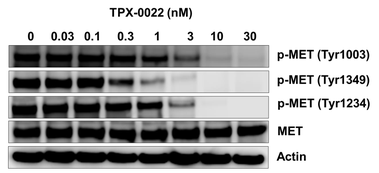
TPX-0022 potently inhibited MET in cell-based assays

- TPX-0022 inhibited cell proliferation in MKN-45 and SNU-5 cell lines with potency that is comparable to capmatinib and is more than 10 fold more potent than crizotinib

	MKN-45 IC_{50} (nM)	SNU-5 IC_{50} (nM)
TPX-0022	<0.2	<0.2
Capmatinib	<0.2	<0.2
Crizotinib	10.5	2.8

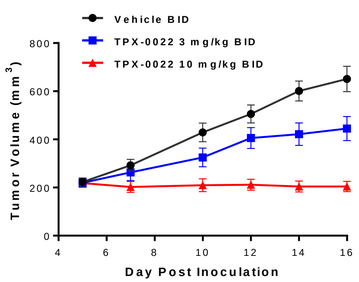
- TPX-0022 inhibited MET phosphorylation in MKN-45 (left) and SNU-5 (right) cell lines
- TPX-0022 suppressed the phosphorylation of MET downstream effectors in MKN-45 cells (left)



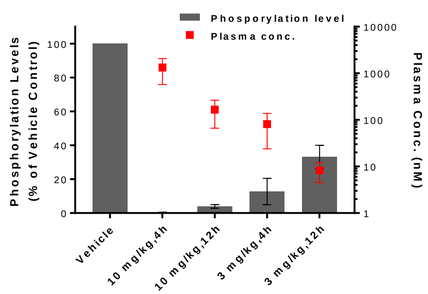


TPX-0022 inhibited MKN-45 tumor growth *in vivo*

Antitumor effect of TPX-0022 in the MKN45 cell-derived xenograft tumor model of gastric cancer with *MET* gene amplification



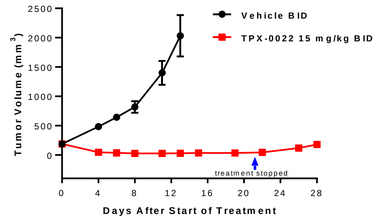
Inhibition of MET phosphorylation by TPX-0022 in the MKN45 cell-derived xenograft tumor model of gastric cancer with *MET* gene amplification

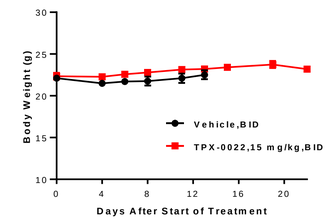


- TPX-0022 demonstrated a dose-dependent inhibition of MKN-45 tumor growth in nude mice
- Treatment with TPX-0022 at 10 mg/kg/BID resulted in 106% tumor growth inhibition (6% tumor regression), corresponding to a > 95% inhibition of MET phosphorylation throughout the treatment period with a free trough plasma concentration of 4.5 nM

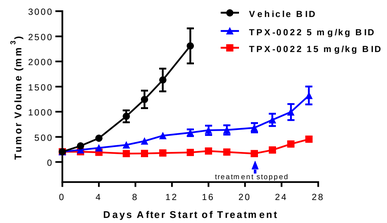
TPX-0022 inhibited tumor growth in PDX models

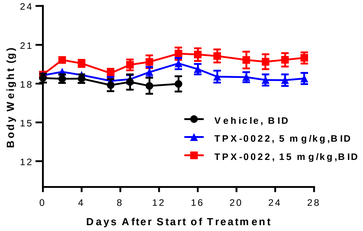
- Treatment with TPX-0022 at 15 mg/kg BID resulted in 85.3% tumor regression in LU2503 HuPrime® lung cancer PDX mouse tumor model, which has *MET* Δex14 mutation and *MET* gene amplification
- No body weight loss and overt abnormality were observed





- TPX-0022 achieved 82.1% tumor growth inhibition and 17.6% tumor regression when dosed at 5 and 15 mg/kg BID, respectively, in LI0612 HuPrime® hepatocellular carcinoma PDX mouse model with *MET* gene amplification
- No body weight loss and overt abnormality were observed





Conclusions

- TPX-0022, a novel compact three-dimensional macrocyclic molecule, designed based on the unique crystal structure of MET to efficiently target the MET kinase in the autoinhibitory conformation
- In biochemical and cell based assays, TPX-0022 is one of the most potent MET inhibitors in clinical development
- TPX-0022 demonstrated marked antitumor effect in the MKN-45 gastric cancer xenograft tumors with *MET* gene amplification, lung cancer PDX tumors harboring *MET*Δex14 mutation and *MET* gene amplification and HCC PDX tumors with *MET* amplification
- TPX-0022 has promising drug-like properties, and the novel polypharmacological profile inhibiting MET/CSF1R/SRC that has the potential to inhibit MET as an oncogenic driver and alter the tumor microenvironment to affect anti-tumor activity *via* inhibition of CSF1R
- TPX-0022 IND submission is planned for the first half of this year and a Phase 1 clinical trial initiation in the second half of this year

Reference

1. Comoglio PM, et al. *Nat Rev Cancer*. **2018**, 18(6):341-358. 2. Ko B, et al. *Ann Transl Med*. **2017**, 5(1):4. 3. Zhang S, et al. *Trends Pharmacol Sci*. **2012**, 33(3):122-128. 4. Yang L, et al. *J Hematol Oncol*. **2017**, 10, 58.

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