373 Mps1 Kinase Inhibitors As Mitotic Regulator for Cancer Therapy

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Lead identification / optimization
Target(MoA)	Inhibitors of Mps1 Kinase as Mitotic Regulators
Brief Description	• Mps1 is overexpressed in both solid and hematological tumors and genetic or chemical inhibition suppresses tumor growth. • Novel small molecule Mps1 inhibitors have been patented. • The lead compounds 1 and 13 inhibit Mps1 kinase enzymatic activity with IC50 values from 0.356 uM to 0.809 uM, and inhibited Mps1-associated cellular functions such as centrosome duplication and the spindle checkpoint in triple negative breast cancer cells. • The most promising analog, compound 13, controls tumor growth without weight loss when given IP daily for 6 weeks in a Cal-51 TNBC xenograft model • The lead molecule is orally bioavailable and brain penetrant • Preliminary in vitro efficacy in hematologic malignancy
Organization	The Ohio State University

Differentiation

□ **Mps1 (monopolar spindle 1 or TTK1) as a therapeutic target**

- Mps1 is critical for genomic integrity
- Mps1 activity is critical in regulating centrosome duplication and spindle assembly checkpoint
- Highly aneuploid cells are susceptible to targeting by Mps1
- TNBC is highly aneuploid and therefore treatable by Mps1 inhibition

□ **Mps1 pipelines**

- CFI-402257 (The Campbell Family Cancer Research Institute): Phase I/II for metastatic HER2-negative breast cancer & phase I for castrate refractory prostate cancer, oral administration
- S-81694 (NMS-P153, Les Laboratoires Servier): Phase II for metastatic breast cancer & phase I for solid tumor, oral administration, studied in in vitro and in vivo models in TNBC, highly selective, MPS1 IC_{50} = 3nM, impressive tumor growth inhibition associated with tumor regression in efficacy studies. proliferation data performed on a large panel of cell lines (>100)
- BAY-1217389 (Bayer): Phase I for advanced solid tumors including TNBC (combination w/paclitaxel), oral administration, moderate efficacy in monotherapy in tumor xenografts studies and unique MoA when combined with paclitaxel
- BOS-172722 (Boston Pharmaceuticals): Phase I for solid tumors including TNBC (combination w/paclitaxel)
- PF-7006 & PF-3837 (Pfizer): Preclinical for breast cancer, tumor-bearing mice treated with PF-7006 exhibit tumor growth inhibition with PD modulation of a downstream biomarker (pHH3-Ser10). In vivo efficacy studies with PF-7006 using an orthotopic xenograft model of basal-a/TNBC breast cancer resulted in only 59% tumor growth inhibition (TGI) at the MTD 25 mg/kg.
- NMS-P715 (NMS Group): Preclinical for GBM, oral administration, oral bioavailability 37% (10 mg/kg), and good PK properties, 53% tumor growth inhibition by 90 mg/kg QDx10 in A2780 ovary carcinoma xenograft model, At this dose, the compound well tolerated and no signs of body weight loss or other overt toxicities. 43% tumor growth inhibition by 100 mg/kg QDx7 in A375 melanoma xenograft model

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Key Data

In vitro assay in panel of breast cancer cell lines

IC_{50} determinations of compounds 1, 7, 9, 13, and known inhibitor, Mps1-IN-1, in panel of breast cancer cell lines.

Cell line			IC_{50} ± SEM (μM)				
		BASAL subtype	Cpd 1	Cpd 7	Cpd 9	Cpd 13	Mps1-IN-1
CAL-51	TNBC	Basal	0.23 ± 0.04	1.26 ± 0.24	0.30 ± 0.01	0.5 ± 0.10	2.92 ± 1.08
HCC1937	TNBC	Basal	0.73 ± 0.25	0.84 ± 0.15	1.10 ± 0.01	1.0 ± 0.07	>10
BT-20	TNBC	Basal A	0.35 ± 0.38	0.06 ± 0.01	1.71 ± 0.21	0.3 ± 0.20	>10
BT-549	TNBC	Basal B	0.81 ± 0.17	2.19 ± 0.59	1.30 ± 0.01	0.0 ± 0.27	1.73 ± 0.71
MDA-MB-436	TNBC	Basal B	0.90 ± 0.28	5.23 ± 3.94	1.23 ± 1.01	0.6 ± 0.35	>10
MDA-MB-468	TNBC	Basal B	0.19 ± 0.07	1.57 ± 0.29	0.32 ± 0.04	0.3 ± 0.22	1.85 ± 0.51
Hs578T	TNBC	Basal B	>10	>10	>10	>10	>10
MDA-MB-231	TNBC	Basal B	>10	0.40 ± 0.05	>10	>10	>10
CAMA-1		Luminal	0.36 ± 0.02	0.84 ± 0.71	0.65 ± 0.13	0.6 ± 0.47	>10
Sk-Br-3		Luminal	>10	0.75 ± 0.22	0.47 ± 0.01	0.4 ± 0.38	>10
AU565		Luminal	>10	>10	>10	0.9 ± 0.15	>10
T47D		Luminal	>10	0.33 ± 0.18	>10	>10	>10
MDA-MB-453		Luminal A	0.82 ± 0.10	>10	>10	0.3 ± 0.06	>10
MCF-7		Luminal A	0.44 ± 0.21	0.35 ± 0.01	0.30 ± 0.09	>10	>10
BT-474		Luminal B	>10	0.47 ± 0.23	0.29 ± 0.04	0.0 ± 0.01	>10

IC_{50} values are averages of replicate independent assays, each determined by ten-point dosage treatments (n = 6 per dose).

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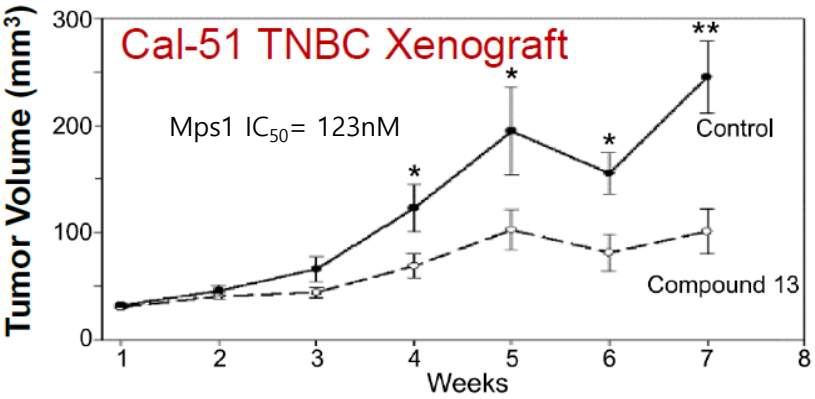
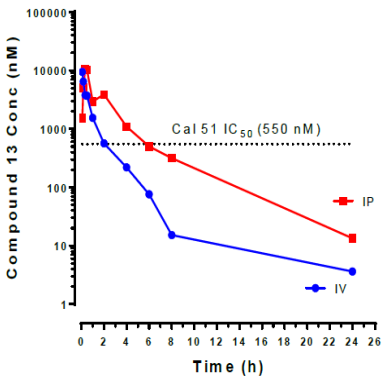
Lead molecule controls tumor growth in a TNBC xenograft model





DMSO or Lead Molecule (10 mg/kg) given IP daily for 6 weeks
Mean ±SEM, * P < 0.05 ** p < 0.01
No significant body weight reduction

IV – 20 mg/kg single dose
IP – 50 mg/kg single dose

Lead molecule is orally available and brain penetrant

	Plasma IV	Plasma PO	Brain IV	Brain PO
Dose (mg/kg)	10	50		
HL_Lambda_z (min)	61.1	387	60.7	264
Tmax (min)	5.00	60.0	5.00	60.0
Cmax (nM)	7900	4776	*1662	*1338
AUCINF_pred(hr*nmol/L)	7733	22700	*1817	*4450
AUClast (hr*nmol/L)	7700	13250	*1340	*3133
Vz_pred (L/kg)	4.50	28.4		
Cl_pred (L/min/kg)	0.0510	0.0510		

*Brain concentrations expressed in molar units; assumes 1mg brain tissue = 1uL volume

IV (10 mg/kg) and PO (50 mg/kg), 3 ICR mice per time point
Brain harvested and compound exposure determined at each time point
Oral Bioavailability = 58.7% (based on AUCinf-pred)

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Intellectual Property

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Country	US

Contact Information

Contact Person	Khountham, Soun
Email	Soun.Khountham@osumc.edu
URL	https://innovate.osu.edu/available_technologies/37724/Pyrrolopyrimidine-Derivatives-as-Mps1TTK-Kinase-Inhibitors-for-Cancer-Therapy