DRUG DEVELOPMENT INSTITUTE (DDI)

TECH BRIEF

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Orally Bioavailable and Brain Penetrant Mps1/TTK Inhibitors as Cancer Therapeutics

Upregulation of the mitotic kinase Mps1/TTK correlates to aggressive phenotypes in both solid and hematological malignancies. Researchers at Ohio State have discovered an orally bioavailable and brain penetrant Mps1/TTK inhibitor that exhibits single agent tumor growth inhibition in a murine xenograft model of human triple-negative breast cancer (TNBC) upon daily administration.

Rationale for Targeting Mps1

- Mps1 activates the spindle assembly checkpoint to ensure faithful segregation of chromosomes during mitosis.
- In the context of the increased chromosomal instability typical of cancer, Mps1 upregulation prevents mitotic catastrophe due to severe aneuploidy.
- In cancer, pharmacologic inhibition of Mps1 causes severe defects in chromosomal segregation, resulting in catastrophic levels of aneuploidy.
- Importantly, Mps1 inhibition synergizes with microtubule-targeted therapy, presenting clear opportunities for combination therapy.

Key Information about Ohio State's Lead Mps1 Inhibitor

- Our lead is designed to provide an advantageous combination of potency and safety to dampen systemic toxicity without sacrificing therapeutic effect.
- Tumor-bearing mice dosed daily for six weeks with an efficacious dose of our lead compound exhibited no adverse effects on body weight.
- Oral bioavailability in mice was 59% with a brain-to-plasma ratio of 0.2.
- Anti-proliferative effect has been demonstrated *in vitro* on cell lines spanning a number of indications.
- *In vitro* functional assays confirm that our lead compound disrupts the proper functioning of the spindle assembly checkpoint and decreases centriole duplication.
- Upcoming preclinical studies are intended to assess PK/PD relationship, efficacy and safety.
- *In vitro* ADME studies and structural characterization of the binding between Mps1 and our lead compound are in progress.
- Mps1 expression level, aneuploidy status and/or genetic background may predict sensitivity to our lead compound.

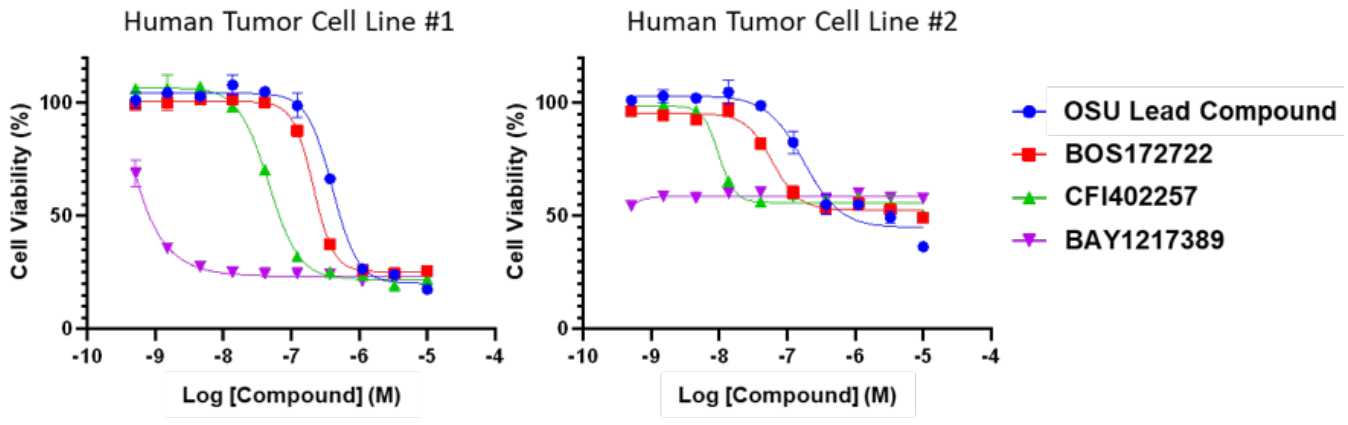

Figure: Two human tumor cell lines were treated for 72 hours with our lead compound or one of three reported Mps1 inhibitor clinical candidates. Our lead compound shows a similar dose-response profile to the clinical candidates with the expected reduced potency. (Reaction Biology Corp.)

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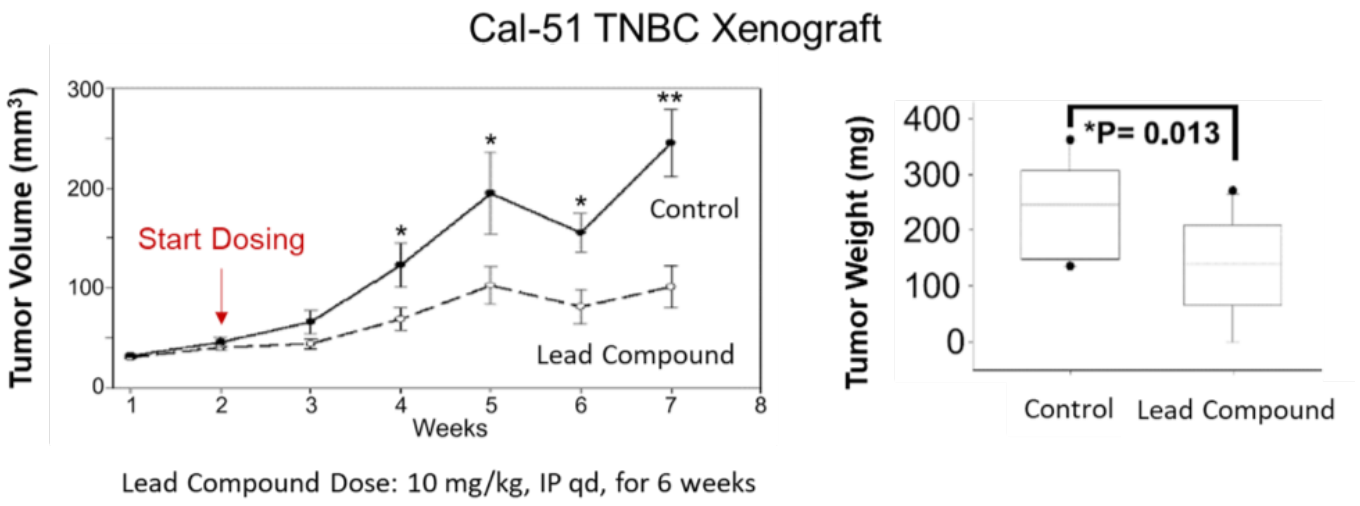
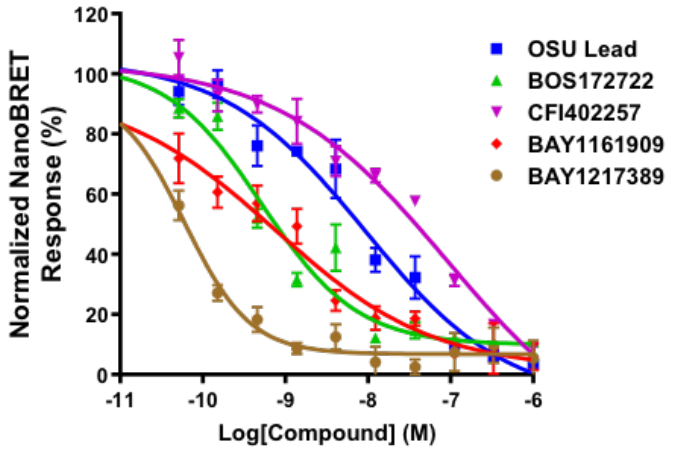


Figure: OSU's lead compound attenuates growth of a Cal-51 Triple Negative Breast Cancer (TNBC) xenograft in mice when dosed daily at 10 mg/kg IP for 6 weeks



	OSU Lead	BOS172722	CFI402257	BAY1161909	BAY1217389
EC50	9.245e-009	5.182e-010	9.433e-008	7.524e-010	6.003e-011

Figure: OSU's lead compound exhibits a 9nM EC_{50} in an Mps1 NanoBRET in-cell target engagement assay (Reaction Biology Corp.)

Publications

Novel pyrrolopyrimidines as Mps1/TTK kinase inhibitors for breast cancer, *Sugimoto, Y., Sawant, D.B., Fisk, H.A., Mao, L., Li, C., Chettiar, S., Li, P.-K., Darby, M.V., and Brueggemeier, R.W.* Bioorg Med Chem 25 (2017) 2156-2166

Intellectual Property

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