**Ohio State Drug Development Institute (DDI) Portfolio Project**

# Mps1 Kinase Inhibitors as Mitotic Regulators for Cancer Therapy

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COMPREHENSIVE CANCER CENTER

# OHIO STATE'S DRUG DEVELOPMENT INSTITUTE (DDI)

Accelerating Innovative Research to Speed Cures to Cancer Patients

## The DDI Advantage

- A pipeline of innovative, early-stage therapeutics
- Independently validated technologies
- Rigorous project milestone management by industry scientists
- A network of industry experts to vet projects
- Focus on external partnership and out-licensing

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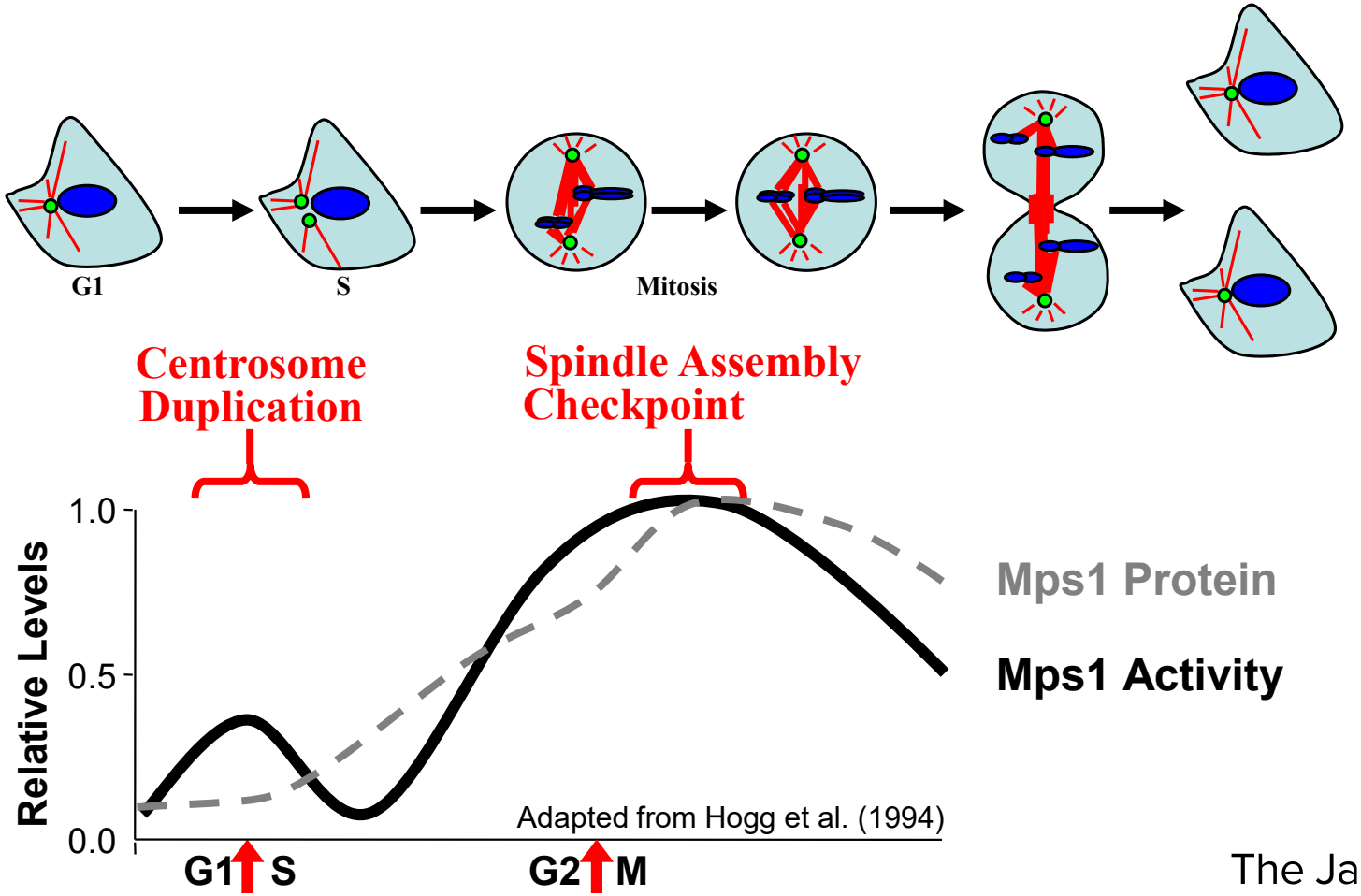
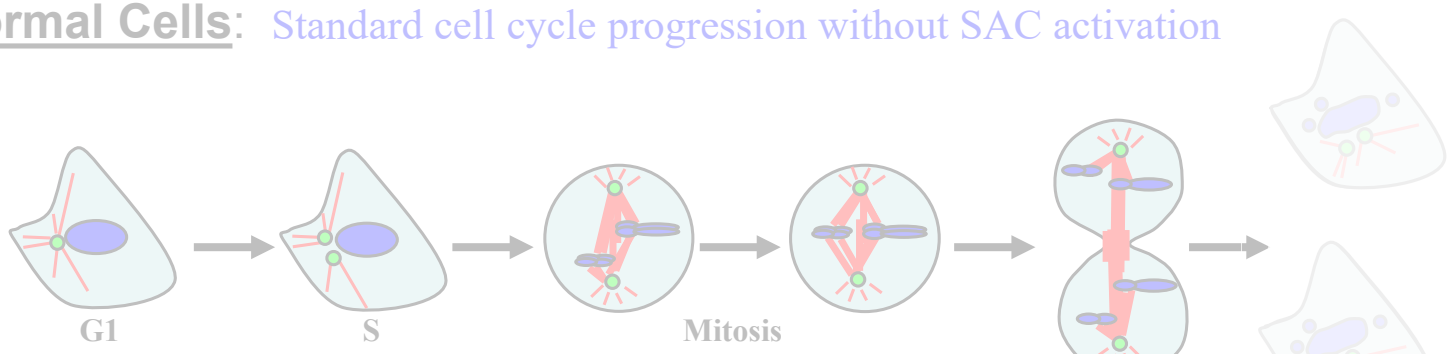
# Mps1 is Critical for Genomic Integrity

- Mps1 regulates centrosome duplication and the spindle assembly checkpoint
- Mps1 prevents anaphase in the absence of proper chromosome segregation



# Mps1 Prevents Mitotic Catastrophe Due to Chromosomal Instability

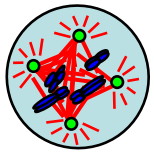
**Normal Cells**: Standard cell cycle progression without SAC activation



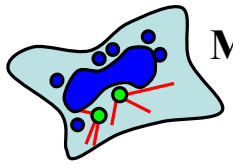

Modest Aneuploidy, Survival

High Mps1 activity = SAC failsafe engaged

**In Cases of High Chromosomal Instability**:



Inhibited Mps1 = SAC failsafe disengaged



**Massive Aneuploidy, Cell Death**

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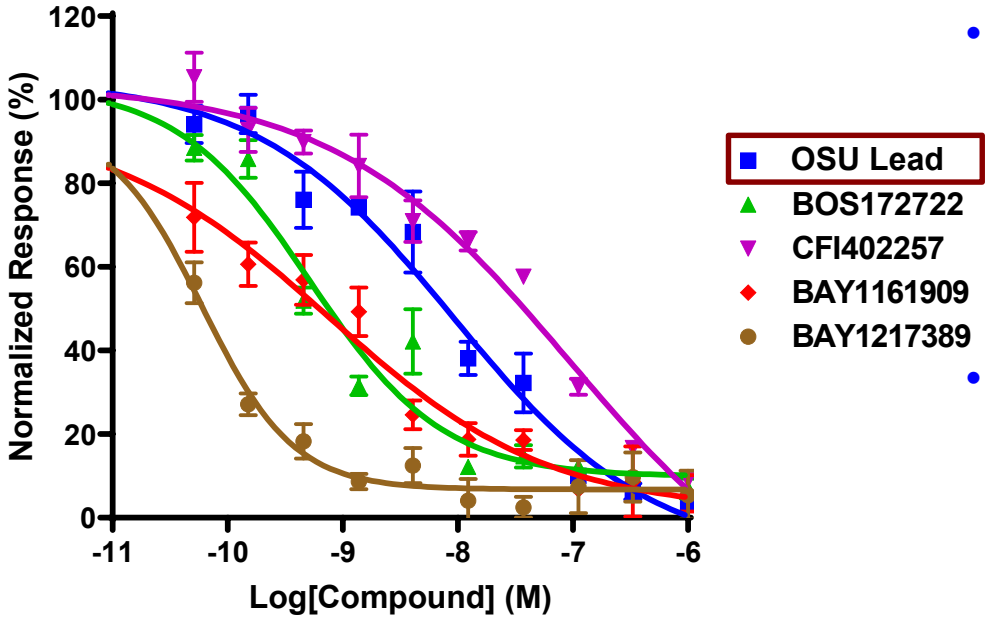
# Current Project Status

- Lead Compound Overview
  - Acceptable in vitro ADME, orally bioavailable in mice
  - Activity profiled against >600 human kinases to understand selectivity and potential polypharmacology; biologically relevant secondary targets have been identified and are under investigation
  - In vitro comparison to known clinical candidates and evaluation in multiple cancer types are underway
  - In vivo studies in multiple indications are being planned to evaluate therapeutic index, mechanism of action, and potential for novel combination strategies

- Intellectual Property
  - US Patent Application 15/524,606, Priority Date: 6 Nov 2014
  - Medicinal chemistry campaign to provide optimized analogs with potential for new IP is underway

# Lead Compound Exhibits 9 nM $EC_{50}$ in NanoBRET In-Cell Target Engagement Assay

- NanoBRET quantifies the relative inhibition of binding of Mps1 to a tracer molecule

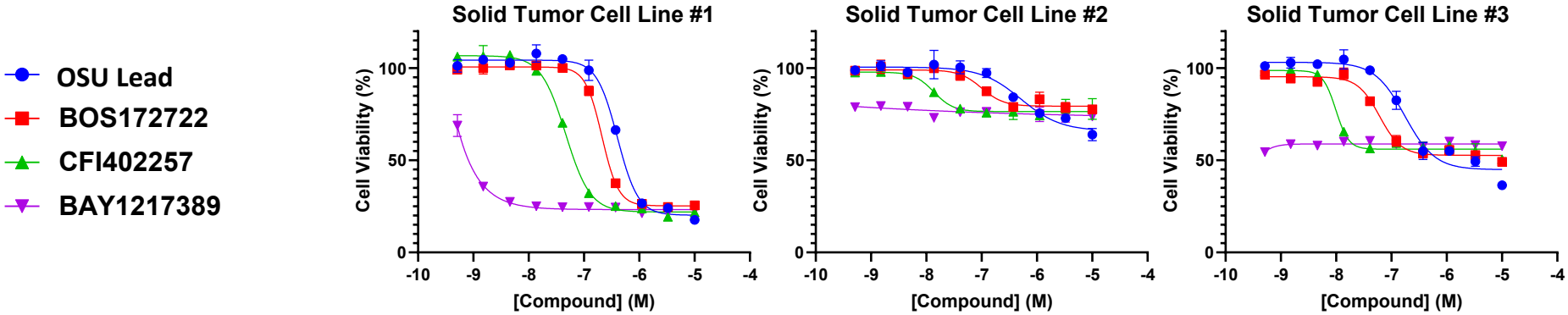



| | OSU Lead | BOS172722 | CFI402257 | BAY1161909 | BAY1217389 |
|---|---|---|---|---|---|
| EC50 | 9.245e-009 | 5.182e-010 | 9.433e-008 | 7.524e-010 | 6.003e-011 |

- OSU's lead exhibits $EC_{50}$ of 9 nM in the NanoBRET assay
  - Consistent with $IC_{50}$ of 3 nM measured in Mps1 biochemical assay
- NanoBRET potency compares favorably to that of Mps1 inhibitor clinical candidates

Assay performed by Reaction Biology Corp.

# Lead Molecule Inhibits *In Vitro* Proliferation of Multiple Human Tumor Cell Lines




- Human solid tumor cell lines were treated with Mps1 inhibitor for 72 hours and relative cell number determined using the CellTiter Glo assay (Promega)
- Similar shape and dynamic range of response suggest OSU lead compound shows on-target mechanism of action

# Lead Exhibits Favorable In Vitro ADME Results

**Aqueous Solubility**: Reasonable Sol.

PBS (pH 7.4) ~25 µM
SGF (pH 1.2) ~ 50 µM
SIF (pH 6.0) ~ 25 µM
FeSSIF (pH 5.0) ~ 5 µM
FaSSIF (pH 6.5) ~ 10 µM

**Plasma Protein Binding:**

Human = 98.8%
Monkey = 99.1%
Dog = 99.3%
Rat = 99.0%
Mouse = 99.2%

**Caco-2**:

$P_{app}$ (A to B) = 6.94 x $10^{-6}$ cm/s
$P_{app}$ (B to A) = 2.05 x $10^{-6}$ cm/s
Efflux Ratio = 0.32
Not likely to be efflux substrate

**Microsomal Stability**: Stable in human liver microsomes

| | | |
|---|---|---|
| Human: | $T_{1/2}$ = 164 min | $CL_{int}$ = 0.457 L/hr/kg |
| Monkey: | $T_{1/2}$ = 23.3 min | $CL_{int}$ = 4.81 L/hr/kg |
| Dog: | $T_{1/2}$ = 79.0 min | $CL_{int}$ = 1.18 L/hr/kg |
| Rat: | $T_{1/2}$ = 8.76 min | $CL_{int}$ = 19.2 L/hr/kg |
| Mouse: | $T_{1/2}$ = 6.71 min | $CL_{int}$ = 48.8 L/hr/kg |

**CYP Inhibition:** ($IC_{50}$) No significant issues

| | | |
|---|---|---|
| 1A2: > 50 µM | 2B6: > 25 µM | 2C8: 13.5 µM |
| 2C9: 13.4 µM | 2C19: 13.8 µM | 2D6: >25 µM |

3A4 (Midazolam): 16.2 µM  3A4 (Testosterone): 9.54 µM

**hERG (FASTPatch®)**: $IC_{50}$ ~ 7 µM

Assays performed by Charles River Laboratories, Inc.

# Lead is Orally Bioavailable and Brain Penetrant in Mice

- IV (10 mg/kg) and PO (50 mg/kg), n=3 ICR mice per time point
- Brain and plasma levels analyzed
- Oral Bioavailability = 58.7% (based on AUC inf_pred)

| | Plasma IV | Brain IV | Plasma PO | Brain PO |
|---|---|---|---|---|
| **Dose (mg/kg)** | 10 | | 50 | |
| **$T_{1/2}$ z (min)** | 61.1 | 60.7 | 387 | 264 |
| **$T_{max}$ (min)** | 5 | 5 | 60 | 60 |
| **$C_{max}$ (nM)** | 7900 | 1662* | 4776 | 1338* |
| **AUC inf_pred (nM·hr)** | 7733 | 1817* | 22700 | 4450* |
| **AUC last (nM·hr)** | 7700 | 1340* | 13250 | 3133* |
| **Vz pred (L/kg)** | 4.5 | | 28.4 | |
| **CL pred (L/min/kg)** | 0.051 | | 0.051 | |

**6 h PO half-life**

**$C_{max}$ and AUC are in the micromolar range**

* Brain concentration assumes 1mg brain tissue = 1µL volume

Data generated by the OSUCCC Pharmacoanalytic Shared Resource

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# Summary and Next Steps

- Lead compound is an orally bioavailable, brain penetrant, single-digit nanomolar inhibitor of Mps1 with acceptable in vitro ADME properties
- Lead optimization is ongoing to provide optimized molecules with potential for new composition of matter patent coverage
- Lead compound will be evaluated in multiple xenograft studies over the coming months
- Ongoing experiments are evaluating mechanism of action, novel combination strategies, and the potential for tuning of beneficial polypharmacology