AACR
Annual Meeting, April 2026
Poster 6044
Poster Section 15 Board 5

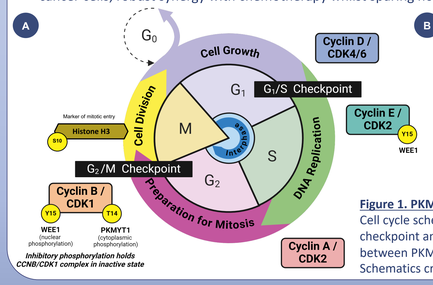
PKMYT1 Inhibition is Synthetically Lethal With CCNE1 Overexpression and Synergizes With Standard of Care Chemotherapy

Natalie Hill, Jeremy Fournier, Srijita Bhowmik, Jenny Zhu, Saranya Chandrasekar, Jamison Buendia, Haneesha Vishwa Sai, Linda Shen, Elizabeth Rumpf, Emily Leong, Ester Fernández-Salas, Samantha S Hodge

ARCUS BIOSCIENCES
3928 Point Eden Way, Hayward, CA 94545 (USA)

Background

- CCNE1 is frequently overexpressed in ovarian, endometrial, & colorectal cancers due to gene amplification, reduced degradation (via FBXW7 mut/del), or increased gene transcription
- High levels of CCNE1 dysregulate the G1/S checkpoint, increase replication stress, and amplify dependence on the G2/M checkpoint to ensure proper DNA damage repair before mitosis
- PKMYT1, a member of the WEE1 family of enzymes, phosphorylates and inhibits CDK1 T14, and to a lesser extent Y15, to regulate the G2/M checkpoint
- Lunresertib (lunre) is the only PKMYT1 inhibitor in clinical trials, currently in a Ph1 combination with the WEE1 inh Debio0123
- The data presented here demonstrate that PKMYT1 inhibition, which inactivates the G2/M checkpoint and pushes cells into mitosis, is synthetically lethal in CCNE1-high cancer cells and synergizes with standard of care chemotherapy *in vitro* and *in vivo*.
- These data highlight that targeting of PKMYT1 with a potent and selective inhibitor results in effective killing of CCNE1-high cancer cells, robust synergy with chemotherapy whilst sparing non-tumorigenic cells



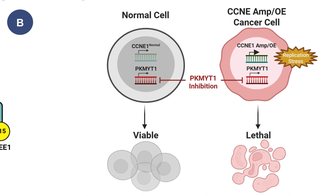


Figure 1. PKMYT1 inhibition is synthetically lethal with CCNE1 overexpression. (A) Cell cycle schematic. PKMYT1 phosphorylates CDK1 at pT14 to enable the G2/M checkpoint and prevent entry into mitosis. **(B)** Schematic illustrating synthetic lethality between PKMYT1 inhibition and CCNE1 amplification (amp) and overexpression (OE). Schematics created with BioRender.

PKMYT1 Inhibition Inhibits Tumor Growth in CCNE1-High Xenografts

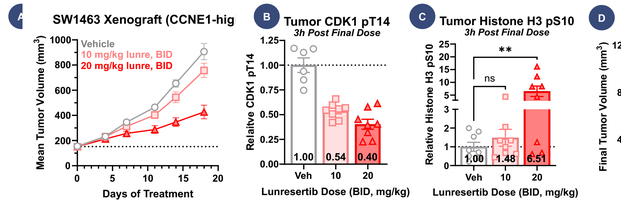


Figure 3. PKMYT1 inhibition decreases tumor growth in CCNE1-high xenografts. Single agent efficacy of lunre was evaluated in the FBXW7mut SW1463 CRC xenograft model. **(A)** Lunre, dosed at 10 and 20 mg/kg BID PO, decreases SW1463 tumor growth in a dose-dependent manner. Levels of tumor **(B)** CDK1 pT14 and **(C)** histone H3 pS10 (mitotic entry) were measured by western blot. **(D)** Correlation of tumor mitotic entry and endpoint tumor volume. Higher lunre doses (red triangles) are associated with significantly increased entry into mitosis and decreased tumor volume.

PKMYT1 Inhibition Synergizes with Chemotherapy in CCNE1-High Cancers

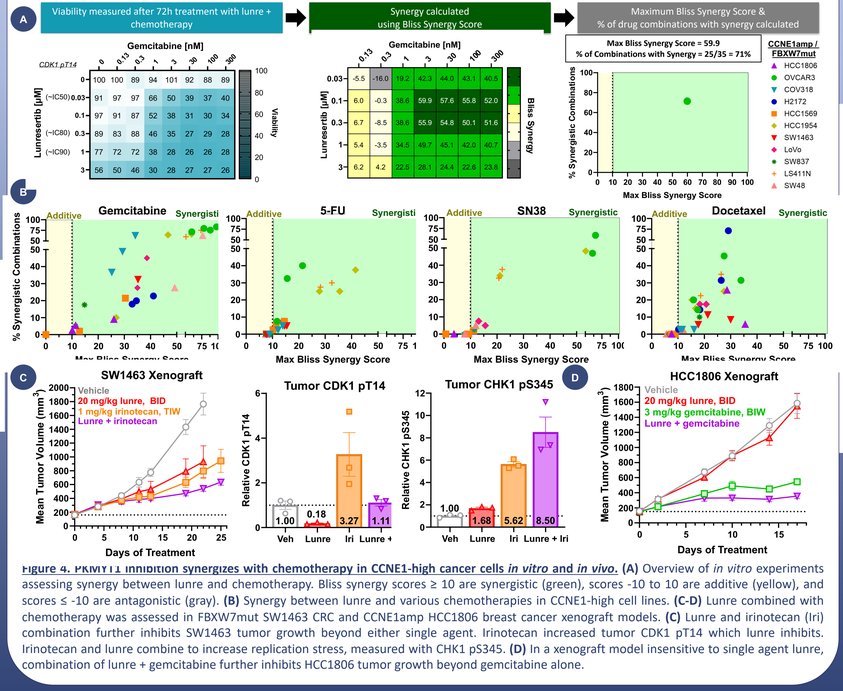
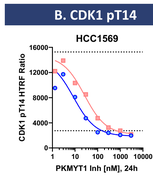


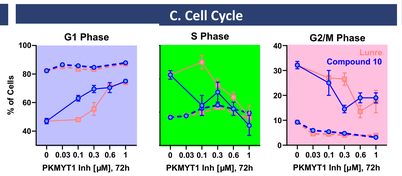
Figure 4. PKMYT1 inhibition synergizes with chemotherapy in CCNE1-high cancer cells *in vitro* and *in vivo*. (A) Overview of *in vitro* experiments assessing synergy between lunre and chemotherapy. Bliss synergy scores ≥ 10 are synergistic (green), scores -10 to 10 are additive (yellow), and scores ≤ -10 are antagonistic (gray). **(B)** Synergy between lunre and various chemotherapies in CCNE1-high cell lines. **(C-D)** Lunre combined with chemotherapy was assessed in FBXW7mut SW1463 CRC and CCNE1amp HCC1806 breast cancer xenograft models. **(C)** Lunre and irinotecan (Iri) combination further inhibits SW1463 tumor growth beyond either single agent. Irinotecan increased tumor CDK1 pT14 which lunre inhibits. Irinotecan and lunre combine to increase replication stress, measured with CHK1 pS345. **(D)** In a xenograft model insensitive to single agent lunre, combination of lunre + gemcitabine further inhibits HCC1806 tumor growth beyond gemcitabine alone.

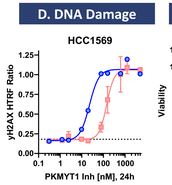
Novel, Potent, and Selective PKMYT1 Inhibitors Synergize with Chemotherapy and Spare Non-Tumorigenic cells

A

		Lunresertib	Compound 10
Biochemical, High ATP	PKMYT1	18 nM	14 nM
	WEE1	4.2 μM	> 10 μM
	LCK	7.6 μM	5.0 μM
	CSF1R	840 nM	840 nM
Cell Based, HCC1569	CDK1 pT14 IC_{50}	26.1 nM	8.5 nM
	γH2AX EC_{50}	134.4 nM	20.4 nM
	Viability IC_{50}	53.4 nM	9.6 nM







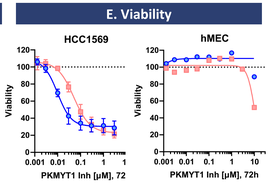
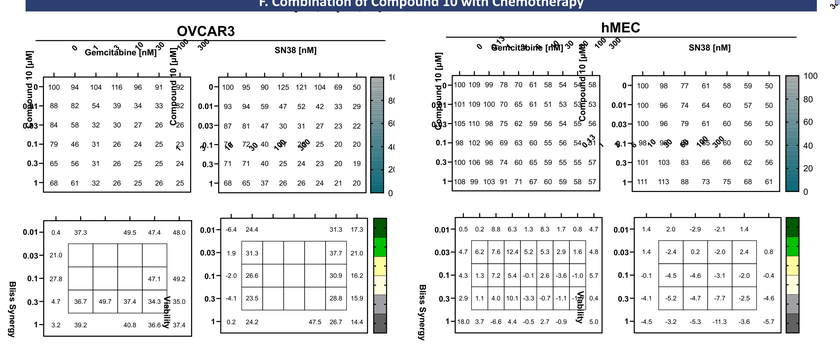
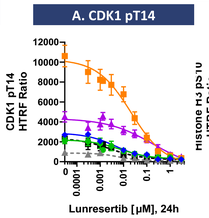
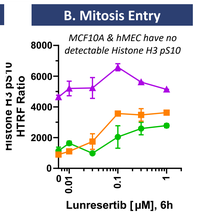


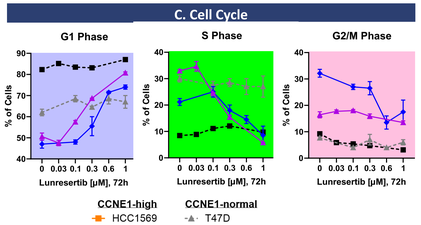
Figure 5. Novel, potent, and selective PKMYT1 inhibitors exhibit robust CCNE1-high cell killing, combination with chemotherapy, and sparing of non-tumorigenic cells. (A) Lunre and Arcus Compound 10 biochemical and cell-based potencies. Compared to lunre, Compound 10 is more potently **(B)** inhibits CDK1 pT14, **(C)** increases G1 and decreases S phases, **(D)** increases DNA damage, and **(E)** decreases viability of CCNE1-high cells. Compound 10 has minimal effect on non-tumorigenic MCF10A and hMEC cells. **(F)** Compound 10 synergizes with gemcitabine and SN38 in CCNE1-high cells. No combination between Compound 10 and chemotherapy is observed in hMEC cells.

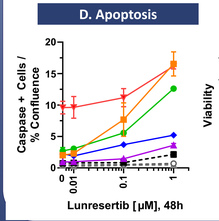


PKMYT1 Inhibition Inactivates the G2/M Checkpoint, Disrupts the Cell Cycle, and Induces Apoptosis in CCNE1-High Cancer Cells









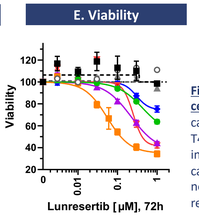


Figure 2. PKMYT1 inhibition inactivates the G2/M checkpoint, disrupting the cell cycle and inducing apoptosis in CCNE1-high cancer cells. In CCNE1-high cancer cells (including genetically engineered CCNE1 overexpressing T47D+CCNE1), PKMYT1 inhibition with lunre **(A)** decreases CDK1 pT14, **(B)** increases mitotic entry, **(C)** increases G1 and decreases S phase, **(D)** increases caspase3/7 activity, and **(E)** decreases viability. CCNE1-normal (T47D) and non-tumorigenic (MCF10A, hMEC) cells exhibit little to no changes in response to PKMYT1 inhibition.

Conclusions

- PKMYT1 inhibition inactivates the G2/M checkpoint, disrupting the cell cycle and inducing apoptosis in CCNE1-high cancer cells.
- Single agent PKMYT1 inhibition decreases tumor growth in CCNE1-high xenografts, and this tumor growth inhibition correlates with increased mitotic entry propagating DNA damage.
- PKMYT1 inhibition synergizes with chemotherapy in CCNE1-high cancer cells *in vitro* and *in vivo*. Single agent chemotherapy increases dependence on the G2/M checkpoint (CDK1 pT14), which PKMYT1 inhibition decreases, resulting in high levels of replication stress.
- Novel, potent, and selective PKMYT1 inhibitors exhibit robust CCNE1-high cell killing, combination with chemotherapy, and sparing of non-tumorigenic cells.

Contact Information: shodge@arcusbio.com **Poster available at** https://arcusbio.com/our-science/publications/