#3230

DISCOVERY OF SELECTIVE BRM (SMARCA2) ATPASE INHIBITORS FOR THE TREATMENT OF BRG1 (SMARCA4) MUTANT CANCERS

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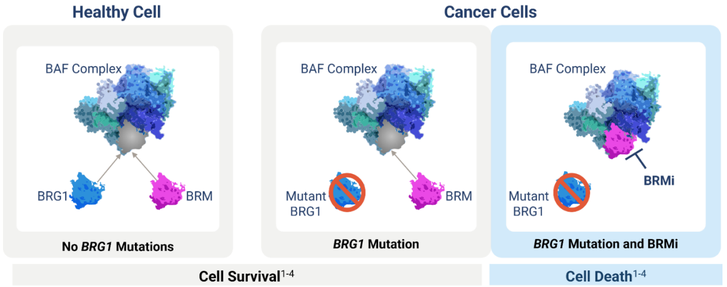
Background

BRM (SMARCA2) and BRG1 (SMARCA4) comprise the catalytic ATPase subunits of the BAF complexes. Either BRM or BRG1 must be present in the BAF complexes for chromatin remodeling to occur. BRM and BRG1 can compensate for each other in cases where one of the paralogs has been lost or damaged. Functional genomic screens have shown a synthetic lethal relationship between BRM and BRG1[2-5].

Gene ID[3]	Protein ID[3]
SMARCA2/BRM	SMARCA2/BRM
SMARCA4/BRG1	SMARCA4/BRG1



In normal cells, which express both BRM and BRG1, BRG1 can compensate for the inhibition of BRM.[3-6] One of the most frequently mutated BAF subunits in cancer is BRG1(SMARCA4). BRG1 mutations are found in a diverse set of cancers including in ~10% of NSCLC.[3] *BRG1* mutant cancer cells are dependent exclusively on BRM ATPase for survival. Selectively targeting BRM ATPase is a potentially effective therapeutic option for *BRG1* mutated cancers.[3-6]

Here, we report the identification and characterization of LY4050784 (aka FHD-909), a novel, highly potent BRM inhibitor that selectively inhibits BRM over BRG1.

Table 1. LY4050784 is a selective inhibitor of BRM-mediated transcription and cell proliferation

Cell-based assays			IC_{50} (nM)
Transcriptional reporter assays	A549-MMTV	BRM-dependent	1.3
	MDA-MMTV	BRG1-dependent	40
	Bin67-Ubc-Luc	BRM and BRG1-independent	>680
Cell Proliferation assays	A549	BRG1 mutant	0.7
	SBC5	BRG1 and BRM deficient	400

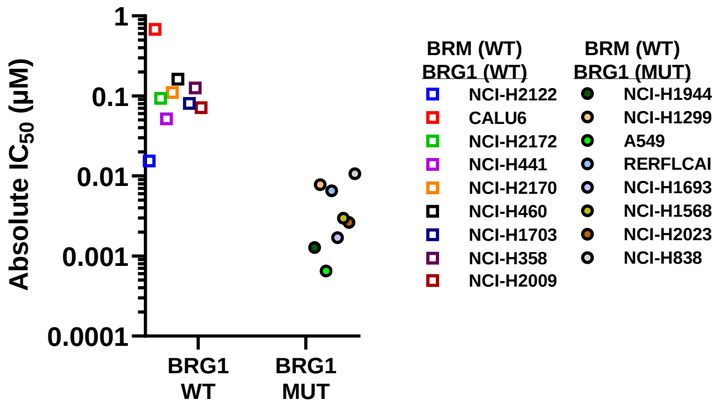
IC_{50} values are corrected for FBS binding. A549 are NSCLC (non-small cell lung cancer); Bin67-Ubc-Luc are SCCOHT (ovarian); SBC5 are SCLC (small cell lung cancer)

In kinase, binding, and functional panels, LY4050784 shows minimal off-target activity

References

1. Zhang B, et al. *Nat Commun*. 2021;12(1):1275; 2. Jancewicz I, et al. *Epigenetics Chromatin*. 2019; 12(1):68; 3. Papillon JPN, et al. *J Med Chem*. 2018;61(22):10155-10172; 4. Helming KC, et al. *Cancer Cell*. 2014;26(3):309-317; 5. Wilson BG, et al. *Mol Cell Biol.* 2014;34(6):1136-1144; 6. Hoffman GR, et al. *Proc Natl Acad Sci U S A*. 2014;111(8):3128-3133.

Fig 1. LY4050784 exhibits more potent anti-proliferative activity in BRG1 mutant cell lines than wild-type cell lines

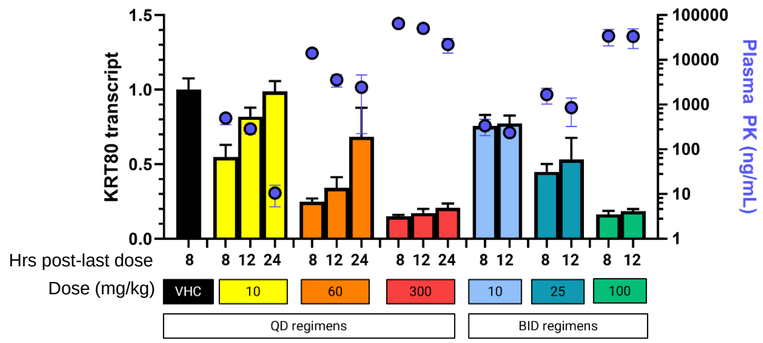


	Median IC_{50} (μM)
BRG1 WT	0.0932
BRG1 MUT	0.0028
Fold diff	33x

IC_{50} values are corrected for FBS binding

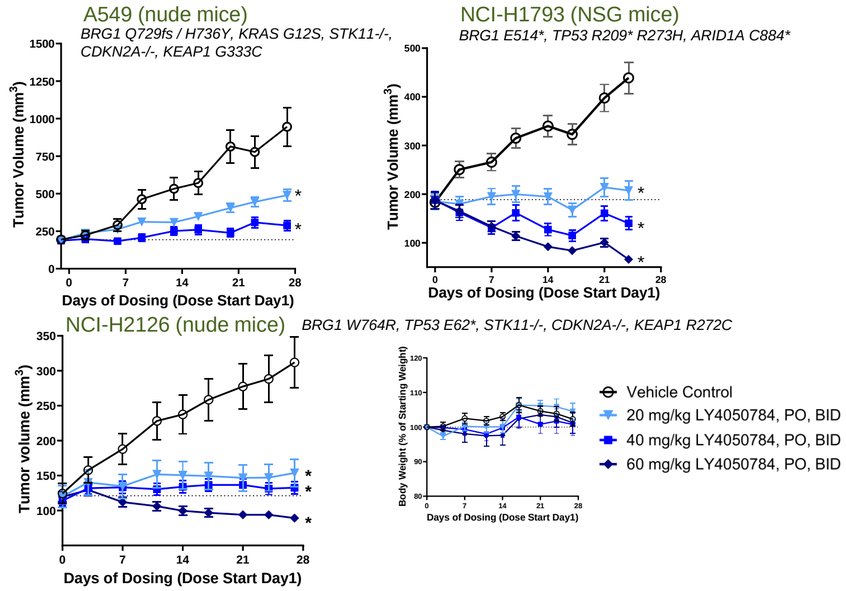
The median IC_{50} of the BRG1 WT cell lines is 33-fold higher than median IC_{50} of the BRG1 mutant cell lines. 9 BRG1 WT and 8 BRG1 MUT cell lines were treated with LY4050784 in a proliferation assay for 10 days. Cell viability was measured using Cell Titer Glo.

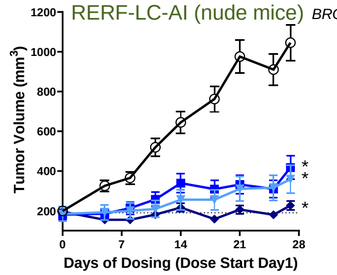
Fig 2. Orally administered LY4050784 demonstrates dose- and time-dependent target inhibition that correlates to exposure



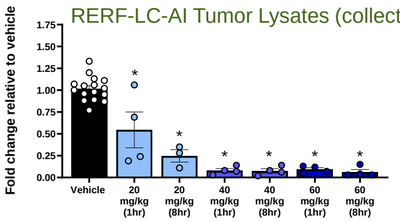
Bars show mean ± SEM *KRT80* mRNA/transcript levels normalized to vehicle (VHC) control; dots represent mean ± SEM PK values. n=4 mice per group. Mice carrying NCI-H1299 xenografts were treated with indicated doses of oral LY4050784 for 3 days. At the indicated times (hours post-last dose), tumors were collected, mRNA was extracted, and qPCR performed to quantitate *KRT80* transcript levels (BRM target gene).

Fig 3. LY4050784 demonstrates significant anti-tumor efficacy in BRG1 mutant lung cancer xenografts





Data are mean ± SEM. *p ≤ 0.001 compared to vehicle control. A549, NCI-H1793, NCI-H2126, or RERF-LC-AI cells were implanted into mice and treated with LY4050784 at indicated doses. All doses were well-tolerated. Dosing holidays were applied at the high dose, as appropriate.



qPCR was performed from tumors collected from RERF-LC-AI cells at the indicated times (hours post-last dose).
qPCR shows the dose-dependent reduction of BRM target gene, *KRT80*, transcript levels.
*p ≤ 0.001 compared to vehicle control.

Conclusions

LY4050784

- is a first-in-class, potent, and selective BRM inhibitor designed to provide therapeutic intervention in patients with BRG1 (SMARCA4)-mutated or deficient cancers
- exhibits >30-fold selectivity against BRM over BRG1 in cell-based assays
- has excellent oral pharmacokinetics
- inhibits BRM target gene expression that correlates with compound exposures *in vivo*
- demonstrates robust anti-tumor activity yielding consistent tumor growth arrest and regression across multiple murine xenograft models of BRG1 (SMARCA4)-mutated non-small cell lung cancer

An IND submission is planned for Q2 of 2024