Discovery of a Novel SOS1-KRASmulti Inhibitor, HM101207, Demonstrates a Broad-Spectrum Antitumor Activity across KRAS-MAPK Mutant Cancers

#LB429

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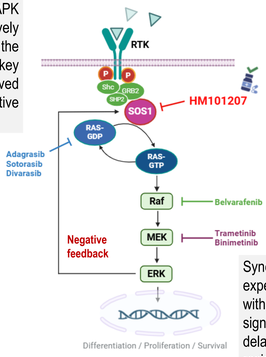
Introduction

The RAS subfamily is a well-known oncogene with the highest mutation rate and poor prognosis among various cancers[1]. Among the RAS subfamily, KRAS is the most frequent mutation isoform, especially with a prevalence of approximately 35%~90% in NSCLC, CRC, and PDAC[2,3]. KRAS protein cycles between "off" (inactive) and "on" (active) states induce downstream signal transduction to promote cell proliferation and survival. Son of sevenless homolog 1 (SOS1) is one of guanine nucleotide exchange factor (GEF) responsible for a binary molecular switch to activate KRAS as well as a node in the negative feedback loop in the RTK-KRAS-MAPK signaling pathway. Targeting SOS1-KRAS interaction has the potential to modulate the GDP-bound state of pan-KRAS, enabling to suppress the various KRAS-driven cancers.

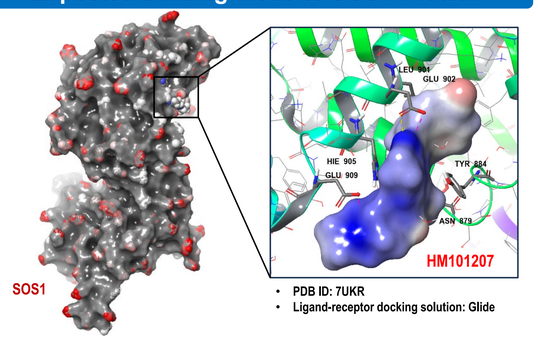
Schematic Signaling Pathway of SOS1 to KRAS[4]

Aberrant activation of MAPK signaling can be effectively attenuated through the inhibition of SOS1, a key upstream regulator involved in the pathway's negative feedback.[5]



Synergistic effects can be expected when combined with upstream/downstream signal target inhibitors and delay the development of resistance.

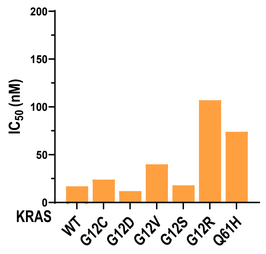
Expected Binding Mode to SOS1 Protein



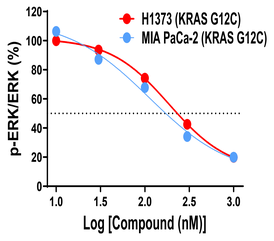
- PDB ID: 7UKR
- Ligand-receptor docking solution: Glide

Pharmacological & Pharmacokinetic Profiles

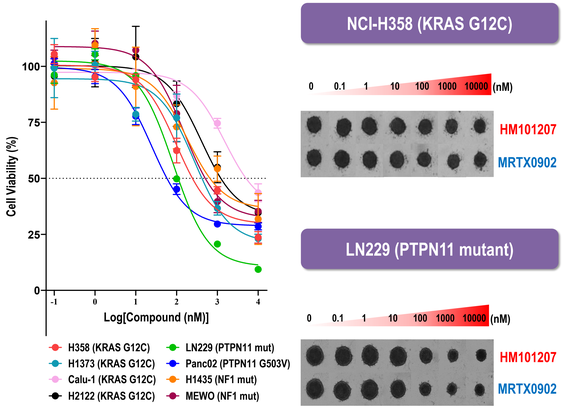
A. Target inhibition activity to SOS1-KRAS GTP exchange



B. Inhibition of ERK phosphorylation



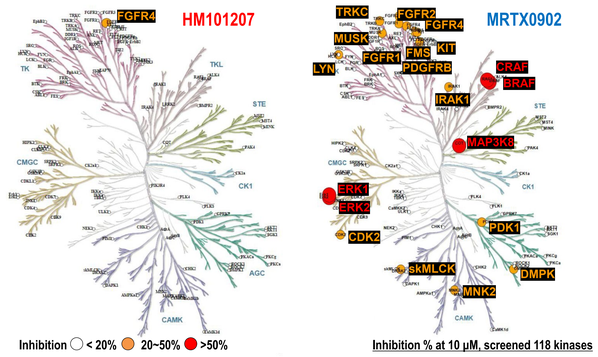
C. Anti-cancer activity of 3D spheroid growth in KRAS-MAPK pathway mutant cancer cell lines



D. Pharmacokinetic profiles

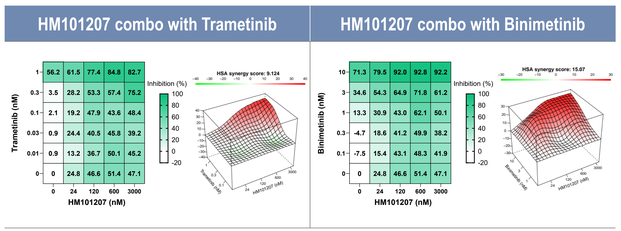
	Compound	HM101207
In vitro	Plasma stability	Moderate to highly stable (for all species)
	CYP isozyme inhibition	Very weak (for 7 isozymes)
	CYP3A TDI	Not calculatable (No TDI)
	PPB	Highly unbound fraction (for all species)
In vivo	Mouse / Rat / Dog	High bioavailability (≥85%)

In vitro Kinase Panel Assay of HM101207 *vs.* MRTX0902



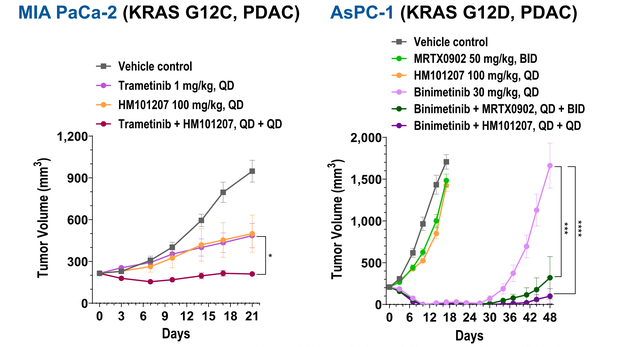
Combination with MEK Inhibitors in KRAS Mutant Cancers[6]

A. *In vitro* synergism (HSA synergy score)



Synergy score analysis by SynergyFinder.: From -10 to 10: The interaction between two drugs is likely to be additive; Larger than 10: The interaction between two drugs is likely to be synergistic

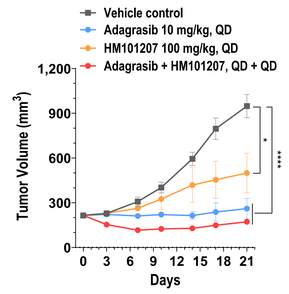
B. *In vivo* efficacy (Xenograft model)

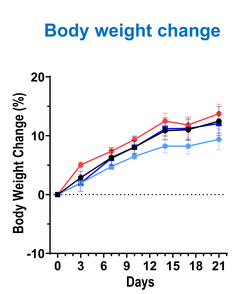


Mean ± SEM / * p<0.05, ***p<0.001, **** p<0.0001 *vs.* MEK inhibitor alone, Data were analyzed using a mixed-effects model

Combination with Adagrasib in KRAS G12C Mutant Cancers

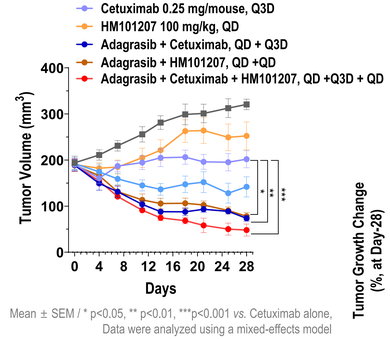
MIA PaCa-2 (PDAC)

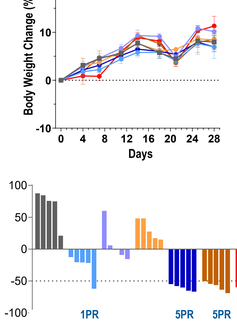




Mean ± SEM / * p<0.05, **** p<0.0001 *vs.* Vehicle control, Data were analyzed using a mixed-effects model

SW837 (CRC)





Mean ± SEM / * p<0.05, ** p<0.01, ***p<0.001 *vs.* Cetuximab alone, Data were analyzed using a mixed-effects model

Concluding Remarks

- HM101207, a SOS1-KRASmulti inhibitor, presents a druggable profile as pan-KRAS therapeutics in KRAS-mutated cancers.
- This study revealed HM101207 as a therapeutics in patients with KRAS-addicted cancers by inhibition of KRAS signaling as well as interruption of negative feedback loop.
- *In vitro* and *in vivo* studies proved synergistic effects of SOS1 inhibitors when combined with KRAS G12C or MEK inhibitors.
- HM101207 is currently preparing IND enabling GLP-toxicity studies and expected to begin in 2H 2025.

References

1) Singhal A, *et al*., *Nature Medicine*., 30, **2024**, 969–983;
2) Uprety D, *et al*., *Cancer Treatment Reviews*., 89, **2020**, 102070;
3) Herdeis L, *et al*., *Current Opinion in Structural Biology*., 71, **2021**, 136–147;
4) Schematic illustration was created with BioRender.com;
5) Marasco M, *et al*., *Cell Reports Medicine*, 5, **2024**, 101818;
6) Pantsar T, *et al*., *Comput Struct Biotechnol J*., 18, **2020**, 189–198.

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