Preclinical characteristic of HMPL-306, a CNS-penetrable dual inhibitor of mutant IDH1 and IDH2

Abstract #543

Na Yang, Jia Hu, Tingwen Li, Zeyu Zhong, Jian Wang, Yang Sai, Weiguo Qing, Guangxiu Dai, Yongxin Ren, Michael Shi and Weiguo Su
HUTCHMED. Building 4, 720 Cai Lun Road, Z.J. Hi-Tech Park, Shanghai, China, 201203

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INTRODUCTION

- Mutations in isocitrate dehydrogenase (IDH) 1 or 2 are frequently identified in several cancers [1]. Accumulated 2-HG caused by mutant IDHs (mIDHs) leads to blockage of cell differentiation, thereby induces malignant transformation.
- Rare cases were identified carrying co-existing mutations in IDH1 and IDH2. mIDH isoform switching from mIDH1 to mIDH2 and vice versa, have been reported as a mechanism of acquired resistance to IDH inhibition [2]. Thus, simultaneous inhibition on both mIDH1 and mIDH2 may be a promising strategy to overcome resistance and improve clinical efficacy.
- HMPL-306, a dual inhibitor of mIDH1 and mIDH2, developed by HUTCHMED, is being evaluated in clinical trials (NCT04272957, NCT04764474 & NCT04762602).

RESULTS

A. HMPL-306 is a dual IDH1/2 inhibitor

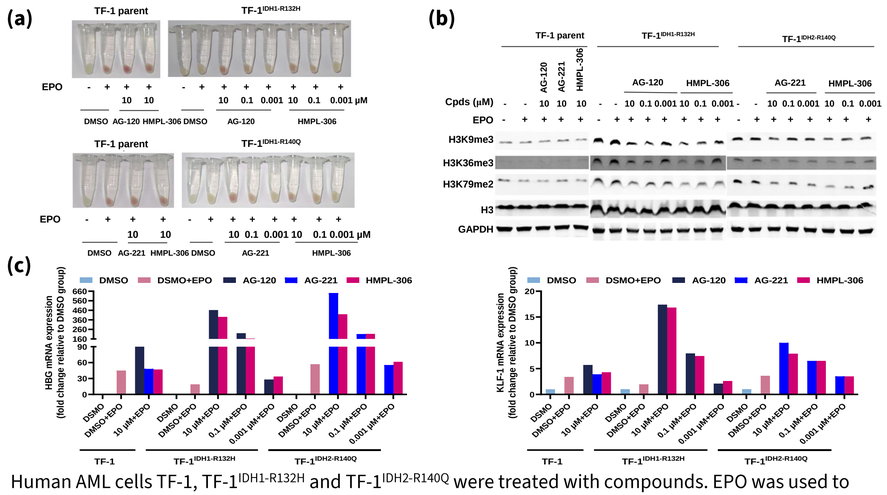
Cellular activities of IDH inhibitors were measured by 2-HG production in cells harboring IDH mutations

	HMPL-306	AG-120	AG-221
Inhibition of Activity of IDH1/2 Mutations in Cells (IC_{50}, μM)			
U87MG$^{IDH1-R132H}$	0.050	0.032	ND
TF1$^{IDH1-R132H}$	0.031	0.068	ND
HT1080 (IDH1-R132C)	0.026	0.009	ND
U87MG $^{IDH2-R140Q}$	0.031	ND	0.043
TF-1$^{IDH2-R140Q}$	0.021	ND	0.055
HEK293$^{IDH2-R172K}$	0.425	ND	5.169
Selectivity (IC_{50}, μM)			
322 Kinase panel	>10	ND	ND
Cerep safety panel (IR %@ 10 μM)			
PDE4D2	64.5	ND	6.7
A2A	43.3	ND	64.3
Adenosine transporter	32.7	ND	98.1
A1	31.4	ND	88.0
CCK1	-8.0	ND	85.5
A3 (antagonist effect)	IC_{50}=8.5 μM	ND	IC_{50}=0.012 μM
Other 82 targets	<50	ND	<50

Abbreviations: IC_{50}= Half maximal inhibitory concentration; ND = not determined. Data are mean value.

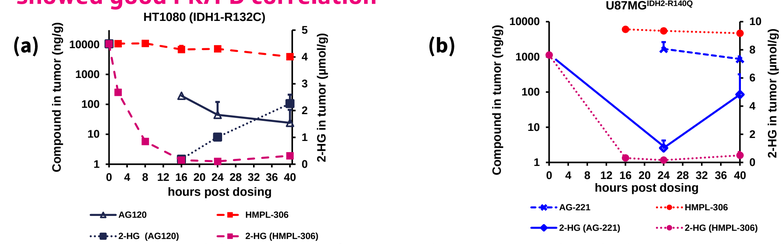
1. Cairns RA. Et al. Cancer Discov. 2013;3 (7):730-741
2. Harding JJ. et al. Cancer Discov.. 2018;8 (12):1540-1547

B. HMPL-306 restore EPO induced cell differentiation in cells harboring mIDHs



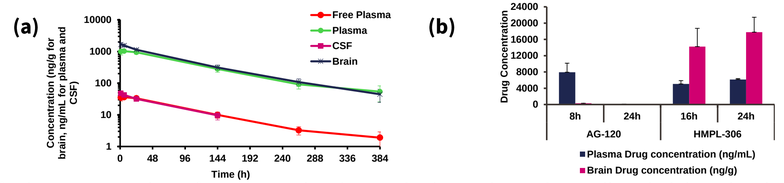
Human AML cells TF-1, TF-1$^{IDH1-R132H}$ and TF-1$^{IDH2-R140Q}$ were treated with compounds. EPO was used to induce erythroid cell differentiation. Hemoglobinization (red color change) **(a)**, the histones methylation in cells by WB **(b)** and KLF1 and HBG RNA levels by qRT-PCR **(c)** were shown.

C. HMPL-306 reduced 2-HG levels in the mIDH tumor xenograft models and showed good PK/PD correlation



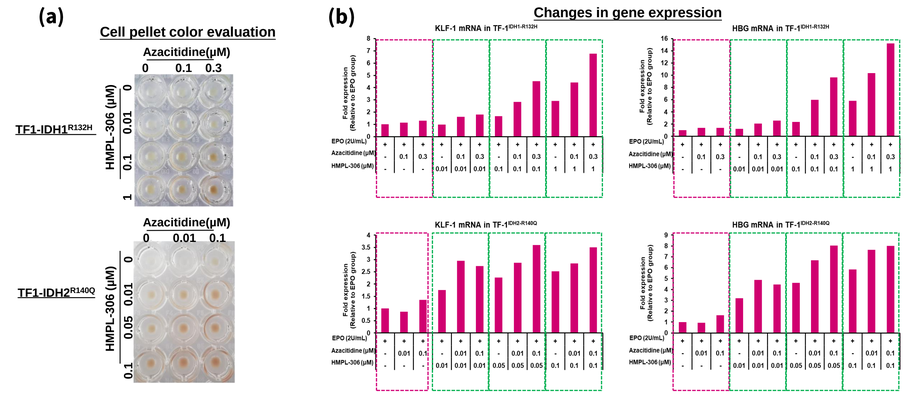
2-HG concentration and the exposure of compounds in tumors with oral administration was detected and analyzed in HT1080 (IDH-R132C) **(a)** and U87MG$^{IDH-R142Q}$ **(b)** subcutaneous xenograft models. Data was shown in mean±SD

D. HMPL-306 showed high brain penetration in rodents



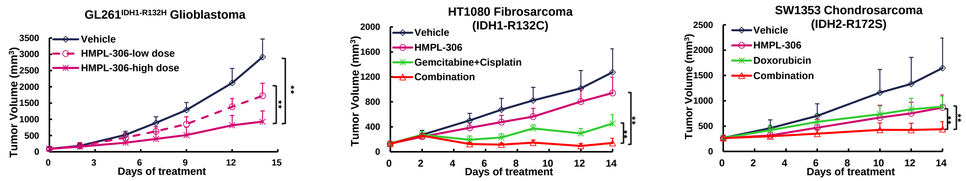
(a) The concentration of HMPL-306 in plasma, brain, and CSF by orally administration in rats (n=6). The concentration of free fraction of HMPL-306 in plasma was calculated using rat plasma PPB (96.47%).
(b). Concentration of HMPL-306 and AG-120 in mice plasma and brain after oral administration. Data was shown in mean±SD.

E. HMPL-306 in combination with azacitidine in the TF1-IDH1^{R132H} or TF1-IDH2^{R140Q} AML cell line increased cell differentiation



Human TF-1, TF-1$^{IDH1-R132H}$ and TF-1$^{IDH2-R140Q}$ cell lines were treated with DMSO, HMPL-306, Azacitidine, or their combination. EPO was used to induce erythroid cell differentiation. Hemoglobinization was evaluated by color change, and KLF1 and HBG mRNA levels was determined by qRT-PCR.

F. HMPL-306 exhibited dose-dependent tumor growth inhibition in mIDH xenograft models and the improved efficacy when combined with chemotherapies



The tumor models were established by subcutaneously implanting tumor cells into immune-deficient mice. HMPL-306 was dosed once daily by oral gavage. Gemcitabine and doxorubicin was administered through intravenous injection once weekly. Cisplatin was administered through intraperitoneal injection once weekly. Data was shown in mean±SD**: P<0.01.

SUMMARY

- **HMPL-306 is a selective and highly potent dual inhibitor targeting IDH 1/2 mutation.**
- **HMPL-306 suppressed 2-HG levels in cells and xenograft tumors through inhibition of both IDH1 and IDH2 mutations.**
- **HMPL-306 showed high brain penetration which was a desirable feature for glioma therapy.**
- **The preclinical studies support clinical evaluations of HMPL-306 as either a single agent or in combination with other therapeutic agents for the treatment of hematologic malignancies and solid tumors with IDH mutation.**