JAB-30355: a highly potent, orally bioavailable p53 Y220C reactivator

Abstract #5940

Qian Zheng, Peng Wang, Chen Liang, Yao Li, Xin Sun, Amin Li, Wei Zhang, Wei Long, Yanping Wang
Address: Jacobio Pharmaceuticals Co., Ltd., Beijing, China
Correspondence: qian.zheng@jacobiopharma.com

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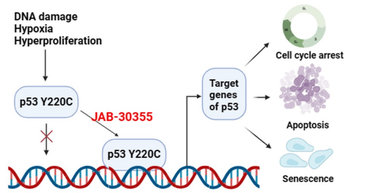
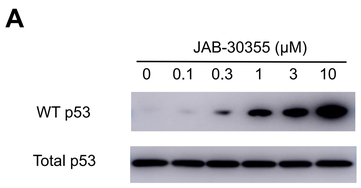
Background

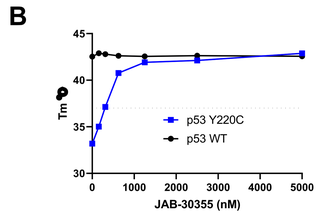
As a key tumor suppressor, p53 precisely regulates cellular events such as cell cycle arrest, apoptosis, senescence, and DNA repair under physiological conditions. The TP53 Y220C is a hotspot loss-of-function mutation occurring in around 1% of solid tumors. Application of p53 Y220C reactivator for restoration of p53 function represents a promising treatment strategy for patients with this mutation.

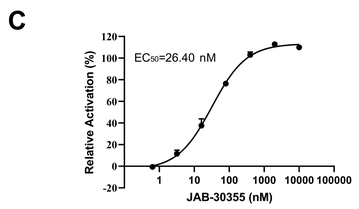


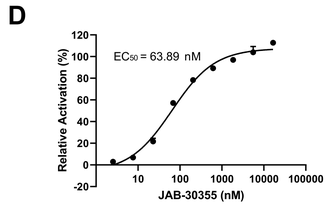
We have developed JAB-30355, a highly potent, selective, and orally bioavailable p53 Y220C reactivator with promising preclinical data. JAB-30355 exhibited dose-dependent anti-tumor activity, inducing tumor stasis or regression in multiple CDX and PDX models of ovarian cancer, pancreatic cancer, gastric cancer, and small cell lung cancer, with overall good tolerability. A phase 1/2a clinical trial to evaluate the safety and efficacy of JAB-30355 in patients with advanced solid tumors is ongoing in the US.

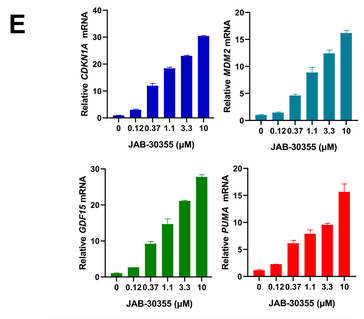
JAB-30355 restores p53 Y220C conformation and transcriptional activity

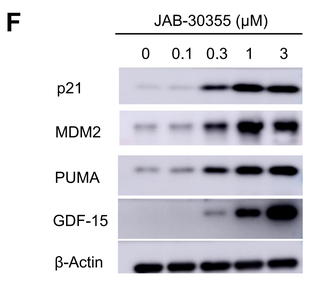


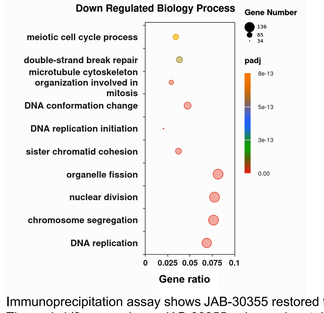


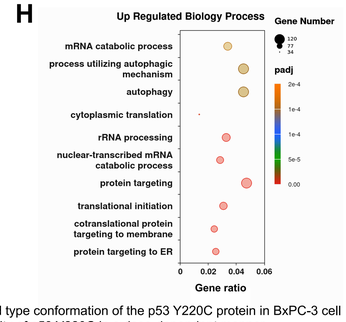






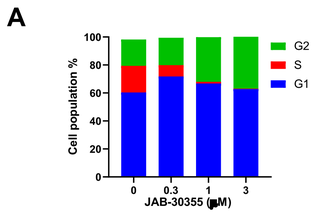


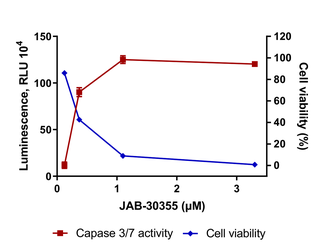


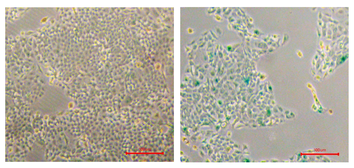


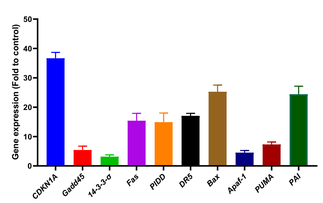
A. Immunoprecipitation assay shows JAB-30355 restored the wild type conformation of the p53 Y220C protein in BxPC-3 cell
B. Thermal shift assay shows JAB-30355 enhanced protein stability of p53 Y220C in a dose-dependent manner
C. DNA Binding assay shows JAB-30355 enhanced the DNA binding activity of p53 Y220C in a dose-dependent manner
D. Cellular reporter assay shows JAB-30355 enhanced p53 Y220C cellular transcriptional activity in NUGC3 cells
E. qPCR assay shows JAB-30355 induced the transcription of p53 target genes in BxPC-3 cells
F. Western blot assay shows JAB-30355 induced the protein expression of p53 target genes in BxPC-3 cells
G. RNA Sequence analyses show JAB-30355 significantly down-regulated pathways involved in cell division and DNA replication in BxPC-3 cells
H. RNA Sequence analyses show JAB-30355 significantly up-regulated pathways involved in protein translocation and RNA processing in BxPC-3 cells

JAB-30355 induces cell cycle arrest, apoptosis and senescence









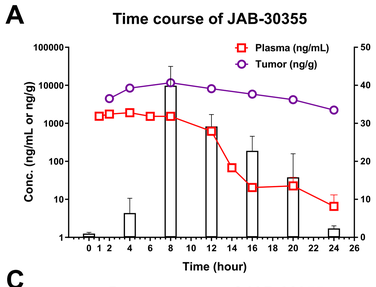
A. FACS assay shows JAB-30355 induced cell arrest in G1 and G2 phase in BxPC-3 cells
B. Caspase 3/7 assay shows JAB-30355 induced apoptosis of MFE-296 cells
C. β–gal staining assay shows JAB-30355 induced senescence of BxPC-3 cells, scale bar is 100μm
D. qPCR assay shows JAB-30355 induced the expression of genes involved in cell cycle arrest, apoptosis and senescence

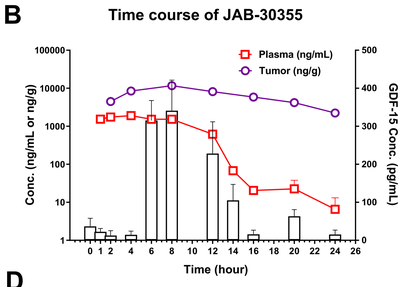
JAB-30355 inhibits the growth of cancer cells harboring TP53 Y220C

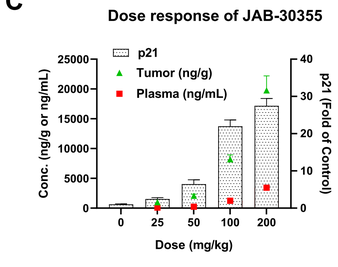
Cell Lines	Tumor Type	TP53 Status	IC_{50} (μM)	Cell Lines	Cell type	TP53	IC_{50}(μM)
BxPC-3	Pancreatic cancer	Y220C	0.17	HUH-7	Hepatic carcinoma	Y220C	0.23
MFE-296	Endometrial cancer	Y220C	0.71	KON	Oral squamous carcinoma	Y220C	0.68
NUGC-3	Gastric cancer	Y220C	0.25	RKN	Ovarian cancer	R175H	>10
NCI-H2085	NSCLC	Y220C	0.28	Calu-1	NSCLC	Null	>10
HCC2935	NSCLC	Y220C	0.19	NUGC-4	Gastric cancer	WT	>10
HCC366	NSCLC	Y220C	0.44	A549	NSCLC	WT	>10
NCI-H2342	NSCLC	Y220C	0.19	MRC-5	Normal Lung fibroblast	WT	>10

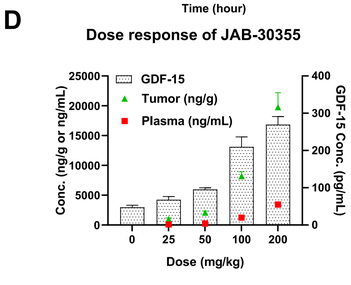
Cell viability assay shows JAB-30355 inhibited the viability of multiple TP53 Y220C mutated cancer cell lines with IC_{50}s ranging from 0.2 to 0.7 μM, and exhibited good selectivity against TP53 wild-type cells, TP53 null cells and TP53 R175H cells

PK/PD study of JAB-30355 in BxPC-3 xenograft model



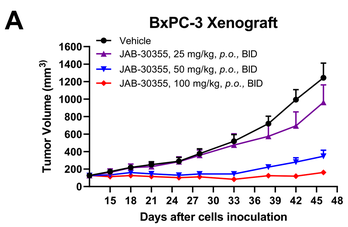


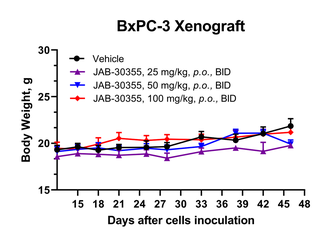


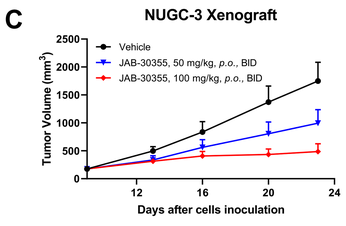


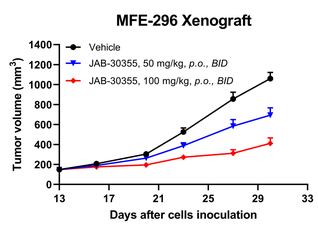
A. Time course of p21 expression in tumor and JAB-30355 concentrations in plasma and tumor in BxPC-3 xenograft.
B. Time course of GDF-15 expression in plasma and JAB-30355 concentrations in plasma and tumor in BxPC-3 xenograft.
C. Dose-dependent increase of p21 expression in tumor and increase of JAB-30355 concentrations in plasma and tumor in BxPC-3 xenograft.
D. Dose-dependent increase of GDF-15 in plasma and increase of JAB-30355 concentrations in plasma and tumor in BxPC-3 xenograft
(A-B) 4 mice/group (C-D) 5 mice/group

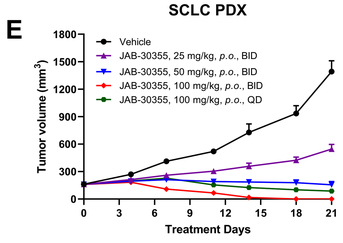
JAB-30355 exhibits potent anti-tumor activity *in vivo*

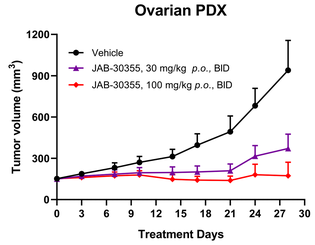






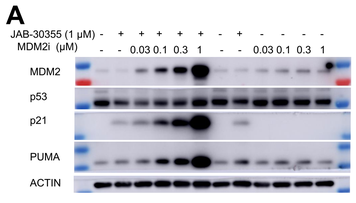


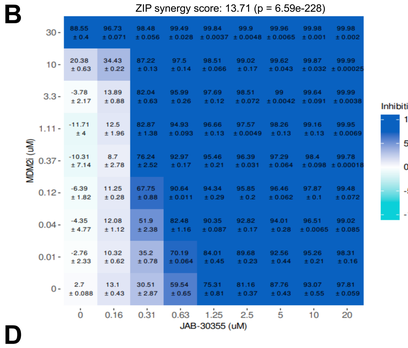


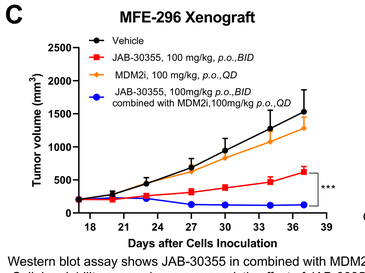


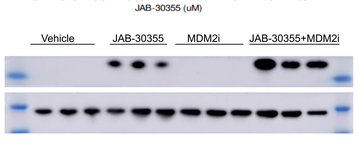
A. Tumor volume change during the treatment of JAB-30355 at indicated doses in BxPC-3 xenograft model.
B. Body weight change during the treatment of JAB-30355 at indicated doses in BxPC-3 xenograft model.
C-D. Tumor volume change during the treatment of JAB-30355 at indicated doses in NUGC-3 xenograft model and MFE-296 xenograft model.
E-F. Tumor volume change during the treatment of JAB-30355 at indicated doses in SCLC PDX and ovarian PDX.
(A-E) 6 mice/group (F) 4 mice/group

JAB-30355 in combination with MDM2i shows enhanced anti-tumor effect









A. Western blot assay shows JAB-30355 in combined with MDM2 inhibitor increased protein expression of p53 target genes in MFE-296 Cells
B. Cellular viability assay shows a synergistic effect of JAB-30355 combined with MDM2 inhibitor in MFE-296 cells
C. *In vivo* MFE-296 xenograft assay shows JAB-30355 combined with MDM2i significantly enhanced the anti-tumor effect
D. Western blot assay shows a higher level of p21 in the MFE-296 tumor tissue of the combination group than monotherapy group

Conclusions

- JAB-30355 is a highly potent, selective, orally bioavailable p53 Y220C reactivator.
- JAB-30355 efficiently restores the protein structure, thermal stability and DNA binding activity of p53 Y220C
- JAB-30355 reactivates p53 signaling pathway and promotes cell cycle arrest, apoptosis and senescence to inhibit the viability of TP53 Y220C mutant cancer cells.
- JAB-30355 shows good PK/PD relationship and strong anti-tumor activity both as monotherapy and in combination with MDM2 inhibitor in multiple CDX and PDX models.

Reference

1) Nat Rev Drug Discov. 2023 Feb;22(2):127-144
2) Nat Rev Cancer . 2018 Feb;18(2):89-102.

Acknowledgment

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