MK256 is a novel CDK8 inhibitor with potent antitumor activity in AML through downregulation of the STAT pathway

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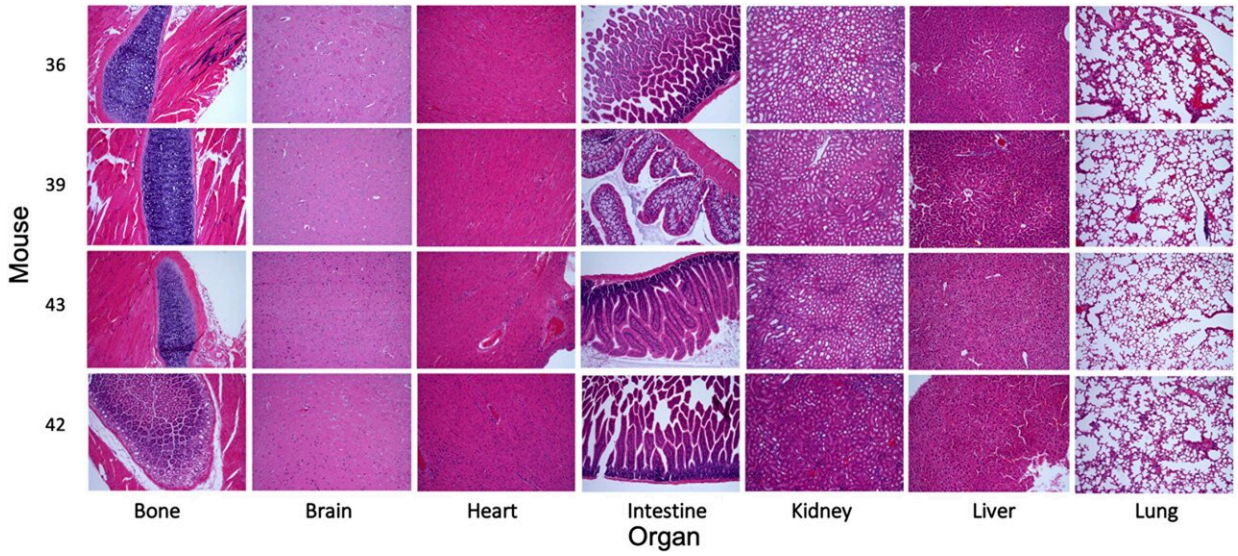

Evaluation of the toxicity of MK256 in vivo. Credit: *Oncotarget* (2022). DOI: 10.18632/oncotarget.28305

A new research paper titled "MK256 is a novel CDK8 inhibitor with potent antitumor activity in AML through downregulation of the STAT pathway" has been published in *Oncotarget*.

Acute myeloid leukemia (AML) is the most lethal form of AML due to disease relapse. Cyclin-dependent kinase 8 (CDK8) is a serine/threonine

kinase that belongs to the family of cyclin-dependent kinases and is an emerging target for the treatment of AML. MK256, a potent, selective, and orally available CDK8 inhibitor, was developed to target AML.

In this new study, researchers Jen-Chieh Lee, Shu Liu, Yucheng Wang, You Liang, and David M. Jablons from the University of California San Francisco and Touro University sought to examine the anticancer effect of MK256 on AML.

"In CD34+/CD38- leukemia stem cells, we found that MK256 induced differentiation and maturation," the researchers wrote.

Treatment of MK256 inhibited proliferation of AML cell lines. Further studies of the inhibitory effect suggested that MK256 not only downregulated phosphorylated STAT1(S727) and STAT5(S726), but also lowered mRNA expressions of MCL-1 and CCL2 in AML cell lines. Efficacy of MK256 was shown in MOLM-14 xenograft models, and the inhibitory effect on phosphorylated STAT1(S727) and STAT5(S726) with treatment of MK256 was observed in vivo.

Pharmacologic dynamics study of MK256 in MOLM-14 xenograft models showed dose-dependent inhibition of the STAT pathway. Both in vitro and in vivo studies suggested that MK256 could effectively downregulate the STAT pathway. In vitro ADME, pharmacological kinetics, and toxicity of MK256 were profiled to evaluate the drug properties of MK256.

The researchers concluded, "Our results show that MK256 is a novel CDK8 inhibitor with a desirable efficacy and safety profile and has great potential to be a promising drug candidate for AML through regulating the STAT pathway."

More information: Jen-Chieh Lee et al, MK256 is a novel CDK8

inhibitor with potent antitumor activity in AML through downregulation of the STAT pathway, *Oncotarget* (2022). DOI: 10.18632/oncotarget.28305