229 Small Molecule Inhibitors of KDM5 histone demethylases

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Lead Identification/optimization
Target(MoA)	KDM5A/B histone inhibitor
Brief Description	• KDM5A/B histone demethylases are amplified and overexpression in multiple solid tumors, making these enzymes ideal targets for cancer therapy • KDM5B loss/inhibition induced robust antitumor immune response, leading to prolong survival of tumor bearing mice in multiple models (Figure below) • Specific inhibitors of KDM5 inhibitors (IC50s of ~20 nM) have been identified. 35 high-resolution crystal structures (1.22-2.29 Å) of KDM5A with various inhibitors are available to support further medicinal chemistry optimization
Organization	Yale University

Differentiation

□ **KDM5 family in cancer**

- The KDM5 family has been implicated in the pathogenesis of several types of cancer and plays a role in drug resistance and in metastasis
- KDM5A is amplified or overexpressed in breast cancer, lung cancer, hepatocellular carcinoma, and gastric cancers. It has been linked to the control of proliferation and senescence by antagonizing the functions of retinoblastoma protein and through direct repression of cyclin-dependent kinase inhibitor genes. Knockout of KDM5A significantly prolonged survival in genetically engineered mouse tumor models
- KDM5B is similarly overexpressed in a variety of cancers, including breast cancer and others, and is associated with a poor prognosis, chemoresistance, and metastasis. KDM5A plays a role in the epithelial–mesenchymal transition and the suppression of invasion and metastasis
- Increased levels of KDM5A have been shown to confer anticancer drug resistance in lung cancer, breast cancer, and glioblastoma

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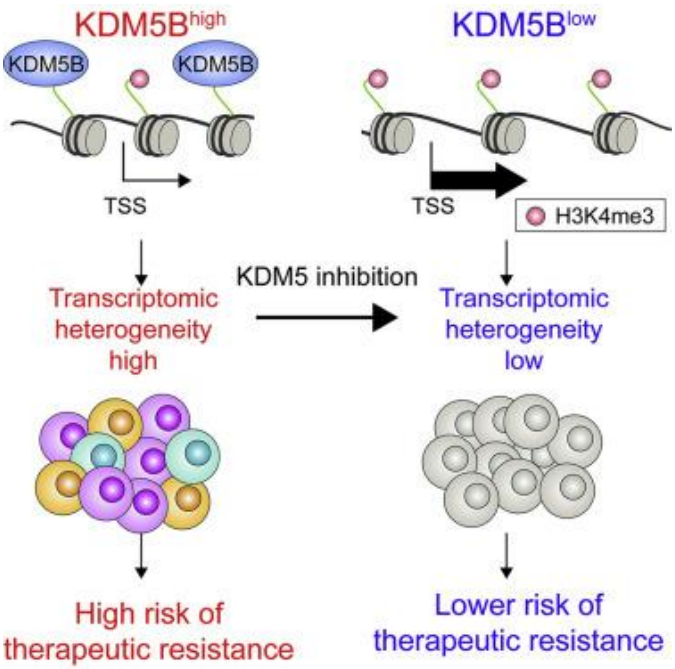
Key Data

KDM5 Histone Demethylase Activity Links Cellular Transcriptomic Heterogeneity to Therapeutic Resistance



Members of the KDM5 histone H3 lysine 4 demethylase family are associated with therapeutic resistance. Inhibition of KDM5 activity increases sensitivity to anti-cancer drugs by decreasing cellular transcriptomic heterogeneity. Anti cancer resistance is due to selection for pre-existing genetically distinct cells, while KDM5 inhibitor resistance is acquired.

Cancer Cell. 2018 Dec 10;34(6):939-953.e9.

Antitumor effect of Small Molecule Inhibitors of KDM5 histone demethylases

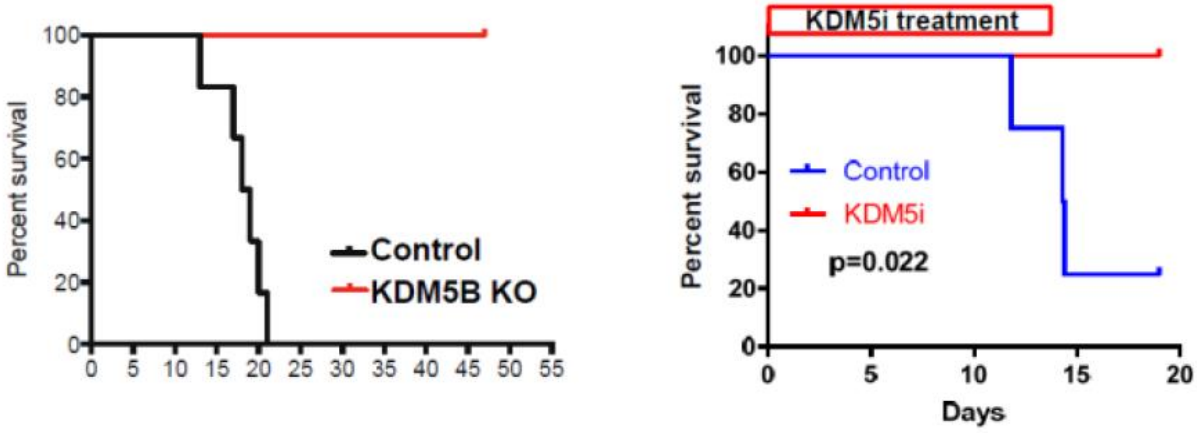


Figure : KDM5B loss (left panel) or KDM5 inhibitor (KDM5i) treatment (right panel) significantly prolonged survival of melanoma bearing mice.

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Intellectual Property

Patent No.	US 2019-0151289 A1
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Status	Application Pending
Country	US

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