A First-in-class SMYD3 Inhibitor ZYZ384 Impairs Hepatocellular Carcinoma Tumor Growth *in vivo* via Reducing H3K4 Trimethylation of Rac1 Promoters

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ABSTRACT

SMYD3 (SET and MYND domain containing 3) is a histone lysine methyltransferase that is highly expressed in different types of cancer(s) and is a promising epigenetic target for the development of novel anti-tumor therapeutics. Currently, no selective inhibitors for this protein have been developed for cancer treatment. Therefore, the current study describes developing and characterizing a novel SMYD3 inhibitor. Virtual screening was initially used to identify a lead compound and followed up by modification to get the novel inhibitors. Several technologies were used to facilitate compound screening about the binding affinities and inhibition activities of these novel inhibitors with SMYD3 protein; the anti-tumor activity has been assessed in vitro using various cancer cell lines. In addition, a tumor-bearing nude mice model was established, and the activity of the selected molecule was determined *in vivo*. Both RNA-seq and chip-seq were performed to explore the anti-tumor mechanism. From this work, a novel SMYD3 inhibitor, ZYZ384 was

identified with anti-tumor activity and impaired hepatocellular carcinoma tumor growth by reducing H3K4 trimethylation of the Rac1 promoter triggering the tumor cell cycle arrest through the AKT pathway.

Keywords: SMYD3; Inhibitor; ZYZ384; Antitumor; H3K4me3; Rac1 promoter

Graphical abstract