Structure-Based Design of Y-Shaped Covalent TEAD Inhibitors Suppresses Defective Hippo Signaling

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The transcription factor TEAD, together with its coactivator YAP/TAZ, is a key transcriptional modulator of the Hippo pathway. Activation of TEAD transcription by YAP has been implicated in a number of malignancies, and this complex represents a promising target for drug discovery. However, both YAP and its extensive binding interfaces to TEAD have been difficult to address using small molecules, mainly due to a lack of druggable pockets[1]. Recently, TEADs were recognized as being palmitoylated in cells, which provides an opportunity to develop cysteine-directed covalent small molecules for TEAD inhibition[2]. Here, we employed covalent fragment screening approach followed by structure-based design to develop an irreversible TEAD inhibitor MYF-03–176. Using a range of in vitro and cell-based assays we demonstrated that through a covalent binding with TEAD palmitate pocket, MYF-03–176 disrupts YAP-TEAD association, suppresses TEAD transcriptional activity and inhibits cell growth of Hippo signaling defective malignant pleural mesothelioma (MPM) in vitro and in vivo. Further, a cell viability screening with a panel of 903 cancer cell lines indicated a high correlation between TEAD-YAP dependency and the sensitivity to MYF-03–176 in cancer cells including those derived from mesothelioma and liposarcoma.

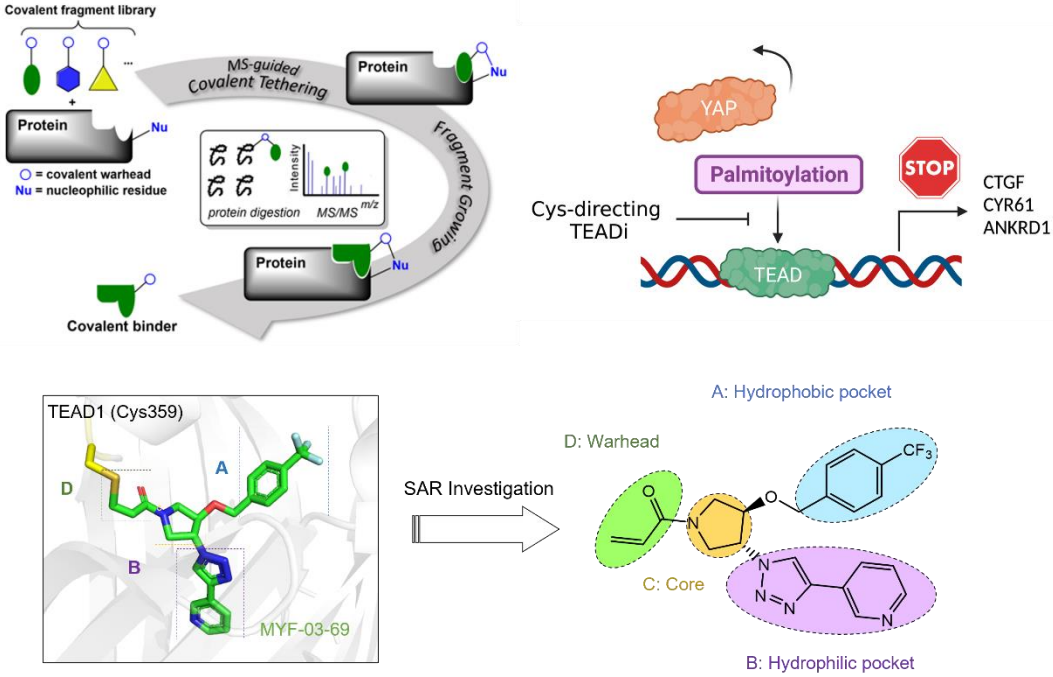

Figure 1. Covalent fragment screen led to the identification of Y-shaped TEAD inhibitors.

References

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2. Chan, P.; Han, X.; Zheng, B.; DeRan, M.; Yu, J.; Jarugumilli, G. K.; Deng, H.; Pan, D.; Luo, X.; Wu, X., Autopalmitoylation of TEAD proteins regulates transcriptional output of the Hippo pathway. *Nat Chem Biol* **2016,** *12* (4), 282-9.