Pharmacological validation of new kinase targets with small molecules

Xianming DENG*
State-province Joint Engineering Laboratory of Targeted Drugs from Natural Products, School of Life Sciences, Xiamen University, Xiamen, Fujian 361102, China.

Protein kinases have been a rich source of targets for drug discovery with 37 small molecules as approved therapeutics. However, most academic and industrial research remains focused on only a small fraction of the kinome for which evidence of therapeutic utility already exists. There's an emerging need to explore the untargeted kinome that have received scant attention.[1] Here we presented the new strategies including "pathway-specific" screening and "compound-centric" approach that led to the discovery of first-in-class kinases MST1/2 inhibitor (XMU-MP-1)[2] and breast tumor kinase (BRK/PTK6) inhibitor (XMU-MP-2)[3] with *in vivo* efficacy. These inhibitors will serve as valuable tools to pharmacologically interrogate MST1/2 and BRK biology, and they provide a starting point for medicinal chemistry efforts aimed at developing related targeted therapeutics.

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Keywords: Untargeted kinome, pathway-specific, compound-centric, first-in-class kinase inhibitors

References

[1] Elkins, J. M.; Fedele, V.; Szklarz, M.; Abdul Azeez, K. R.; Salah, E.; Mikolajczyk, J.; Romanov, S.; Sepetov, N.; Huang, X. P.; Roth, B. L.; Al Haj Zen, A.; Fourches, D.; Muratov, E.; Tropsha, A.; Morris, J.; Teicher, B. A.; Kunkel, M.; Polley, E.; Lackey, K. E.; Atkinson, F. L.; Overington, J. P.; Bamborough, P.; Muller, S.; Price, D. J.; Willson, T. M.; Drewry, D. H.; Knapp, S.; Zuercher, W. J. Comprehensive characterization of the Published Kinase Inhibitor Set. *Nat Biotechnol* **2016,** 34, 95-103.

[2] Fan, F.; He, Z.; Kong, L. L.; Chen, Q.; Yuan, Q.; Zhang, S.; Ye, J.; Liu, H.; Sun, X.; Geng, J.; Yuan, L.; Hong, L.; Xiao, C.; Zhang, W.; Li, Y.; Wang, P.; Huang, L.; Wu, X.; Ji, Z.; Wu, Q.; Xia, N. S.; Gray, N. S.; Chen, L.; Yun, C. H.*; **Deng, X.***; Zhou, D.* Pharmacological targeting of kinases MST1 and MST2 augments tissue repair and regeneration. *Sci Transl Med* **2016,** 8, 352ra108.

[3] Jiang, J.; Gui, F.; He, Z.; Li, L.; Li, Y.; Li, S.; Wu, X.; Deng, Z.; Sun, X.; Huang, X.; Huang, W.; Han, S.; Zhang, T.; Wang, Z.; Jiao, B.; Song, S.; Wang, H.; Chen, L.; Zhou, D.; Liu, Q.; Ren, R.*; Zhang, J.*; **Deng, X.***; Targeting BRK-Positive Breast Cancers with Small-Molecule Kinase Inhibitors. *Cancer Res* **2017,** 77, 175-186.