PROTACs as a target deconvolution tool of Hedgehog Pathway Inhibitor 1

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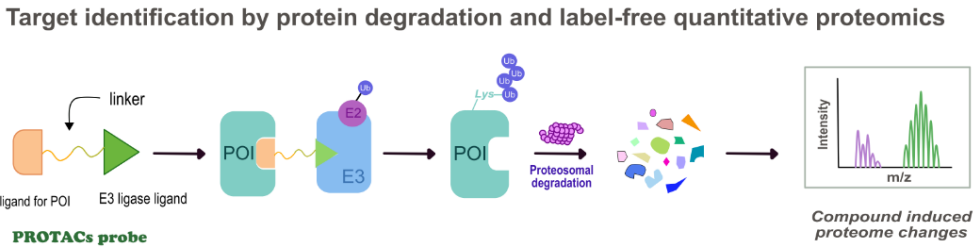
The Hedgehog (Hh) signaling pathway is pivotal for embryonic development of vertebrates, however abnormal activation can lead to tumorigenesis. The current FDA approved drugs targeting the Hh pathway act on the upstream protein Smoothened and suffer from acquired resistance, rendering essential to find new inhibitors with a different target[1] . Hedgehog Pathway Inhibitor 1 (HPI-1) was reported as a downstream inhibitor by Hyman et al and has subsequently been shown to have anti-cancer activity, but its cellular target has remained elusive for many years[2].



To reveal the molecular targets of HPI-1 we designed a proteolysis-targeting chimeras (PROTACs) approach, that involves heterobifunctional molecules consisting of two-headed small ligands which bind to two different proteins; an E3 ligase and a target protein (POI) that is to be degraded through the ubiquitin-proteasome system[3]. The POI can eventually be identified by mass spectrometry-based proteomics. Using this strategy, we discovered the BET bromodomains as the targets of HPI-1, extending the scope of PROTACs as a novel target deconvolution technique.

1. M. Athar, C. Li, A. L. Kim, V. S. Spiegelman, D. R. Bickers, *Cancer Res.* **2014**, 74 (18), 4967–4975.
2. J. M. Hyman, A. J. Firestone, V. M. Heine, Y. Zhao, C. A. Ocasio, K. Han, M. Sun, P. G. Rack, S. Sinha, J. J. Wu, D. E. Solow-Cordero, J. Jiang, D. H. Rowitch, J. K. Chen, *Proc. Natl. Acad. Sci.* **2009**, 106 (33), 14132–14137.
3. K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, R. J. Deshaies, *Proc. Natl. Acad. Sci. U. S. A.* **2001**, 98 (15), 8554–8559.