SOCIÉTÉ CHIMIQUE DE GENÈVE

Target elucidation through target degradation: discovery of BET bromodomains as the target of Hedgehog Pathway Inhibitor-1

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Phenotypic screens are powerful to identify small molecules that act on a biological process of interest, but the elucidation of the cellular target and/or mechanism of action of the hit compounds presents a major challenge. Consequently, hit compounds often do not reach their full potential as pharmacological leads or chemical biology tool compounds.

Exemplary of this, Hedgehog Pathway Inhibitor 1 (HPI-1) was found as a hit in a phenotypic screen for the Hedgehog (Hh) signaling pathway – a major developmental signaling cascade that establishes the embryonic body plan, and dysregulation of which underlies various cancers. HPI-1 robustly inhibits the Hh pathway in a variety of cell lines, downstream of the activator Smoothened, yet its cellular target has remained elusive for many years.

Here, we present the target elucidation of HPI-1 through the design, synthesis, and evaluation of corresponding proteolysis targeting chimeras (Hedgehog Pathway PROTACs, HPPs) coupled with label-free quantitative proteomics. We show that HPP-9 robustly reports on HPI-1 action on various BET bromodomain proteins, epigenetic modulators known to be important for Hedgehog signal transduction, through their degradation. Moreover, HPP-9 is the first example of a PROTAC targeting the Hedgehog pathway, enabling novel pharmacological strategies to combat Hh pathway-driven disease.

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