PROTAC mediated protein degradation and development of new E3 ligands

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Small molecule degraders such as PROTACs (PROtein Targeting Chimeras) have emerged as new promising pharmacological modalities that recently entered clinical testing. The catalytic properties of PROTACs, acting as chemical degraders of proteins of interest (POIs), represents an attractive new mechanism for drug development. However, the development and characterization of PROTACs requires an array of additional assay systems compared to conventional small molecules that track the degradation pathway highlighting critical steps for PROTAC optimization. I will discuss how PROTACs are developed based on their complex mechanism of action and how we evaluated PROTACs as chemical tools. I also present recent examples of PROTACs targeting Aurora A and data on crystallographic fragment screening campaigns leading to first ligands for new E3 ligases that will expand the portfolio of tool compounds for PROTAC development.