

Extended Abstract

Expanding the Toolbox of E3 Ligases for Protein Degradation: Targeting the “Undruggable” Fbw7 E3 Ligase [†]

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Proteolysis targeting chimera molecules (PROTACS) are heterobifunctional small molecules designed to induce intracellular protein degradation. The approach works through a validated sub-stoichiometrically catalytic mechanism based on a dual interaction. One tail of the PROTACS binds to a *Protein Of Interest* (POI) while the other tail recruits a specific E3 ligase, forming a ternary complex that allows ubiquitin transfer from the E3 ligase to the POI, which leads to the POI degradation.

The first generation of PROTACS were mainly peptides either for the E3 ligase or for the POI head-ligands; thus, the PROTAC approach had remained largely dormant for over a decade. The recent development and identification of a handful number of specific drug-like molecules targeting E3 ligases has exceptionally improved the perspectives of the PROTAC approach. However, only 7 out of the more than 600 human E3s have reportedly been used to generate PROTACS. The development of small molecules targeting E3 ligases has been rewarded with limited success, partly because modulating their activity and regulation requires targeting protein–protein interactions.

In this talk, I will develop how, following a novel computational, biophysical, and fragment-based approach, we have been able to identify small molecules able to bind to the Fbw7 E3 ligase, which have been considered an *undruggable* target until now.

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