

Pioneering Plant PROTACs: Expanding the Agrochemical Toolbox

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Targeted Protein Degradators (TPDs) are small chemical molecules capable of inducing the degradation of specific target proteins¹. Within this class, PROTACs (PROteolysis-Targeting Chimeras) have gained considerable interest in the pharma sector, although their potential in plant biology remains largely unexplored^{2,3}. PROTACs are hetero-bifunctional molecules composed of a ligand that binds to the target protein, a ligand that recruits an E3 ubiquitin ligase, and a chemical linker connecting both ligands. By promoting the formation of a ternary complex, PROTACs induce the ubiquitination and subsequent degradation of the target protein by the 26S proteasome⁴. In this pioneering project, we aim to develop a proof-of-concept for the first plant PROTAC. We have designed and synthesized PROTAC1, which incorporates an abscisic acid (ABA) moiety linked to an E3 ligase binder. This E3 ligase shares a high degree of homology with a human E3 ligase, both at sequence and structural levels. Moreover, conservation is almost total in a certain domain which is key for establishing interactions with the ligand that recruits the E3. On the other hand, we followed structure-guided ligand design to develop an ABA analog which specifically binds to ABA-receptor proteins *in vitro* and *in vivo*. Connecting the E3 binder and the ABA-receptor ligand through a PEG-based linker we synthesized PROTAC1. Treatment with PROTAC1 shows ABA-receptor degradation activity *in vivo*, as confirmed by Western blot analysis while the E3-binder alone did not show any effect on ABA-receptor protein levels. Furthermore, degradation of ABA-receptors by PROTAC1 reduces the transcriptional activation promoted by ABA, as expected for an ABA-receptor degrader. Although further work is still needed, these results are encouraging and open the door to establishing PROTACs as an innovative tool for fundamental plant research and a new modality for the agrochemical market.

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