

RNA-PROTACs targeting aggregate prone RNA-Binding Proteins

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Proteolysis Targeting Chimeras (PROTACs) are bifunctional molecules that exploit the Ubiquitin-Proteasome system to degrade proteins. These chimeric compounds consist of a ligand for the target protein and a ligand for a Ubiquitin E3 ligase [1]. By employing PROTACs, proteins previously considered "undruggable," such as non-enzymatic or structural proteins, can now be effectively targeted for degradation [2]. The versatility of PROTACs extends beyond cellular mechanism studies, as several PROTACs have progressed into clinical trials, showcasing their therapeutic potential [3].

Despite the significant role played by RNA-binding proteins in the onset of numerous diseases, developing conventional drugs to effectively target them has proven challenging [4]. One such protein of interest is Tar DNA-binding protein 43 (TDP-43), an RNA-binding protein involved in splicing regulation, primarily located in the nucleus. In conditions like amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration (FTLD), TDP-43 undergoes abnormal post-translational modifications, leading to cytosolic aggregation and eventually death of motoneurons [5]. Similarly, mutations in the C-terminal region of the Fused in Sarcoma (FUS) protein are associated with ALS and can result in cytoplasmic aggregation of FUS [6]. Hence, it is crucial to explore methods for selectively degrading aberrant cytosolic forms of TDP-43 and FUS.

Previously, our laboratory introduced the concept of RNA-PROTACs, demonstrating their efficacy in inducing degradation of the RNA-binding protein Lin28 [7]. The initial RNA-PROTAC utilized a chemically modified 7-mer oligonucleotide to target Lin28. In this study, we present an enhanced version of the RNA-PROTAC employing a chemically modified RNA structure to target a regulatory protein. Furthermore, we report our initial progress in developing an RNA-PROTAC specifically designed to target cytosolic aggregated RNA-binding proteins.

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