RNA-PROTACs targeting aggregate prone RNA-Binding Proteins

C. Weller[1], J. P. Becker[1], J. Hall[1]*

[1]Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH Zürich, Switzerland; 2Institute of Physiology, University of Zurich, Switzerland

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.

[1] Sakamoto K. et al. (2001) Proceeding of National Academy of Sciences of the United States of America, 98(15), 8554-8559
[2] Schneider M, Radoux C. Hercules A. et al. (2021) Nature Reviews Drug Discovery, 789-797, 20(1)
[3] Hu Z, Crews C. (2021), ChemBioChem, 1-23
[4] Wang E. T., Matthew T. J., Lee J-A., Sudhakaran I. P., Rossoll W., Gross C., Moss K. R, Bassell G. J., J. Neurosci. 2016, 36, 11418–11426
[5] Larrière F, Maniecka Z, Pérez-Berlanga M. et al. (2019) Nature Neuroscience, 65-77, 22(1)
[6] Scekic-Zahirovic J., Sanjuan-Ruiz I., Kan V. et al. (2021) Nature Communications, 12(1)
[7] Ghidini A., Cléry A., Halloy F. et al. (2021) Angewandte Chemie, 3163-3169, 60(6)