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Targeted Protein Modification: A Revolutionary Approach in Neurodegenerative Disease Therapy

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Abstract

TPM heralds a paradigm shift in the definition of therapeutic strategies against complex diseases, such as neurodegenerative disorders, particularly Parkinson's disease, Alzheimer's disease, and Huntington's disease. Unlike conventional small-molecule inhibitors, TPM uses bifunctional agents to control protein activity or degradation pathways against previously undruggable targets. Novel approaches, including proteolysis-targeting chimeras and autophagy-tethering compounds, represent new modalities for reducing the levels of pathological proteins, such as misfolded or aggregated alpha-synuclein and tau, which are believed to play a central role in the pathogenesis of these disorders. Neurodegenerative diseases are characterized by toxic protein aggregates disrupting cellular homeostasis and contributing to synaptic and neuronal loss(1). TPM strategies exploit either the UPS or autophagy-lysosome pathway for aggregate degradation and, thus, afford a particular and effective therapeutic intervention. Recent advances have emphasized the potential of bifunctional molecules that selectively bind pathological proteins, thereby tethering them to the cellular degradation machinery and stimulating their removal with minimal impact on normal proteins. Such specificity minimizes off-target effects—a critical limitation of conventional therapies. This review represents recent progress in TPM technologies, highlighting the design of small-molecule ligands capable of inducing protein degradation and stabilization. We review various applications related to the modulation of neurotoxic protein aggregates, attenuation of oxidative stress, and restoration of cellular homeostasis pertaining to neurodegenerative diseases. Modern tools of TPM, integrating ATTECs targeting autophagy pathways with PROTACs inducing ubiquitination of pathogenic proteins, highlight a strong potential for halting disease progression

and promoting neuronal function and survival recovery. These results point to the role of TPM as a transformative intervention in the field of neurodegenerative disease treatment, filling critical gaps in current therapies. The development of this area opens unparalleled opportunities for drug discovery and points toward the possibility of personalized and disease-modifying interventions, marking a significant leap in combating such destructive disorders(2).

Keywords: targeted protein modification, neurodegenerative diseases, autophagy, protein aggregation, therapeutic innovation

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