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Biomolecular High-throughput Screening for Protein Misfolding Diseases: Cyclic Peptides as Novel Rescuers of R120g Ab-crystallin Aggregation in Cataracts

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Cataracts, a leading cause of blindness worldwide, are often associated with mutations in αB-crystallin, a molecular chaperone critical for maintaining lens transparency. The R120G mutation induces protein misfolding and aggregation, forming insoluble aggregates that impair eye vision and chaperon activity in the lens. In this study, we employed an ultrahigh-throughput biomolecular screening platform to identify small cyclic peptides capable of rescuing αB-crystallin misfolding. Using fluorescence-activated cell sorting (FACS) and next-generation sequencing (NGS), we isolated two cyclic hexapeptides that significantly reduce aggregation in HEK cells. In vitro testing with transmission electron microscopy (TEM) and eukaryotic cell assays (HEK293T) revealed a striking absence of aggregated structures in peptide-treated samples, confirming a direct effect on the protein aggregation pathway. These results suggest that small cyclic peptides can act as a potential anti-aggregation approach to misfolding disorders. By shifting the paradigm of cataract treatment from surgical correction to molecular rescue, this work opens new avenues for targeted pharmacological interventions in protein aggregation diseases.