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Methods for Treating Protein Aggregation-Associated Diseases

Researchers at Stanford have found that nascent polypeptide-associated complex (NAC) and the apical domain of CCT1, as well as peptide fragments and fusion proteins containing them, can be used to suppress pathological protein aggregation. This discovery is potentially useful for treating diseases associated with polyglutamine (polyQ) aggregation such as **Huntington's disease** and **spinocerebellar ataxia**, **Alzheimer's disease**, associated with amyloid protein aggregation, and **Parkinson's disease**, associated with alpha-synuclein. Late-onset neurodegenerative disorders are caused by the accumulation of toxic protein aggregation species directly responsible for neuronal dysfunction and death. As a defense mechanism against these toxic species, the cell deploys molecular chaperones which normally bind misfolded and non-native proteins and facilitate their folding or degradation. Recent evidence highlights the therapeutic importance of enhancing or replacing this protein folding machinery as it becomes over-burdened or less effective during the aging process.

Stage of Development
The researchers have shown that elevated levels of the full length CCT1 subunit suppress neurotoxicity associated with Huntington's disease in yeast model systems and tissue culture cells. In a system with purified components, ApiCCT1 (the 140 amino acid apical domain of CCT1) specifically and efficiently inhibits polyQ aggregation of huntingtin exon1. With attachment of the bNAC N-terminal sequence, the fused protein works even more potently to inhibit huntingtin exon1 aggregation, as it can suppress aggregation even at sub-molar ratios.

Applications

- Treatment of aggregation-associated diseases including Huntington's disease, dentatorubral-pallidoluysian atrophy (DRPLA), spinal and bulbar muscular

atrophy (SBMA) or Kennedy's disease, spinocerebellar ataxia (SCA), and amyloid beta aggregation-associated diseases such as Alzheimer's disease.

Advantages

- This novel approach provides a robust avenue for therapeutic applications with several advantages over existing methods:
  - Highly specific targeting
  - Minimal off-target effects on cellular protein folding machinery
  - ApiCCT1 along with its modified form ApiCCT1-bNAC are both small and stable polypeptides
  - Versatile scaffold for the design of optimized aggregation inhibitors beyond Huntington's disease

Patents

- Published Application: WO2020180938
- Published Application: 20220259273
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