Identification and analysis of protein aggregation inhibitors

by

Ali Reza Abbas Ladiwala

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Approved by the
Examining Committee:

_____
Prof. Peter M. Tessier, Thesis Adviser

_____
Prof. Jonathan S. Dordick, Thesis Adviser

_____
Prof. Steven M. Cramer, Member

_____
Prof. Chunyu Wang, Member

Rensselaer Polytechnic Institute
Troy, New York

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ABSTRACT

Protein aggregation is the seminal event in human disorders ranging from Alzheimer's disease to infectious prion diseases. We have investigated how molecules ranging from small aromatic compounds to large antibodies can be used to prevent and reverse toxic protein aggregation. We find that subtle differences in the structures of aromatic small molecules with anti-aggregation activity lead to profound differences in their abilities and mechanisms for neutralizing toxic protein aggregates. Importantly, we identified multiple polyaromatic compounds that selectively target toxic protein aggregates and fail to recognize benign aggregates. We also have developed a novel approach for designing sequence-specific antibody inhibitors of toxic protein aggregation. We demonstrate that grafting small hydrophobic peptides from several amyloidogenic proteins (Aβ42 associated with Alzheimer's disease, α-Synuclein associated with Parkinson's disease, and IAPP associated with Type 2 diabetes) into the complementarity determining regions of small antibodies generates antibody variants that potently inhibit amyloid fibril formation. These Grafted AMyloid-Motif AntiBODIES (gammabodies) prevent amyloid formation at substoichiometric antibody concentrations (1:10 antibody:monomer molar ratio), while conventional antibodies obtained via immunization are unable to prevent aggregation at the same antibody concentration. We expect that our antibody design approach – which eliminates the need for immunization or screening to identify sequence-specific antibodies – can be readily extended to generate potent antibody inhibitors for other amyloidogenic polypeptides linked to human disease.