

Exploiting PrP for the diagnosis and treatment of protein aggregation diseases

<https://www.neurodegenerationresearch.eu/survey/exploiting-prp-for-the-diagnosis-and-treatment-of-protein-aggregation-diseases/>

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Research Abstract

DESCRIPTION (provided by applicant): Neurodegenerative diseases are a major public health problem that affects tens of millions of Americans and compelling evidence indicates that oligomerization and fibrillization of specific proteins is a common facet of almost all such

disorders. Two of the most widely studied proteins involved in neurodegeneration are the prion protein (PrP) and the amyloid b-protein (Ab). Amid controversy, provocative data have emerged which suggest that PrP may serve as a receptor that mediates Ab toxicity. While the pathological significance of Ab binding to PrP remains contentious, there is complete agreement that PrP binds Ab oligomers with high affinity and that PrP is a sub-stoichiometric inhibitor of Ab aggregation. Agents with such properties have potential for use in both the diagnosis and treatment of Alzheimer's disease, but until now efforts to target and detect disease-associated protein oligomers have largely depended on the use of antibodies. Based on our demonstration that PrP is superior to lead conformation-specific antibodies in terms of affinity, specificity and anti-aggregation activity, we propose to exploit PrP to generate highly potent anti-oligomer reagents. However, little is known about the molecular basis that underlies PrP's ability to bind Ab oligomers and prevent the aggregation of Ab monomer. Therefore, we propose to identify the amino acids in PrP that are involved in the recognition of Ab and to modify these to further enhance PrP's ability to bind Ab oligomers and inhibit Ab aggregation. Two stretches of sequence within PrP are implicated in oligomer binding and we will focus our efforts on these. Identification of the key residues and further optimization of PrP's binding to Ab oligomers will be achieved by an iterative process of introducing "design mutations" in these two sites. At each step we will test if the mutagenized PrP can bind to Ab oligomers or prevent Ab aggregation. This approach should produce a recombinant PrP derivative – a 'super-binder' that can be used for both the quantification and the targeting of toxic Ab oligomers. However, the potential uses of PrP derivatives may go beyond Alzheimer's disease. Since PrP is known to bind oligomeric forms of certain designed b-sheet-rich peptides, we hypothesize that PrP will be capable of binding to other protein oligomers. Consequently we will investigate if PrP can bind to oligomers and/or prevent the aggregation of a-synuclein which is associated with Parkinson's disease, and of tau which is associated with frontotemporal dementia. In so doing, we will determine whether PrP's activity is specific for Ab or is a property that extends to other key disease-implicated protein oligomers. We will also transplant sequences from the two PrP oligomer-binding sites into an IgG to produce a unique type of chimeric antibody and test if this antibody can recognize and protect against Ab oligomers isolated from human brain. Finally, we will generate additional antibodies containing PrP sequences we optimize in our PrP mutagenesis studies and test these against a-synuclein and tau oligomers. In this way we will generate new tools to detect and neutralize toxic oligomers centrally implicated in human neurodegeneration.

Further information available at:

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