

Therapies targeting alpha-synuclein will be the treatment of choice in PD

To develop a truly disease-modifying therapeutic, it will be necessary to stop the progression of the underlying pathophysiology. A tremendous amount of research has been devoted to understanding the role of misfolding and aggregation of the synaptic protein alpha-synuclein (ASYN).

Both human genetic studies and experiments in animals provide compelling links between the dysregulation of ASYN and PD. The neuropathological hallmark of PD and other synucleinopathies is the accumulation of alpha-synuclein (ASYN) containing cytosolic inclusions, called Lewy-bodies. As with other misfolded proteins, it is likely that in PD the microscopically detectable Lewy bodies containing ASYN polymers are final deposits while earlier stages of aggregates are involved in the pathogenic process. Recent studies further suggest that membrane-embedded oligomers of ASYN may be a particularly toxic form of ASYN, resulting in disruption of synaptic function, loss of cell membrane integrity and ultimately, in neuronal degeneration.

Treatments that prevent the formation and accumulation of these toxic membrane-embedded oligomeric aggregates of ASYN may prevent further decay or even restore synaptic function in impaired systems and slow the rate of degeneration, thus providing a therapeutic benefit for patients. Treatment approaches that target the misfolding and aggregation process are currently being explored in early clinical studies with antibodies, vaccination and small molecules.

Another, therapeutic principle is to enhance the clearance of these protein aggregates by rectifying defects in a dysregulated clearance mechanism . Approaches aimed at enhancing clearance are still at the animal-testing stage but hold out promise because they may prove to be effective even after the disease has progressed to its later stages.

We have developed molecules based on both approaches – inhibition of aggregation and enhancement of clearance – with convincing effects on alpha-synuclein reduction and in the ‘clinical’ assessments in these animal models.

In summary, while the physiological role of ASYN is currently not fully understood, it is clear that the accumulation of misfolded forms of ASYN contributes to the pathology of PD and that preventing the formation of toxic oligomers and/or enhancing cellular clearance mechanisms may be viable therapeutic approaches to halt or slow disease progression.