



## Fixing the misfolded proteins that cause dementia and heart failure

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#### ABOUT THE LECTURE

Neurodegenerative diseases impact millions of people around the globe, and yet, few treatments address the underlying cause of these conditions. In his Front Row lecture, Jeffery Kelly discussed how these diseases are largely driven by protein misfolding and aggregation, representing a major shift in recent thinking across the field. He highlighted how stabilizing the normal shapes of these proteins, preventing misfolded and aggregated proteins from forming, can help slow or even prevent neurodegenerative diseases, as shown through tafamidis—a drug invented by Kelly and approved to treat transthyretin (TTR) familial amyloid polyneuropathy and TTR cardiomyopathy.

#### TOP TAKEAWAY POINTS

1. Neurodegenerative diseases affect millions of people across the world, including devastating conditions like Alzheimer's disease, Parkinson's and transthyretin amyloidosis. These conditions cause neuronal dysfunction and loss, severely impacting brain connectivity and cognitive function. They can destroy the functions of different organ systems as well.
2. These diseases are sometimes referred to as amyloid diseases, due to the misassembled protein amyloid fibrils that accumulate in the brain and other parts of the body. Initially, it was thought that these amyloid fibrils were the main drivers of neurodegenerative disease pathology, but scientists like Jeffery Kelly have been helping clarify the outsized contributions from other non-native protein assemblies underlying these conditions.
3. Using a multi-disciplinary approach, Kelly has shown that neurodegenerative diseases actually result from protein misfolding, which leads to aggregation and disrupted cellular function. Neurons are especially vulnerable to protein misfolding, as they do not easily regenerate. When the body's protein degradation mechanisms weaken with age, misfolded proteins accumulate, driving disease progression to an even greater extent.
4. To address the underlying cause of neurodegeneration, Kelly and his team have pioneered the development of small molecule drugs called kinetic stabilizers. These prevent proteins from misfolding and aggregating by stabilizing their correct three-dimensional structures. One such kinetic stabilizer Kelly invented is tafamidis (Vyndaqel® and Vyndamax®)—an approved drug that significantly stabilizes the transthyretin protein, thereby slowing the progression of familial amyloid polyneuropathy and TTR cardiomyopathy.
5. Kelly's research into protein stabilization and aggregation has greatly influenced our modern understanding of other neurodegenerative diseases, including Alzheimer's and Parkinson's. In addition to Kelly, numerous other scientists are now investigating treatments that prevent protein aggregation, and emerging research is validating that preventing protein aggregation is effective at slowing—even potentially stopping—these maladies.