One of the hallmark pathological features of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis is the abnormal deposition of misfolded protein in the brains of patients who suffer from these diseases. This observation has led to the hypothesis that protein misfolding may cause neurodegeneration. But if so, what aspect of protein misfolding is responsible? Is it the formation of deposits or particular aggregation intermediates? Or the generation of particular protein structures? And how might protein aggregation cause neurodegeneration and could it be a therapeutic target? In this talk, using cell and structural biology we will describe results from models of neurodegenerative disease that have enabled us to observe the dynamics of protein misfolding and dyshomeostasis in individual living neurons and to understand better which factors predict their fate. In turn, these models have directed the development of a new promising therapeutic strategy that might have efficacy in multiple neurodegenerative diseases.