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A unified model of dementias and age-related neurodegeneration

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Those working with Alzheimer's and other dementias have been frustrated by the implacability of these diseases. Regardless of limited symptomatic treatment,1 there are no proven disease-modifying interventions. Despite huge and growing costs of care,2 a pipeline of candidate drugs,3 >400 registered trials,4 tens of thousands of patients,5 billions of dollars in both US federal6 and pharmaceutical company investment,7,8 more than a century of clinical expertise, and thousands of professional careers, dozens of pharmaceutical and biotechnology firms have foundered and failed9 in attempts to prevent, slow, or alter the course of the dementias. This article presents a novel model to explain the relationships between age-related neurodegenerative disorders (eg, dementias) and the underlying molecular mechanisms of the aging process. The hypothesis is prompted by the fact that accepted conceptual models have failed to yield effective interventions for Alzheimer's or other dementias.10 This article is a specific response to the Alzheimer's & Dementia editorial of November 2015,11 which called for a systemic re-evaluation of our current models and their ability to answer fundamental questions regarding complex brain disorders and their relationship to clinical dementia, as well as the failure to yield effective clinical interventions. The article is divided into three parts. The first part explores current models of age-related neurogenerative diseases. The second part proposes a specific model and details both itsworking and its implications. The third part applies the model to answering the 10 key questions proposed by the Alzheimer's & Dementia editorial. The intent is to provide a conceptual model that accords with known data and proposes a novel point of clinical intervention. The model is intended to provoke discussion and provide a point of departure, rather than to offer a complete and final model for age-related neurodegenerative disease. The value of any such model rests on the outcome of clinical trials, but the model offers potentially innovative pathways to such trials. effective intervention, there is growing consensus that a major factor is the lack of a comprehensive model for the dementias.12 Over the past century,13 several models have attained varying degrees of acceptance.

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