Understanding Alzheimers Disease in the Context of the Aging Brain

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Principal Investigators

CUERVO, ANA MARIA

Institution

ALBERT EINSTEIN COLLEGE OF MEDICINE, INC

Contact information of lead PI
Country

USA

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Understanding Alzheimers Disease in the Context of the Aging Brain

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NIH (NIA)

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15/08/2016

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract
Abstract This proposal investigates the role and impact of defective maintenance of protein

homeostasis (proteostasis) of the aging brain, in the development and progression of Alzheimer's disease. Disturbances in the systems that maintain neuronal proteostasis have been observed in Alzheimer's disease, but the extent to which loss of proteostasis in the aging brain constitutes a risk factor for development of Alzheimer's disease remains unknown. We will focus in chaperone-mediated autophagy (CMA), a protein quality control system that mediates selective degradation of cytosolic proteins in lysosomes. We have previously found that CMA activity decreases with age and that restoring CMA activity in old mice livers prevents their degeneration and preserves organ function. We propose that 1) the physiological decline of CMA with age increases the susceptibility of the aging brain to Alzheimer's disease-related pathology and that 2) interventions to restore normal CMA activity in the aging brain will prevent or slow down progression of Alzheimer's disease neurodegeneration. To test this hypothesis we intend to: 1) determine the spatiotemporal sequence of CMA changes in the aging brain to identify areas of higher susceptibility to proteotoxicity and points of "no return" to proteostasis; 2) investigate if characteristics of the Alzheimer's disease brain are phenocopied by neuronal CMA blockage; 3) test if genetic or chemical enhancement of CMA in the aging brain increases its resistance to AD-relevant proteotoxicity and improves neuronal homeostasis and function. Significance: This study will elucidate how functional decline of CMA contributes to brain aging and if it increases Alzheimer's disease risk in the aging brain. Our findings could help in developing new approaches to preserve old brain homeostasis and function and reduce its risk to Alzheimer's disease neuropathology.

Lay Summary
Project Narrative Loss of brain function with age results in part from a failure of the systems responsible for the maintenance of neuronal quality control. We propose that malfunctioning of these surveillance systems is also behind the higher risk of the aging brain for neurodegenerative conditions such as Alzheimer's disease. This proposal focuses on one of the mechanisms that contributes to neuronal cleaning, which we have found to malfunction in aging and in brains from Alzheimer's patients. We will investigate if failure of this system predisposes to Alzheimer's disease neuropathology, and have designed experiments to test the possible therapeutic value of enhancing the activity of this quality control system in the Alzheimer's disease brain.

Further information available at:

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Investments > €500k

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United States of America

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