CELL AND MOLECULAR PATHOBIOLGY OF ALZHEIMERS DISEASE

https://neurodegenerationresearch.eu/survey/cell-and-molecular-pathobiolgy-of-alzheimers-disease/

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Country

USA

Title of project or programme

CELL AND MOLECULAR PATHOBIOLGY OF ALZHEIMERS DISEASE

Source of funding information

NIH (NIA)

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15/02/2000

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15

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

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

Research Abstract

DESCRIPTION (provided by applicant) In the past PPG term, we have unequivocally linked the

genes causing early onset Alzheimer’s disease (AD) directly to functions’ within endocytic and autophagic pathways of the lysosomal system, documenting specific impairment of these functions beginning at the earliest stages of AD. We propose to validate further our novel conceptual framework that positions the lysosomal system as a common primary target for disruption by diverse genetic and environmental AD-risk factors. Preliminary data support the working hypothesis that cumulative “”hits”” to multiple sites within the endocytic and autophagy pathways in AD cause selective failures of vesicular retrograde transport and signaling, impaired clearance of pathogenic proteins including AP, neurotic dystrophy, and neurodegeneration. The four Projects apply a tightly integrated multidisciplinary approach to study the highly dynamic interplay among lysosome pathway compartments. Individual Projects focus mainly on distinct facets of the entire lysosomal system – the biological and genetic regulation of early endosome signaling (Projects 1, 4 respectively), late endosome/exosome biology (Project 3), and autophagy/lysosome function (Project 2) – thus enabling us to define comprehensively how specific major AD-risk factors disrupt the lysosomal system with significant pathogenic consequences. Innovative technologies from single-neuron gene profiling to video microscopy and high voltage immunogold EM imaging will be applied to patient cells and our novel mouse models. In addition to defining the mechanisms underlying pathobiology induced by key AD-risk factors (APP, cholesterol, presenilin, cystatin C, neurotrophin deprivation), we will provide the rationale and validation for innovative therapeutic approaches to AD, including modulators of endocytosis and lipid-mediated AD pathologies (Project 1), autophagy/lysosomal remediation (Project 2), exosome-based modulation and cystatin C-based therapies (Project 3), and drug target identification within APP/neurotrophin signaling pathways promoting neuron survival (Project 4). Validation for one or more of these new approaches will have significant impact on realizing therapeutics for AD and other major aging-related neurodegenerative diseases.

Lay Summary
Addressing an urgent need for additional perspectives on effective therapies for Alzheimer’s Disease, our Program advances a novel biological framework for understanding how AD develops and that identifies new directions for the therapy of AD and possibly other aging-related diseases. Exploiting this framework, we propose to validate multiple innovative therapeutic approaches for AD.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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