Super-Resolution Microscopy of Small Quantum Dots to Elucidate the Mechanisms of Alzheimers Disease

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Country

USA

Title of project or programme

Super-Resolution Microscopy of Small Quantum Dots to Elucidate the Mechanisms of Alzheimers Disease

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NIH (NIA)

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Quantum Dots, Glutamate Receptor, Microscopy, Alzheimer's Disease, Synaptic plasticity

Research Abstract

PROJECT SUMMARY / ABSTRACT Alzheimer’s disease (AD) afflicts more than 5 million Americans, yet no known drug is able to prevent or stop the disease. Before AD fully develops with insoluble amyloid-? plaque deposits and neurodegeneration, there is a progressive cognitive decline associated with the impairment of synaptic plasticity that underlies learning and memory. This abnormal synaptic plasticity is likely caused by soluble amyloid-? oligomers affecting the synaptic levels of AMPA and NMDA receptors, two glutamatergic receptors that mediate induction and expression of synaptic plasticity. However, the underlying detailed mechanisms are not known and are exceptionally challenging to study due to the complex behavior of these receptors and the small nanometer-scale dimensions of the synaptic domains in which they reside. The goal of this proposal is to understand the molecular details of abnormal synaptic plasticity present in early AD by developing small nanoparticle-based optical probes and new microscopy techniques to analyze the position and dynamics of AMPA and NMDA receptors in normal and AD brains. This goal will be accomplished through the individual and collective efforts of three principle investigators, Paul Selvin (microscopy), Andrew Smith (quantum dots) and Hee Jung Chung (neurobiology). They have previously worked as a team to publish two manuscripts on generating small quantum dots (sQD) (< 10 nm diameter) that can enter the neuronal synapse and accurately follow the receptor number and dynamic placement in dissociated cultured neurons. To achieve this goal, Aim 1 will optimize super-resolution imaging techniques for sQDs in dissociated hippocampal culture and thick hippocampal slices with intact circuitry, specifically focusing on 1- and 2-photon excitation with FIONA and PALM/STORM microscopy. This will allow < 20 nm resolution in all three dimensions. Aim 2 will develop a novel set of sQDs that are smaller, stable, and monovalent with minimal non-specific interaction with tissue. Aim 3 will apply sQDs and super-resolution optical methods to perform single-molecule imaging of glutamate receptors during synaptic plasticity in hippocampal culture and acute slices from wild-type and AD transgenic model mice. Because of our on-going successful collaboration, we are able to work with the AD model immediately, while new microscopy and quantum dots are being generated. This research will increase our understanding of the early pathogenesis of AD and therefore foster the development of new therapeutic strategies that could specifically inhibit the progression of cognitive decline of this disease.

Lay Summary

NARRATIVE Cognitive decline in the early stages of Alzheimer’s disease is associated with the abnormal communication between neurons at inter-cellular junctions called synapses. In this proposal we will develop new microscopy techniques and new optical probes for super-resolution imaging of synapses, which will provide novel insights into this deadly disease and eventually lead to improved clinical therapies.

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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