# Presenilin Variants in the Modulation of Hippocampal Neurogenesis

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**Country**

USA

**Title of project or programme**

Presenilin Variants in the Modulation of Hippocampal Neurogenesis

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

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**Start date of award**

01/07/2016

**Total duration of award in years**

6

**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... Genetics... Neurodegenerative... Neurosciences... Stem Cell Research... Stem Cell Research - Nonembryonic - Non-Human

**Research Abstract**

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD), a progressive neurodegenerative disease, is characterized by impairments in memory and cognition, neuronal loss and deposition of A? peptides. Early-onset familial AD [FAD] is caused by inheritance of mutated genes encoding presenilin 1 and presenilin 2 variants. The central thesis of our proposal is that in AD, cellular mechanisms responsible for the proliferation and differentiation o hippocampal neural progenitor cells (HNPCs) towards neurogenic fates are impaired, thus resulting in memory impairments in patients. Consistent with this view, we have demonstrated that ubiquitous expression of human FAD-linked PS1 variants in transgenic mice impairs environmental enrichment (EE)-induced hippocampal NPC proliferation and neurogenesis (Choi et al., 2008). Moreover, the effects of expressing mutant PS1 on HNPC phenotypes are driven by non-cell autonomous processes that involve factors released by other cells in the neurogenic microenvironment. Our studies also highlight the importance of microglial cells in mediating the effects of expressing mutant PS1 as these cells secrete factors that impair proliferation and neuronal lineage commitment of PS1hWT NPCs in vitro and transcripts encoding these factors are altered in microglia purified from mice expressing mutant PS1 following EE. These findings suggest that FAD-linked mutant PS1 impair NPC phenotypes in vivo by cell-non autonomous mechanisms that are mediated, at least in part, by microglia. Our Specific Aims are focused on elucidating the cellular and molecular mechanisms underlying the effects of FAD-linked PS1 on proliferation and differentiation of adult hippocampal NPCs. Specific Aim 1: To assess the secretome of neonatal microglia from mice expressing PS1hWT or FAD-linked PS1 mutants and to assess the role of microglia in mediating the effects of mutant PS1 on EE-mediated AHNPC proliferation and differentiation deficits in vivo. Specific Aim 2: To determine the impact of CC11-CCR3 signaling in mediating the effects of mutant PS1 on NPC deficits in vitro and in vivo.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: Alzheimer disease (AD), the most prevalent dementing disorder of the elderly, is characterized by memory loss and neurodegeneration. It is established that the birth of new neurons, termed neurogenesis in the hippocampus, a region of the brain that plays a central role in memory formation slows down with aging and is impaired in Alzheimer’s disease. To these findings, we have reported that mutant presenilin (PS) genes that cause familial forms of AD impairs this process now offers opportunities to dissect the molecular mechanisms of adult neurogenesis that will lead to the identification of novel therapeutic modalities to enhance memory function in the elderly.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Alzheimer's disease & other dementias

**Years:**
2016

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N/A

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