Mechanism and Synergy of gamma-Secretase Modulators

https://neurodegenerationresearch.eu/survey/mechanism-and-synergy-of-gamma-secretase-modulators/

Principal Investigators

LI, YUEMING

Institution

SLOAN-KETTERING INST CAN RESEARCH

Contact information of lead PI
Country

USA

Title of project or programme

Mechanism and Synergy of gamma-Secretase Modulators

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,769,038.53

Start date of award

01/06/2016

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

gamma secretase, Imidazole, Generations, Active Sites, Binding Sites

Research Abstract
? DESCRIPTION (provided by applicant): The overall objectives of this proposal are to elucidate the mechanism of action of different classes of next generation ?-secretase modulators (GSMs), to determine their synergistic effect, and to apply them in examining the role of A?42, A?38 and

A?37 in amyloid pathology, synaptic plasticity and learning and memory. The development of GSMs that suppress ?-secretase activity for A?42 production and yet do not affect overall APP processing and cleavages of other substrates has emerged as a promising strategy for AD therapy. Progress in the development of these clinical candidates depends on a deeper understanding of the drug-target interactions. To this end we propose to map the binding site of acid GSMs within the ?-secretase complex and to investigate the structural basis of ?-secretase modulation. Additionally, we will determine the mechanism of cooperatively between the ?-secretase active site and the imidazole based GSM binding site(s). Finally, we will examine the synergistic effect of two classes of GSMs in cellular and animal models with a focus on safety, synaptic plasticity and learning and memory. The proposed research will provide mechanistic insights into GSM modulation of ?-secretase, the function of A? in disease and new therapeutic strategies, shaping our understanding of GSM selectivity and advancing our ability to design effective treatment.

Lay Summary
PUBLIC HEALTH RELEVANCE: Presenilins and ?-secretase play a vital role in amyloid pathology, synaptic plasticity and learning and memory. ?-Secretase modulators (GSMs) have emerged to the forefront of Alzheimer’s disease (AD) research due to their potential for illuminating the mechanism of AD and as disease modifying agents. We propose to investigate the mechanisms of GSMs and the functional role of A?42 in cognition. The findings from these studies can lead to the development of more effective and safe ?-secretase-based AD therapy.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A