Investigating the RhoA/ROCK pathway for the treatment of Alzheimers disease

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Country

USA

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Investigating the RhoA/ROCK pathway for the treatment of Alzheimers disease

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5

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

Research Abstract

Project Summary/Abstract Candidate: My career goal is to be a successful, independent academic research scientist with a laboratory that contributes important insights into Alzheimer's disease (AD) as well as other neurodegenerative diseases and fosters the training of students and fellows. My long-term research goals are to translate basic science discoveries about the mechanisms of neurodegeneration and AD pathogenesis into rational therapies. The K99/R00 Pathway to Independence award will facilitate important career training that will provide a path to establish my own independent research group and initiate new avenues of AD research. Training: Dr. James Lah will be my primary mentor and Dr. Allan Levey will be my co-mentor for the K99 phase of this application, and working together we have developed a plan to provide the necessary career training that will allow for the execution of the proposed research and my transition to independence. In addition to my mentors, a committee of faculty members, including Drs. Gary Bassell, David Weinshenker, Marla Gearing, Ranjita Betarbet, and Richard Kahn, will provide intellectual guidance and technical support during the K99 phase. Drs. Bassell will share his expertise with state-of-the-art microscopy techniques, while Dr. Weinshenker will provide training for rodent behavioral testing. Drs. Gearing and Betarbet will assist with immunohistochemical studies of postmortem human brain tissues and stereotaxic injection of mice, respectively, and Dr. Kahn will offer wisdom and career guidance to facilitate my transition to independence. In the first year of the K99 phase, I will attend a Cold Springs Harbor Laboratory training course in Molecular Neurology and Neuropathology and the Analytical & Quantitative Light Microscopy course at the Marine Biological Laboratory in Woods Hole. In year two, I will attend the University of Pittsburgh Course in Scientific Management and Leadership which is an interactive learning forum designed to equip senior postdoctoral fellows with the knowledge and professional competencies to lead innovative and productive research programs. As a postdoctoral fellow, I have presented my research every year at the annual Society for Neuroscience meeting, and I will continue this tradition through the K99 and R00 phases. I also will present my findings at the International Conference on Alzheimer's disease in 2013. I will attend weekly seminars in the Dept. of Neurology and Cell Biology and participate in a training course on scientific ethics sponsored by the Emory University Office of Postdoctoral Education. Research: Cognitive decline is a clinical hallmark of progression from healthy brain aging to Alzheimer's disease (AD), while increased production and accumulation of amyloid-? (A?) is a pathological hallmark of AD. There is strong evidence that the observed cognitive impairment in AD is in part due to A?'s negative impact on synaptic plasticity. Therefore, designing therapeutics that simultaneously boost cognitive reserve and function as well as decrease A? production may prevent AD onset and treat end-stage disease. RhoA, a Rho GTPase family member, is a well-studied regulator of neuronal outgrowth and synaptic plasticity. The principle downstream effectors of RhoA are the Rho-associated coiled-coil containing protein kinases (ROCK), ROCK1 and ROCK2. Active RhoA promotes antagonistic effects on synaptic plasticity, and extracellular A? induces RhoA activity. Furthermore, there is an accordant relationship between RhoA activity and A? generation. Development of AD pathology likely begins many years prior to clinical symptom onset, and during this time, we propose that A? accumulation activates the RhoA/ROCK pathway which thereby negatively impacts synaptic plasticity and fuels production of A?. The RhoA/ROCK pathway is an exciting target for pharmacologic intervention, but progress is hampered by the ambiguity of which downstream RhoA signaling events are attributable to ROCK1 or ROCK2 in brain. Importantly, the proposed studies will be the first to evaluate targeted disruption of ROCK1 or ROCK2 in the same experimental model system in vivo. We hypothesize that RhoA/ROCK activity increases as AD progresses and that inhibition of the RhoA-ROCK2 pathway will improve cognitive

function in AD. To test this postulate, we will determine if RhoA/ROCK activity is amplified in asymptomatic AD (early stages of disease) and symptomatic AD (end-stage disease) cases by measuring RhoA, ROCK1, and ROCK2 activity in control, asymptomatic AD, and symptomatic AD brains. Next, we will determine how targeted knockdown of ROCK1 or ROCK2 affects cognition dysfunction and A? deposition in an AD mouse model by delivering adeno-associated virus expressing ROCK isoform specific shRNA to the hippocampus. Finally, we will test the model that activation or inhibition of RhoA reflects ROCK2-mediated effects in brain by measuring changes in dendritic spine morphology as well as A? production following pharmacological modulation of RhoA activity coupled with targeted shRNA reduction of ROCK1 or ROCK2. Results from these studies will facilitate future development of drugs targeted against the RhoA/ROCK pathway for the treatment and prevention of AD. In addition, the intellectual and technical skills I acquire over the K99 training period will allow me to establish an independent research program to investigate the functional importance of specific ROCK isoforms in AD as well as other models of neurological disorders.

Lay Summary
Project Narrative There are no known therapies for the underlying disease-causing mechanisms of Alzheimer’s disease, the leading cause of dementia. The RhoA/ROCK pathway influences critical aspects of Alzheimer’s disease pathogenesis, including cognitive decline and amyloid accumulation. Studying the RhoA/ROCK pathway will facilitate the development of drugs targeted against this pathway for the treatment and prevention of Alzheimer’s disease.

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

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