Development of peptide inhibitors for neuroinflammation and neurodegeneration

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Principal Investigators

SRINIVASAN, MYTHILY

Institution

PROVAIDYA, INC.

Contact information of lead PI
Country

USA

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Development of peptide inhibitors for neuroinflammation and neurodegeneration

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1

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Research Abstract

? DESCRIPTION (provided by applicant): The prevalence of Alzheimer’s disease (AD) is poised to increase exponentially with the growing aging population worldwide. In the United States, total annual costs of AD care are projected to increase from $226 billion in 2015 to over $1 trillion in 2050. Paucity of disease modifying therapies capable of slowing the disease

progression is an acute unmet need. Considerable evidence suggests that dysregulated activation of nuclear factor kappa B (NF-??) in the central nervous system (CNS) contributes significantly to the beta amyloid (A?) deposition, inflammation and neurodegeneration in AD. The goal of biological therapies is to restore healthy balance by targeting specific molecules that promote imbalanced responses. Provaidya LLC has identified an innovative strategy to selectively target activated p65, the NF-?? subunit that perpetuates neuroinflammation and neurodegeneration. Glucocorticoid induced leucine zipper (GILZ), is a NF-?? interacting protein that binds the transactivation domain of p65 (p65-TAD) exposed in activated cells and suppresses activation of pathological mediators. Structurally the proline rich p65 binding motif of GILZ adopts polyproline type II (PPII) helical conformation. PPII helices at intermolecular interfaces behave as adaptable gloves in obtaining the correct binding orientation with the partner protein and are considered excellent drug targets. In the GILZ:p65- TAD complex, the critical proline of GILZ adopts PPII helix at interface with the highly conserved phenylalanine residues in p65-TAD. Scientists at Provaidya developed rationally designed analogs of the p65 binding motif of GILZ by introducing residue substitutions with increased propensity to form and stabilize PPII helix in the context of p65-TAD. Homology modeling and docking analyses showed that select Provaidya GILZ analogs (PGA) exhibit structural similarity, near native docking and similar binding kinetics with p65-TAD as wild type GILZ. Functional evaluation of top 5 PGA showed that the peptides are well tolerated with half minimal lethal dose (LD50) comparable to known peptide drugs. Two peptides, PGA-2 and PGA-4 protected human brain cells against A? induced toxicity in-vitro. Specific aims of this Phase-I STTR proposal are: 1) to investigate the effects of PGA-2 and PGA-4 on cellular morphology and A? production in an in-vitro neurodegeneration model in which human fetal neuronal cell derived cultures exhibit differentiated neurons and proliferative glia, 2) to evaluate the therapeutic efficacy of PGA-2 and PGA-4 in R1.40 transgenic AD mouse model of AD that shares many characteristics of human AD and 3) to transform efficacious PGA into small molecules. Successful completion of these studies will prepare for investigational new drug evaluations of PGA. Preliminary data suggest that the PGA will likely impact several aspects of AD pathology including A? deposition, inflammation and neuronal apoptosis. Provaidya strongly believes that upon successful development, PGA will have a tremendous impact on disease progression and greatly improve the quality of life in AD.

Further information available at:

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United States of America

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