Project Information

1R43AG071064-01

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Title: DEVELOPMENT OF A NOVEL CHEMOKINE RECEPTOR ANTAGONIST PEPTIDE AS A SYNAPSE PROTECTING TREATMENT FOR NEURODEGENERATION IN ALZHEIMER'S DISEASE

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Abstract Text:

7. Project Summary In response to PAS-19-319, Creative Bio-Peptides, Inc. will develop the multi-chemokine receptor (CCR2/CCR5/CXCR4) antagonist peptide R103 to prevent, even reverse, synapse loss and neurodegeneration relevant to Alzheimer's Disease (AD). Functional impairment in AD results from loss of neuronal spines and dendrites, preceding and independent of neuronal death. Cofilin-actin rods (rods) are a 1:1 complex of actin and cofilin whose formation is linked to a cellular prion protein (PrPC) and NADPH oxidase (NOX)-dependent signaling pathway and represents an early AD pathology. Rods form in neuronal processes (neurites) under conditions of energetic and oxidative stress, such as occur in neuroinflammation, and lead to neurite distal atrophy. Synapse function declines in neurites in which rods have formed compared neurites without rods from the same neuron and rods are significantly increased in animal models of AD and in human AD brain. Conversely, cognitive deficits in mouse models of AD are alleviated by decreasing cofilin activity in neurons, reducing its expression, or by inhibiting rod formation through blockage of the (PrPC)/NOX-dependent signaling pathway. Cofilin plays important roles in dendritic spine dynamics and receptor trafficking and the sequestering of cofilin into rods is detrimental to synaptic function. Recently, antagonists of the chemokine receptor CCR5 have been shown to be a translational target for restoring synapse loss and motor function in brain injury, stroke and Parkinson's Disease and our data shows that chemokine antagonists block rod formation. An earlier clinical analog of R103, the CCR5 antagonist octapeptide DAPTA which has been safely administered to over 400 persons, prevents synapse loss and in multiple phase 2 trials reversed cognitive deficits and improved functional brain scans in neuro-AIDS. In AD animal models DAPTA prevented cortical neuronal loss in basal nucleus lesioned aged animals and microglial/astrocyte activation in dentate gyrus, and was protective in ischemic stroke. We will leverage decades of basic and clinical research on chemokine antagonist peptides in neuro-AIDS to establish synapse protecting benefits of the peptide R103 in AD. We hypothesize that antagonizing R5/X4 activation with the oral peptide R103 will deliver cognitive benefits in AD and other dementias by preventing rod formation and thus preserving and restoring synapses. We will determine the ability of R103 to block rods, preserve dendritic spines, and protect synapse function using patch-clamp measurements of synaptic currents. As a bridge to human clinical endpoints we will make a quantitative PET assessment of R103 inhibition of uptake of the TSPO ligand 18F-FEPPA, a probe of brain neuroinflammation.

Project Terms:

Actins; Adult; age related cognitive disorder; aged; Algorithmic Analysis; Alzheimer's Disease; Alzheimer's disease brain; Alzheimer's disease model; Alzheimer's disease pathology; AMD3100; Amyloid beta-Protein; analog; Animal Disease Models; Animal Model; Animals; Astrocytes; Atrophic; axonal sprouting; Basal Ganglia; base; Basic Science; Brain; Brain Injuries; Brain scan; CCR5 gene; Cell Line; Cessation of life; chemokine; chemokine receptor; Classification; Clinical; Clinical Research; cofilin; Cognitive; cognitive benefits; Cognitive deficits; Complex; Contracts; Corpus striatum structure; CXCR4 gene; CXCR4 Receptors; cytokine; Data; Dementia; Dendrites; Dendritic Spines; dentate gyrus; Development; dimer; Distal; Dyes; Evaluation; functional decline; functional disability; Functional disorder; Health; Hippocampus (Brain); HIV-associated neurocognitive disorder; Human; human embryonic stem cell; Image; improved; in vitro Model; in vivo; Infiltration; Inflammatory; Infusion procedures; Ischemic Stroke; Lead; Length; Lesion; Ligands; Link; Lipopolysaccharides; male; Measurement; Measures; Mediating; Microglia; monocyte; Morphology; Motor; mouse model; Mus; NADPH Oxidase; Natural regeneration; Nerve Degeneration; Neurites; neuroAIDS; Neuroglia; neuroinflammation; neuron loss; Neurons; neurotoxic; neurotoxicity; novel; novel therapeutics; Oral; Oxidative Stress; Parkinson Disease; patch clamp; Pathology; Peptides; Persons; Pharmaceutical Preparations; Phase; phase II trial; Play; Population; Positron-Emission Tomography; pre-clinical; preservation; prevent; Process; Proteins; PrP; Rat-1; Rattus; receptor; Receptor Activation; response; Rivers; Rod; Role; Signal Pathway; Slice; Stroke; Synapses; synaptic function; time use; TLR4 gene; trafficking; United States National Institutes of Health; uptake; Vertebral column; Wild Type Mouse