Anti-RPS23RG1 Nanoantibody as Novel Therapeutic and Research Reagents for Alzheimer’s Disease.

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USA

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Anti-RPS23RG1 Nanoantibody as Novel Therapeutic and Research Reagents for Alzheimer’s Disease.

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Research Abstract

Abstract Alzheimer’s disease (AD) is the most common dementia in the elderly. Currently, there

is no cure for the disease. Pathologically, AD is characterized by the presence of extracellular ?-amyloid (A?) plaques and intracellular tau-neurofibrillary tangles in patient’s brain. Although being vigorously pursued, multiple attempts targeting on A? generation/clearance have been failed in Clinical trials, mainly due to toxic side effects and lack of efficacy. As reported recently in Scientific Reports, we identified the human RPS23RG1 gene with the ability to reduce A? production and tau phosphorylation. We also showed that RPS23RG1 overexpression counteracted A? oligomer (oA?)-induced synaptic loss and cognitive impairments by activating adenylate cyclase/PKA signaling pathways, which in turn caused the activation of CREB (an important transcription factor regulating learning and memory) and the inactivation of GSK-3?/? (an important kinase inducing tau hyperphosphorylation). Thus, RPS23RG1 can be further exploited for its therapeutic potential in AD. The purpose of this project is to generate an agonistic (activating) nanoantibody targeting RPS23RG1 to promote RPS23RG1-mediated synaptic and cognitive protection against AD. Nanantibody (nAb) is a distinctive type of antibody fragment derived from camelid heavy-chain only antibody (HCAb). As a therapeutic candidate, nAb holds many superior properties over conventional antibodies. In addition, agonistic (activating) antibodies have been widely reported and used in many areas of research and therapy, including those targeting G-protein-coupled receptors (GPCRs). In this proposal, we will generate humanized nanoantibodies that will bind RPS23RG1 and activate downstream signaling pathways. We will examine the expression of RPS23RG1 in AD postmortem brains and its correlation with the severity of premortem cognitive decline in human patients with severe memory loss, mild memory impairment (MCI), or normal cognition as control. We will also examine its ability to activate downstream signaling pathways to counteract synaptic and cognitive decline in both in vitro and in vivo animal models of AD. We expect that RPS23RG1 is downregulated in AD patient brains and its reduction correlates with the severity of dementia in AD and MCI patients, and that agonistic RPS23RG1 nanoantibodies reduce A? and phosphorylated-tau levels, and mitigate synaptic loss and cognitive impairment in an PKA-dependent manner in AD mice. Our results should lay a foundation for the future development of RPS23RG1 nanoantibodies as therapeutics in AD.

Further information available at:

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