UT Southwestern
Medical Center

Center for Translational
Neurodegeneration Research

Department of Molecular Genetics

Darrell K Royal Research Fund for Alzheimer's Disease
PO Box 5839
Austin, TX 78763
866-946-3606

August 27, 2015

Re: *First year report by Drs. Murat Durakoglugil and Florian Plattner of the project:*
NMDA receptor regulation in Alzheimer's disease and memory enhancement

Dear Mrs. Edith Royal, Board of Directors, and Scientific Review Committee:

We wish to thank you again for your support of our research and are happy to give you this report of our first year's progress.

Alzheimer's disease (A.D) is characterized by memory impairment, for which cognitive enhancement is considered a valid treatment strategy. Due to its fundamental role in memory formation, as well as, its implications for loss of function in A.D., we have targeted a specific type of molecule on the cell surface (NMDA receptors). We recently characterized a novel molecular mechanism that controls the cell surface levels of these receptors (Plattner *et al.*, 2014). Based on this novel mechanism, we developed small drug-like interfering peptides (NR2B-siP) that facilitate neurotransmission and enhance memory in rodents. We hypothesized that NR2B-siP may be useful for examining the role of the receptor dysfunction in Alzheimer`s Disease and those new drugs could alleviate neuronal deficits and memory impairments in mouse models of familial AD. For this purpose, we first established a breeding colony of a well-characterized AD mouse model (3xTg AD mouse line; Oddo *et al.*, 2003). We then performed a biochemical and neurophysiological analysis of 8-10 month-old AD mice that exhibit neuropathological hallmarks of AD and deficits in neurotransmission and memory. We evaluated the effect of NR2B-siP on neurophysiological properties and found that NR2B-siP treatment of brain tissue from AD mice had no adverse effects and could, in fact, facilitate neurotransmission. This enhancement could be maintained for several hours. Together, these results indicate that the molecular mechanism targeted by the NR2B-siP is not disrupted in AD mice and hence may be indeed targeted to enhance memory. We will try to address this idea in our future work by assessing whether NR2B-siP can rescue or minimize the memory impairment in the AD mice.

Sincerely,

Murat S. Durakoglugil, M.D., Ph.D.

FlorianPlattner, Ph.D.

5323 Harry Hines Boulevard, Dallas, Texas 75390-9046 Ph: 214-648-5633 Telefax: 214-648-8804
joachim.herz@utsouthwestern.edu utsouthwestern.edu

Darrell K Royal Research Fund for Alzheimer's Disease

First year report by Drs Murat Durakoglugil and Florian Plattner of the project:

NMDA receptor regulation in Alzheimer's disease and memory enhancement

Alzheimer's disease (AD) is characterized by memory impairment, for which cognitive enhancement is considered a valid treatment strategy. Due to its fundamental role in memory formation, as well as, its implication in loss of function in AD, we have studied a cell surface molecule, called NMDA receptor. We recently characterized a novel molecular mechanism that controls the cell surface levels of these receptors (Plattner *et al.,* 2014). Based on this novel mechanism, we developed small drug-like interfering peptides (NR2B-siP) that facilitate neurotransmission and enhance memory in rodents.

We hypothesized that the NR2B-siP may be useful for examining the role of NMDA receptor function in AD-related processes and that NR2B-siP treatment may alleviate neuronal deficits and memory impairment in mouse models of familial AD. For this purpose, we firstly established a breeding colony of a well-characterized AD mouse model (3xTg AD mouse line; Oddo *et al.,* 2003). We then performed a biochemical and neurophysiological analysis of 8-10 month-old AD mice that exhibit neuropathological hallmarks of AD and deficits in neurotransmission and memory. We evaluated the effect of NR2B-siP on neurophysiological properties and found that NR2B-siP treatment of brain tissue from AD mice had no adverse effects and could, in fact, facilitate neurotransmission. This enhancement could be maintained for several hours. Together, these results indicate that the molecular mechanism targeted by the NR2B-siP is not disrupted in AD mice and hence may be indeed targeted to enhance memory. We will try to address this idea in our future work by assessing whether NR2B-siP can rescue or minimize the memory impairment in the AD mice.