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Donor Progress Report for the Darrell K Royal Research Fund for Alzheimer's Disease of the Dallas Foundation

Prepared by: Yingfei Wang, Ph.D., Principal Investigator
Assistant Professor, Departments of Pathology and Neurology & Neurotherapeutics

The Role of a Novel AIF3 Isoform in Dementia

Dementia severely interferes with patients' daily lives. Neuronal cell death is a key feature in dementia and causes problems with memory, thinking and behavior. Understanding the underlying mechanisms of neuronal cell death in dementia may help us develop an effective treatment. The goal of our study is to understand the role of newly identified apoptosis-inducing factor isoform (AIF3) in dementia. As stated in our previous report, we found that AIF3 was induced in dementia-associated diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD).

Induction of AIF3 expression leads to mitochondrial dysfunction and progressive neuronal cell death, supporting our hypothesis that AIF3 is induced in dementia-related human diseases and might promote dementia pathogenesis. Moreover, we have also identified five key elements in AIF intron regions which regulate AIF3 splicing.

We also showed that AIF3 expression was induced in the human cortex and hippocampus tissues from AD patients at both mRNA and protein levels. The expression of AIF3 was also further confirmed by the Sanger sequencing. In order to study the role of AIF3 *in vivo*, we have successfully established a tamoxifen-inducible mouse model to induce AIF3 expression in the adult mouse brain. We characterized AIF3 expression and neuron morphology changes at 7 days, 14 days, 1 month, 2 months and 4 months after tamoxifen induction. We found that AIF3 expression did not induce obvious brain structure changes during the first 4 months, but it started to induce mild neuron loss in the cortex at 4 months after tamoxifen induction. We will continuously check AIF3 effects at 6 months, 12 months, and 18 months.

On the other hand, using another enhanced CamKII-alpha iCre, AIF3 expression induced obvious mitochondral dysfunction and reduced ATP synthesis. More importantly, we identified five highly repeated noncoding sequences in AIF gene intron regions. Using CRISPR gRNAs to knockout these repeated sequences, we were able to significantly reduce AIF3 splicing. Next, we will further identify the key splicing regulators that control AIF3 expression. The project is going as we planned. Our current progress data support our hypothesis that AIF3 is induced in dementia-related human diseases and might promote dementia pathogenesis.