Name of Institution: Louisiana State University Health Sciences Center in Shreveport

Project Title: CDP-ethanolamine as a possible inhibitor of α-synuclein-induced pathology and behavioral deficits in a progressive mouse model of Parkinson’s disease-A pilot study.

Investigators/Authors Bio/Pictures:

**Stephan N. Witt, Ph.D.**

Dr. Witt is professor in the departments of Biochemistry & Molecular Biology and Pharmacology, Toxicology & Neuroscience at the Louisiana State University Health Sciences Center in Shreveport. He attended the California Institute of Technology and Stanford for his graduate and postdoctoral studies, respectively. He has conducted research on Parkinson’s disease (PD)—supported by funds from the NIH and the APDA—for over ten years. Dr. Witt is one of the pioneers that established and validated yeast as a model system for studying how the Parkinson’s disease-associated protein α-synuclein triggers cell death. A major finding from his lab is that yeast cells that have a low level of the phospholipid phosphatidylethanolamine (PE), which is a key component of cell membranes, have a high level of α-synuclein. Like a “see-saw”, when cellular PE goes down, α-synuclein goes up—which is very, very bad because cells with too much α-synuclein gradually die off. There is evidence that the level of PE in the brain in some people slowly decreases with age, and the concern is that such a decrease triggers α-synuclein to accumulate and harm neurons. The Witt group seeks to evaluate the ability of the drug cytidine diphosphate ethanolamine (CDP-ethanolamine) to boost PE in the brain of Parkinson’s disease mice. Increasing PE in the mouse brain should prevent or slow down the accumulation of toxic forms of α-synuclein. If CDP-ethanolamine-treated mice have fewer symptoms and live longer than the untreated mice, then further study of this drug would be warranted. Overall, the goals of the Witt research group are to (i) understand at a molecular level how α-synuclein kills cells, (ii) elucidate the molecular connections between melanoma and PD, and (iii) find neuroprotective and neurorestorative drugs for PD.

**Xiao-Hong Lu, Ph.D.**

Dr. Lu is an assistant professor in the department of Pharmacology, Toxicology & Neuroscience at the LSU Health Sciences Center in Shreveport. Coming from a long line of physicians and professors, Dr. Lu is a psychiatrist and a pharmacologist. He completed his postdoctoral training with a focus on molecular genetics and neuroscience, and he recently started his independent research at LSUHSC. He has extensive experience in developing and applying molecular genetics technologies for probing brain function in health and disease, especially in generating genetically modified animal models using Bacterial Artificial Chromosome (BAC) transgenesis and gene targeting.
He developed the BAC transgenic PD mouse model that recapitulates cardinal features of PD at the UCLA UDALL Center (J Neurosci, 2009). His translational studies in BACHD mouse model of Huntington’s disease (HD) have identified a novel therapeutic strategy (Sci. Transl. Med., 2014 and highlighted by Nature Review Drug Discovery, 2015). Dr. Lu led and carried out multiple preclinical studies using transgenic animal models of neurodegeneration for NINDS, NCGC, CHDI and Astra Zeneca. He was awarded a NARSAD Young Investigator Award to generate a next-generation genetic mouse model for schizophrenia. He recently co-invented a single-neuron transgenic technology called MORF (Mosaicism with Repeat Frameshift, Patent pending), which is a powerful genetic tool to provide sparse and stochastic genetic access to single neurons for the study neurodegeneration and neuropsychopharmacolgy at the single neuron level in vivo. On a quest for the “holy grail” of pharmacotherapy, the ultimate goal of his laboratory is to meld genetics and pharmacology to develop neural circuit-selective therapies for neuropsychiatric disorders.

**Objective:** We will conduct preclinical tests to determine whether the drug CDP-ethanolamine (CDP-ETA) protects against α-synuclein-induced pathology and behavioral deficits in a progressive mouse model of Parkinson’s disease. The mice we will use express human α-synuclein in their brains.

**Background:** The Witt group recently discovered that α-synuclein accumulates and is toxic to yeast cells that have chronically low levels of the membrane phospholipid phosphatidylethanolamine (PE) (see structure below).

In contrast, α-synuclein is non-toxic to yeast cells that have a normal level of PE. We showed that treating such cells with the naturally occurring metabolite ethanolamine, which is a constituent of PE, has salutary effects on cells: added ethanolamine increases PE, decreases α-synuclein, and cells then grow normally. Our work was validated by Guy and Kim Caldwell (University of Alabama), who showed that supplemental ethanolamine significantly protects α-synuclein–expressing worms from age-dependent neurodegeneration. The combined results from the two groups were published and form the basis of this study (Wang et al (2014) Phosphatidylethanolamine deficiency disrupts α-synuclein homeostasis in yeast and worm models of Parkinson disease. Proc Natl Acad Sci USA 111: E3976–E3985). Because ethanolamine protects worm dopaminergic neurons from age-dependent neurodegeneration, we have sought funds to conduct a preclinical test of a related compound, that is, CDP-ethanolamine in a progressive mouse model of Parkinson’s disease.

**Methods/Design:** There are two phases to our proposed work. Phase 1 is a pharmacokinetic analysis of CDP-ethanolamine. The goals are to determine the steady-state level of the drug in the periphery and brain of mice and the half-life of the drug.
This information will be used to guide us as to the appropriate dose and dosing schedule for the administration of the drug to mice. Phase 2 is the administration of daily injections of CDP-ethanolamine to PD mice to determine whether the drug ameliorates the α-synuclein-induced pathology and behavioral deficits (compared to untreated control animals) typically seen in PD mice. We expect that the treatment will last 6 months, and during this time we will assess behavior using 5-6 different tests. At the end of the study, the mice will be sacrificed and we will analyze their brains for markers of inflammation and for deposits of α-synuclein. The expected results are that CDP-ethanolamine will block or delay α-synuclein-induced pathology and ameliorate behavioral deficits.

Relevance to the Treatment of Parkinson's disease: Although the metabolite ethanolamine is present in all bodily fluids, its function is not well understood. It is used to synthesize PE, and it also forms when enzymes degrade PE and other lipids. Our hope is that CDP-ethanolamine, which is an activated form of ethanolamine, can be used as a supplement on a long-term basis to protect neurons from the type of neurodegeneration that occurs in PD.