



Dissertation Defense

Pharmacoperone approach to treat early infantile epileptic encephalopathy associated with NaCT deficiency

Presented by:

Valeria Jaramillo-Martinez

Ph.D. Candidate

Translational Neuroscience and Pharmacology

Tuesday, March 14, 2023

TTUHSC | ACB220

10:00 a.m. – 11:00 a.m.

ABSTRACT:

Early infantile epileptic encephalopathy type 25 (EIEE25) is a disease that causes epileptic seizures in infants shortly after birth and lasts throughout their lives. EIEE25 symptoms include difficulty in speaking and slow and limited motor skills. Currently, there is no treatment for EIEE25.

This disease is associated with single-point loss-of-function mutations in the human sodium-coupled citrate transporter (NaCT, Solute Carrier SLC13A5, or mINDY). NaCT is responsible for transporting Na⁺ and citrate³⁻ into the cell. Importantly, NaCT is the mammalian ortholog of *Drosophila* INDY (I'm Not Dead Yet, INDY), a lifespan determinant in this organism. In humans, NaCT is primarily expressed in the brain, liver, testes, bone, and teeth. In the brain, NaCT is expressed exclusively in neurons and astrocytes, where citrate plays key roles in the synthesis of neurotransmitters, and energy generation.

In contrast, Slc13a5-null mice exhibit minimal evidence of neurological dysfunction, but have a beneficial metabolic phenotype related to the loss of function of the transporter in liver; the beneficial features include resistance to diet-induced obesity, and protection against diabetes, insulin resistance, and metabolic syndrome. The absence of epilepsy in Slc13a5-null mice might be due to the C57BL/6 background because these mice are known to be resistant to epilepsy. To date, 22 missense disease-causing mutations have been identified in human NaCT and eight of them have been studied. The underlying defect varies in these eight mutants that cause loss of function. Some mutations exhibit normal plasma membrane protein expression, but the transport function is diminished while other mutations appear to affect protein folding and proteolytic stability, which may lead to defective trafficking to the cell surface. Published studies, done in cells with heterologous expression, show contradictory results in protein expression of mutant NaCTs, largely due to the lack of NaCT-specific antibodies that recognize the human protein in immunofluorescence and/or Western blot studies.

My research project characterizes the six most common missense mutations, which brings us one step closer to understanding the defects of disease-causing mutations at the molecular level, allowing us to begin dissecting NaCT-trafficking pathway(s). Additionally, it establishes an in vitro assay for discovery-screening of small molecules that can restore the trafficking defects and transport function in Class II mutants of NaCT

Persons with disabilities who may need auxiliary aids or services are requested to contact [Lisa Moran](#) at 806.743.1280 at least 24 hours prior to this meeting so that appropriate arrangements can be made.