**Angelman syndrome (AS)** is a genetic neurodevelopmental disorder that occurs in about 1/15,000 live births. AS is caused by the loss of the maternal copy of the UBE3A gene and is characterized by developmental delays, lack of speech, motor dysfunction, epilepsy, and intellectual disability. The brain regions implicated in AS correlate with aberrant cellular excitability and abnormalities in cellular pathways involved in the maintenance of neuronal bioenergetic and metabolic homeostasis. Moreover, as in many other neurodevelopmental disorders, a therapeutic approach that can either prevent or mitigate autistic-related symptoms remains to be developed and validated.

Cellular excitability is highly dependent on the ability of neuronal metabolism to support the bioenergetic requirements of these cells. One approach to manipulating neuronal excitability and associated metabolic activity is the delivery of a weak current to the brain via the scalp. **Transcranial direct-current stimulation (****tDCS)** is a technique that employs a portable wearable system wherein electrodes positioned on the scalp can stimulate a specific brain region in a location-specific fashion. tDCS has been shown to have an immediate and lasting effect on different brain functions. At the cellular level, tDCS can modulate neuronal metabolism and affect neuronal firing by strengthening synaptic transmission. In recent years, tDCS has been explored as a means of treating several other clinical conditions, including depression, schizophrenia, aphasia, addiction, epilepsy, chronic pain, and attention/motor rehabilitation. tDCS has also been evaluated for use in non-medical applications such as accelerated learning and focus. However, the lack of insight into the mechanistic basis for the efficacy of tDCS has hindered efforts to further optimize this therapeutic platform. Therefore, understanding the cellular and physiological effect of tDCS on the brain will resolve ambiguity regarding its efficacy while allowing for more reliable therapeutic optimization, elevating the translational potential of this technology and enabling its synergistic use with other therapeutic approaches.

One of the goals of the FY22 ARP Idea Development Award is the assessment of novel therapeutic approaches using valid preclinical models. The AS mouse model is an efficient tool for investigating the molecular basis for this disease, as it recapitulates many of the features of human AS including motor dysfunction, aberrant behavior, and cognitive deficits. Based on our studies, we have concluded that tDCS treatment can rescue certain behavioral deficits in AS model mice. However, the mechanism and the duration over which tDCS remains efficacious remain unknown. As such, it is critical that both the short- and long-term effects of this technique on behavior, neuronal metabolism, intrinsic and extrinsic excitability, and damage to brain tissue be studied to support the future clinical and non-clinical application of this promising technique.

This proposal offers an innovative approach that comprehensively addresses the short- and long-term effects of tDCS on neuronal metabolism, intrinsic and extrinsic excitability, and behavior in AS and wild-type (WT) mice. Specifically, **Electrophysiology** studies will be employed to determine the short-lived and persistent excitability changes that arise upon tDCS treatments. **Behavioral studies** will be performed to determine the short and long-term effect tDCS has on AS-related behavioral parameters. A high-resolution metabolomics strategy (**Metabolomic NMR**) will be applied to clarify immediate brain metabolic responses to tDCS stimulation and to determine the effective duration of those metabolic changes. Furthermore, we will evaluate the **residual effects of tDCS** on brain tissue.

The impact of the successful completion of this proposed research is twofold. In the short term, this study will establish tDCS as a supportive treatment for AS patients that will significantly improve patients' well-being and quality of life and alleviate the substantial burden on their families and caregivers associated with the chronic and severe nature of the clinical features. The long-term impact of this proposal lies in the understanding of the cellular mechanisms responsible for the etiology of AS and which are affected by tDCS. This information will enable the exploration of other approaches that will enhance the efficiency of tDCS treatment and shed more light on the metabolic changes responsible for AS pathogenesis. As the pathophysiology of AS resembles that of other neurodevelopmental disorders, developing tDCS as a viable treatment approach will enable its use to treat other autistic disorders, offering additional supportive treatment approaches that will improve the quality of life of patients, family members, and caretakers.