Intersection of Epigenetic Regulation and Mitochrondrial Function in Autism

Twiss, J.L.[1*], Bagasra, O.[2], Boccuto, L.[3], Champagne, K.[4], Freeman, L.[5], Frizzell, N.[6], Lizarraga, S.[1], Mathew, S.[7] and Turner, J.[7]

[1]Dept. Biological Sciences, Univ. South Carolina, [2]Dept. Biology, Claflin Univ., [3]Greenwood Genetics Center, [4]Dept. Bioengineeering, Clemson Univ., [5]Dept. Biology, Furman Univ., [6]Dept. Pharmacology, Physiology, and Neuroscience, Univ. South Carolina, and [7]Dept. Drug Discovery and Biomedical Sciences, Univ. South Carolina.
*twiss@mailbox.sc.edu

Keywords: autism spectrum disorder, tryptophan, nicotinomide riboside, histone acetylation, gene expression, stem cells.

Autism represents a growing public health concern worldwide. Severity of autistic symptoms encompasses a spectrum, which is often cumulatively referred to as Autism Spectrum Disorders (ASD). ASD is more common in males than females and it affects 1 in 68 children in the US, and may be even higher in South Carolina. Our research seeks to build a greater understanding of the biological underpinnings of ASD. We build upon preliminary studies from Boccuto and Lizarraga that link ASD phenotypes to altered metabolism and gene expression converging on mitochondrial function. Specifically, cells from ASD children have deficits in tryptophan utilization compared to cells from typically developing children. Children from mothers treated with valproic acid (VPA) during pregnancy are at much higher risk for ASD, and VPA alters expression of nuclear-encoded mitochondrial protein genes in human stem cell-derived neurons. Additionally, Bagasra has detected sex differences in gene expression in neural cell lines that may point to male vs. female ASD susceptibility. In this award, we will test whether metabolism and epigenetic regulation of gene expression converge on mitochondrial function as a contributing factor in ASD pathophysiology. We will capitalize on existing cellular models across our labs (lymphoblasts, primary rodent neurons, and human iPSC-derived neurons) to determine the effect of VPA on mitochondrial function, potential sex differences in response to VPA and tryptophan metabolism, and how gene expression converges on metabolic phenotypes. In parallel, we will leverage Freeman's interests in how diet affects the brain to determine if manipulations of tryptophan metabolites, specifically dietary supplementation with tryptophan metabolites that are used to generate nicotinamide dinucleotide (NAD/NADH) for mitochondrial energy production, alter VPA-induced phenotypes and cellular functions in an *in utero* VPA exposure mouse model. We anticipate that these approaches will provide a unique perspective of ASD pathophysiology, with data integrated across model systems that we could not achieve without this multi-disciplinary research team or through investigators at a single South Carolina Institution.