Metabolic contributors to stress pathology in the *mdx* mouse model of Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a genetic muscle wasting disease resulting from loss of dystrophin protein. Identifying molecular biomarkers and novel phenotypes that can delineate stages of DMD disease progression and inform on targetable pathways may help to extend patient lifespan. Disease progression in the *mdx* mouse model of DMD is generally milder than the human DMD disease course. However, our lab recently uncovered unique and severe stress response phenotypes exhibited by *mdx* mice, ranging from tonic immobility after scruff handling to significant lethality after psychosocial stress. Strikingly, *mdx* mice with transgenic restoration of nearly full-length dystrophin or utrophin protein in skeletal muscle are protected against stress-induced inactivity and lethality. Our data suggests an essential role for skeletal muscle dystrophinopathy in *mdx* susceptibility to graded forms of stress. A recent study shows that DMD patients exhibit a stress-induced startle response that may mirror *mdx* stress susceptibility, urging an investigation into potential DMD psychosocial stress pathology.

My research employs genetic engineering and biochemical approaches, along with metabolomics technology, to identify biomarkers and metabolic pathways that are mechanistically relevant to *mdx* stress pathology. The kynurenine pathway (KP), a major route for hepatic tryptophan degradation and *de novo* NAD^+ synthesis, is dysregulated in *mdx* skeletal muscle and hypothesized to mediate detrimental *mdx* stress phenotypes. My work has ruled out a direct role for the KP in *mdx* stress-induced inactivity and lethality. Recent work from other labs implicates CD38, an NAD^+-catabolizing ectoenzyme, in *mdx* β-agonist-induced mortality, suggesting that CD38 hyperactivity may dysregulate canonical stress signaling pathways. I have characterized NAD^+ metabolic shifts in *mdx* skeletal muscle after psychosocial stress, with results that support increased CD38 catabolism. Elucidating impairments in a dystrophic stress response will be translationally impactful in developing therapies for improved DMD patient quality of life.