THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

Lauren Covert, MD

Assistant Professor
Department of Pediatrics

Duke University

Bioengineered Human Muscle as a Platform for Drug Discovery and a Cure for Juvenile Dermatomyositis

Juvenile Dermatomyositis (JDM) is the most common childhood-onset inflammatory disease of muscle in the US, with around 3,000 to 5,000 existing cases and approximately 250 newly diagnosed children each year. Children typically develop rash and weakness that can progress from difficulty performing daily activities to inability to move, swallow, or breathe effectively if left untreated. The condition is believed to be an autoimmune disease but the causes of JDM are not understood. Treatments are limited to medications that greatly increase the risk of infection, have toxic side effects, and do not always improve outcomes for children. In fact, two out of three children with JDM suffer from chronic impairment despite standard treatment. Over the past six decades, the therapy has remained imprecise with unpredictable patient-centered efficacy; there are still no FDA approved medications for JDM. This slow progress stems principally from the lack of an adequate model for how this disease occurs. Furthermore, current treatments for JDM are based on evidence from clinical trials in adults, not children, which is common across many pediatric diseases. These research barriers highlight the importance of developing better platforms to study childhood disease. Therefore, to expedite therapeutic development for children with JDM, I propose to resolve how muscle weakness occurs in JDM using a human tissue-derived muscle model called myobundles, which mimic human skeletal muscle's structure, function, and response to drugs. With myobundles made from JDM patient muscle cells, I will examine the link between type I interferons (IFN), which are highly upregulated proteins known to decrease muscle contractility, and a cluster of downregulated genes I have identified that are associated with mitochondria, the energy source of muscle cells. As no prior investigation has characterized how IFN impacts mitochondrial remodeling, I will test my hypothesis that exposure of skeletal muscle to IFN leads to dysfunctional remodeling of mitochondria, which sustains a feed-forward cycle of IFN production. Considering that mitochondrial organelles contain a distinct form of DNA, that if leaked outside of the organelle can trigger inflammatory signaling and the production of IFN, I will determine whether skeletal muscle alone, without interaction with other cell types or exogenous IFN, is triggered to produce IFN and create subsequent muscle weakness. If I am successful in identifying a druggable target pathway for JDM, it will expedite discovery of less toxic therapies, which will give hope to families and improve the quality of life of affected children.