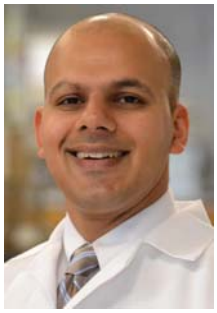
THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

Saptarsi Haldar, MD

Assistant Professor
Department of Medicine

Case Western Reserve University



Creating a New Treatment Approach for Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a devastating and incurable muscle wasting disease of childhood, affecting 1 in 3,500 newborn boys in the United States. It is a genetic disorder that occurs when a child inherits a nonfunctional copy of the dystrophin gene which leads to a decrease in the amount of the dystrophin protein. Despite modern medical care, DMD patients are typically wheelchair bound by age 12, require breathing-assistive machines by late teens, and are dead in their twenties. Unfortunately, the only approved drugs that slow the pace of DMD progression are the glucocorticoid class of steroids, which have severe side effects for growing children. Glucocorticoids can cause significant morbidity and suffering when taken chronically, including osteoporosis, cataracts, hypertension, weight gain, fluid retention, immune suppression, neuropsychiatric abnormalities brittle bones, high blood pressure, and behavioral disturbances. An alternative to glucocorticoid steroids is urgently needed. To address this unmet need, Saptarsi demonstrated in mice that this glucocorticoid-mediated increase in KLF15 improves the ability of skeletal muscle to efficiently burn fuel (fats and amino acids) and thus renders muscle more "metabolically fit" for the demands of exercise. Since this ability to efficiently burn fuel is absolutely essential for healthy muscle function, he hypothesized that children with DMD might have inappropriately low levels of KLF15 and abnormalities in muscle metabolism. He confirmed that levels of KLF15 and its key metabolic functions are low in muscles of patients and animals with DMD and subsequently demonstrated in a fish model system that low levels of KLF15 make this disease much worse. Based upon his discovery that one of the body's own steroid hormones can boost muscle transcription factor KLF15 levels during exercise, he proposes that KLF-15 is a drugable target whose activation could be used as a steroid-sparing therapeutic strategy to treat children affected with DMD. To address this possibility he plans to use a mouse model of DMD and high-throughput screening of small drug molecules to identify novel drugs that will activate KLF-15. If his strategy works to boost KLF15 levels by this approach, it will provide an effective alternative to oral glucocorticoid therapy that avoids the undesirable associated side effects. If he is successful, it will mean a significant increase in the quality of life and longevity of children suffering from DMD.