THE HARTWELL FOUNDATION

2022 Individual Biomedical Research Award

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Targeting Recovery of Muscle Function Following Botulinum Neurotoxin Therapy in Cerebral Palsy

Cerebral Palsy (CP) is the most common cause of childhood physical and movement disability in the United States and affects 1 out of every 345 children. CP is a disability caused typically by a nonprogressive neurological injury that occurs at or near the time of birth and spans a lifetime. Sadly, each year approximately 10,000 babies and children are newly diagnosed. Often described as a progressive skeletal muscle disorder, the muscles of an affected child do not grow properly and over time become relatively smaller and stiffer, exacerbating already impaired movement due to muscle hyperactivity (excessive tone or tension) and related weakness from the initial neurological injury. As the child grows, increasingly stiff muscles result in prolonged muscle contraction (spasticity), which causes bones to adapt and become deformed. Over time, joints are exceedingly hard to move and ultimately, require invasive muscle, tendon, and bone surgeries to relieve discomfort. Lifelong physical therapy can be useful to reduce muscle tightness and delay surgery, but a common regimen includes Botulinum neurotoxin (BoNT). Muscle injections of BoNT induce local paralysis, reducing muscle hyperactivity and associated stiffness. However, detrimental consequences are now recognized with long-term BoNT therapy in CP where, contrary to intentions, repeated injections of BoNT work to impair muscle growth, decrease muscle function, and potentially speed up time to critical surgery. In children with CP, the challenge will be to differentiate muscle changes due to BoNT from those caused by CP related muscle impairments, as the two occur concurrently. To derive a target strategy to optimize muscle function, I will examine the effect of BoNT injections with a controlled juvenile mouse model before shifting to impaired models and humans in future studies. My focus will be how the BoNT time course effect induces structural and passive mechanical changes in muscle, from macro-scale to the nanostructure, including reduced mass, increased stiffness, altered architecture, and altered extracellular matrix structure, changes that occur simultaneously with an elevated immune response. To identify targets for intervention, I will explore the immune response and stem cell impairment as driving forces that shape change, deploying ex-vivo and in-silico computational models to explore how a change in tissue structure contributes to altered mechanical properties. If I am successful in determining how BoNT affects muscles in children with CP, it should be possible to develop a target strategy that reduces stiffness and optimizes muscle function in children with CP during long-term BoNT therapy. Such an effect would be to delay/prevent invasive surgeries, decrease caregiver burden, and generally improve the quality of life in affected children.