THE HARTWELL FOUNDATION

2014 Individual Biomedical Research Award

Yong-Chao Ma, Ph.D.

Assistant Professor
Department of Pediatrics

Northwestern University

Rescuing Motor Neuron Degeneration in Spinal Muscular Atrophy by Reducing the Traffic Jam of Mitochondria

Spinal Muscular Atrophy (SMA) is a fatal pediatric neuromuscular disease that affects approximately 1 in 6000 live births in the United States. It ranks as the number one genetic cause of infant mortality. Remarkably, there are approximately 6 million genetic carriers of SMA in the United States. Similar to amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), SMA is characterized by the degeneration of motor neurons (nerve cells that control muscle movement), causing progressive wasting and paralysis of muscles, respiratory distress and, ultimately, death. Most SMA patients die before the age of 4. In the final years of illness the financial burden to an affected family is substantial, with the emotional toll incalculable. Currently, there is no effective treatment to prevent, halt or reverse this devastating disorder, as the molecular and cellular mechanisms underlying motor neuron death are unknown. In this regard, Yong-Chao has recently discovered a previously unrecognized pathogenic mechanism for SMA, where the activity of particular proteins, cyclin-dependent kinase 5 (Cdk5) and the phosphate form of histone deacetylase 5 (HDAC5), is significantly increased in spinal motor neurons affected by the disease. Based upon his preliminary data, he hypothesizes that the high level of Cdk5 activity may lead to defects in the transport of mitochondria (a specialized part of a cell analogous to an organ) along the long nerve fibers that connect motor nerve cells with their muscle targets — in effect, causing a *traffic jam* of mitochondria. Because mitochondria are essential for generating energy and maintaining the balance of calcium within cells, his hypothesis is that gridlock in mitochondrial transport compromises the energy supply for proper motor neuron function and survival, thus leading to motor neuron degeneration. By contrast, he predicts that inhibition of Cdk5 kinase activity and the subsequent reduction in enzymatic modification (phosphorylation) of HDAC5 will reduce the mitochondrial traffic jam, alleviate SMA disease symptoms and potentially halt the progression of this disease. Yong-Chao proposes to test this novel mechanism underlying SMA motor neuron degeneration in a mouse model. If he is successful, it will be possible to facilitate the development of an exciting new treatment for children affected with SMA, with ultimate success achieved when motor neuron degeneration is reversed and normal motor function restored, benefitting the thousands of affected children in the United States who otherwise face certain death from this debilitating muscle-wasting disease.