

Exciting IRSF Studies in Motion: Investigators pursue potential HDAC6 inhibitor Rett therapy

We are happy to report that IRSF funded investigator Dr. Alan Kozikowski from the Department of Medicinal Chemistry at the University of Illinois-Chicago has recently published work in *Nature Medicine* that a compound in the SMART library demonstrates curative effects in a mouse model of the peripheral neuropathy disorder called the Charcot-Marie-Tooth (CMT). CMT is a disorder of the peripheral nervous system and is characterized by a slowly progressive degeneration of the muscles of the limbs and extremities. Although the complete spectrum of symptoms associated with CMT differs from those of Rett syndrome (RTT), these two disorders do share some commonalities at the cellular level, where the neurons are not functioning normally. Within the neurons associated with CMT or RTT, there is evidence that the transport of essential cellular components is inefficient, and this results in impaired neuronal cell communication.

In this recent report, Dr. Kozikowski and colleagues have shown that a compound called Tubastatin A can restore the transport deficiency of CMT cells and correct the motor and sensory deficiencies found in a CMT mouse model. Tubastatin A is a compound that can inhibit a protein called HDAC6, which plays a large role in regulating cellular transport systems and may also influence the expression of many genes including *MECP2* (the gene mutated in RTT).

During the 12th Annual Rett syndrome Symposium this past June, IRSF funded scientists Dr. John Christodoulou from the University of Sydney, Dr. James Eubanks from the Toronto Western Research Institute, and Dr. Yi Eve Sun from the University of California-Los Angeles have laid additional groundwork that suggests HDAC6 may be a key target in RTT mice. Their preliminary work shows the potential of Tubastatin A in decreasing symptoms such as seizures in RTT mice. Further studies are under way to determine whether these improvements may be a result of restoring the transport systems within the neuron cells. IRSF is playing a major role in moving research forward to examine Tubastatin A and other compounds in the SMART library that hold promise as potential therapeutics in the treatment of Rett syndrome.