Arginine Methylation as a Regulator of SMN activities in Motor Neurons

Objective: We will study and obtain more information about the role of a novel protein, called PRMT8, which is present at the surface of the cells that are most affected in SMA, the motor neurons in lower spinal cord.
Research Strategy: We will test the possibility that PRMT8 may be able to make the SMN that is still present in small amounts in SMA patient cells, more active. Preliminary results obtained in our laboratory suggested to us that PRMT8 could regulate the binding of specific proteins to a region of the SMN protein called the Tudor domain in motor neurons.
Significance of the Project: Stimulating the activity of the protein, PRMT8, could potentially have beneficial influence on the activity of SMN that is still present inside SMA cells. Thus our work has the potential to lead to completely new strategies for SMA therapies as well as a greater understanding of how SMN functions specifically in motor neurons.

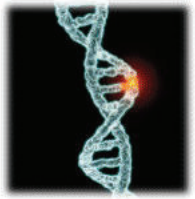
Progress to Date Made on this Project:
Amongst the first things we wanted to confirm for this project to be viable was whether or not this protein, PRMT8, was indeed present at the surface of spinal cord motor neurons, the cells that are most affected in SMA. We are happy to say that we have been able to confirm that PRMT8 is present at the surface of moror neurons, and that at a similar level in SMA spinal cord relative to unaffected animals. We have performed these experiments using various mouse and cell culture models of SMA, and we would still like to confirm this in human motor neurons. We have also demonstrated, using motor neurons grown in a petri dish, that PRMT8, similar to SMN, is playing an important role for the normal function of these cells and for their survival. Confirming that it may indeed represent a good therapeutic target.

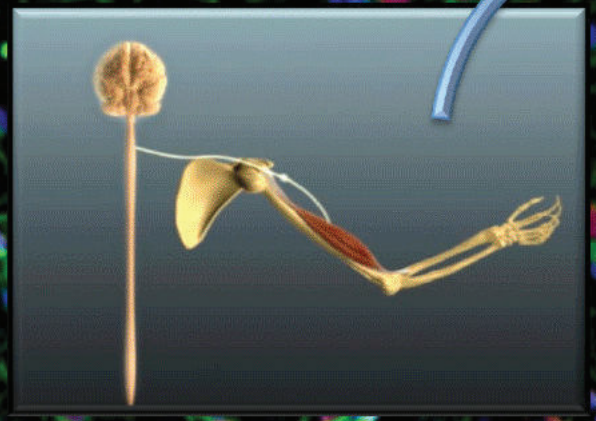
In a second Research Objective we wanted to investigate in more details 'how' PRMT8 might be influencing SMN function. One simple way to look at this is to picture SMN as part of a 'lock-and-key' mechanism, where SMN constitutes the 'lock' and the 'key' would be proteins that are decorated with a special modification or mark called a 'methyl group'. This is where these enzymes called PRMTs come in, as they are the ones that will add this special mark on proteins, in turn making them a good 'fit' for binding to SMN. We have now identified and characterized at the molecular and biochemical level a number of proteins that can be modified by PRMT8 to become better interacting partners for SMN.

In a 3rd and final objective, we have been testing more directly, again using either motor neurons grown in petri dishes or mouse models of SMA, whether an increase in levels and/or activity of PRMT8 in motor neurons could indeed lead to some molecular and, more importantly, functional benefits. These last set of experiments are currently ongoing and should be completed by the end of next summer.

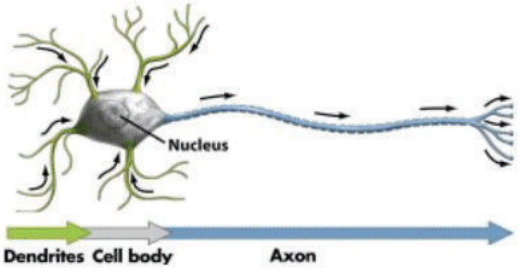
Spinal Muscular Atrophy (SMA)

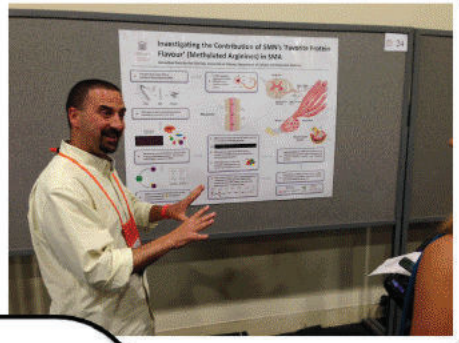
SMA is caused by mutation of SMN gene





Motor neuron disease





mRNA
SMN
RBP

SMN travels along neuronal axons in RNA granules to deliver key molecules to neuromuscular junctions

SMN