

Blazeman's War on ALS The Front at Wake Forest School of Medicine Fall 2011

In the Spring of 2010, Ramon Jimenez-Moreno, Ph.D. a postdoctoral fellow and amateur triathlete gave a presentation at the Packard Center for ALS Research at Johns Hopkins. In this presentation he outlined a potential project that would begin to investigate if a possible therapeutic approach for ALS could be to induce the positive effects of exercise, (increase mitochondria number and size, switch fiber type towards a more resistant phenotype, prevent atrophy, and increase vasculature) but without any of the possible negative effects (exercise induced-injury). Although the motoneurons that control

muscle movement become dysfunctional and die, muscle weakness due to denervation is the first diagnostic sign of ALS. From physiological studies, large motor neurons that innervate fast-type muscle fibers are the most vulnerable in ALS. Endurance athlete's muscles are characterized by a higher percentage of slow-type fibers innervated by motoneurons thought to be resistant in ALS. Some of the physiological adaptations to endurance exercise are: increased mitochondria size and number, increased vasculature, and higher proportion of slow type fibers. From what we understand about ALS, these adaptations should be beneficial to promoting motoneuron health and function. One would then expect that endurance athletes are less susceptible to ALS; however, this is not the case. One possible explanation for this dichotomy could be that exercise induced-injury could be an explanation for the lack of exercise benefit, where the effects of this injury negate muscle adaptations that promote motoneuron health. The project had a logical rationale, but initial experiments did not produce positive results. This was because Ramon had learned that the agent that they purchased was not the same as the one used by investigators who published positive results. The differences between the two sources of the agent most likely involved purity, but the major concern for Ramon was cost and lack of funding to purchase the agent shown to be effective.

AICAR is a chemical that was given to mice that did no exercise. These mice could then run 44% farther on a treadmill than those that did not receive the drug. The same study showed that AICAR treated mice had more muscles with characteristics slow-type fibers than the untreated mice. While there is much controversy regarding the use of AICAR to substitute for exercise and its use in athletes, this chemical could provide the endurance exercise benefits to ALS patients while allowing them to avoid the exercise induced-injury. Furthermore, AICAR has been tested in humans for a variety of conditions.

AICAR activates AMPK. AMPK is a fuel-sensing serine/threonine kinase in cells that is activated under conditions of energetic demands, such as exercise, to restore energy balance (2). Chronic administration of AICAR activates AMPK increasing the expression of genes implicated in oxidative metabolism, mitochondrial biogenesis and in muscles a switch to slow-type fibers.

Thanks to the Blazeman Foundation for ALS, Ramon, working with Carol Milligan, Ph.D., Ron Oppenheim, Ph.D. and the ALS Translational Research Group at Wake Forest School of Medicine has been able to begin to investigate if AICAR has therapeutic value in the mouse model of ALS.

The group has completed aim 1 and shown that AICAR induces the expected results in the mice. Administration of AICAR activates and increases expression of AICAR, and appears to increase mitochondria in muscle and spinal cord. The experiments were essential to determine that the agent works as expected.

The second aim of the study is to administer AICAR and determine if early muscle denervation is diminished in treated animals. These experiments are poised to begin and will provide the data to determine if AICAR is a candidate for ALS therapy. If the results of aim two's experiments are positive, then more extensive experiments to determine if AICAR slows disease progression and significantly extends lifespan of the animals will begin. Together, the results of the AICAR experiments will serve as a pre-clinical trial that may lead to clinical trials and a potential therapeutic.



Pictured are some of the members of the ALS research team: from left to right, bottom row, Ramon Jimenez-Moreno, Ron Oppenheim, Carol Milligan, Jane Strupe; top row, David Gifondorwa, David Prevette and Carol Mansfield.