Title of Program: Experimental Therapy for Muscular Dystrophies

Dept/Center/Lab: McColl-Lockwood Laboratory
Department of Neurology
Carolinas Medical Center

Principal Mentor: Guqi Wang, PhD
Research Scientist

Bo Wu, PhD
Research Scientist

Xiaohua Wu, PhD
Research Scientist

Other Faculty: Qi Lu, PhD
Director

Summary Description:
Our laboratory carries out biochemical, molecular, and cellular biological research designed to improve our understanding of muscular dystrophy and to develop therapy for the disease.

Project 1. Antisense oligonucleotides therapy uses fragments of gene sequence to target specific regions (called exons) of the human dystrophin gene. This removes the defected part of the dystrophin gene and restores the expression of dystrophin protein which is missing in the DMD patients. Our laboratory has made significant progress in this area and specifically has demonstrated restoration of dystrophin expression in bodywide muscles through systemic delivery of antisense oligomers. Long-term maintenance of dystrophin expression and functional improvement of muscles can also be achieved. The results have been published in several prestigious journals including PNAS (2005) and Nature Medicine (2003 and 2006). Clinical trials are being planned. More recently, full restoration of dystrophin in all body muscles including heart muscle has been accomplished (PNAS, 2008 Sept 30 online). The project for this summer student will be to access the effect of oligomer for skipping of human dystrophin exon as part of preparation of clinic trials.

Project 2. An increase of intracellular calcium is widely thought to be an important factor in the dystrophic pathogenesis. The abnormal dystrophin-glycoprotein complex results in the loss of linkage between the extracellular matrix and the actin membrane cytoskeleton. Excitation - contraction coupling and overall calcium-handling is impaired. Stress-induced calcium channels are activated and calcium-leak channels are introduced into the muscle periphery thereby triggering a pathophysiological calcium level in muscle fiber. The elevated calcium levels increase proteolytic degradation of muscle proteins. Osteopenia is common in muscular dystrophic patient. Calcium antiresorptive drugs that have the ability to simultaneously bind/chelate calcium. The drugs can slow down bone loss and may reduce muscular calcium, therefore, decrease muscle inflammation, apoptosis, and delay/inhibit dystrophic pathogenesis. The project for this summer student research program will be the studies of role of calcium antiresorptive drugs on intracellular calcium concentration and oxidative stress in skeletal muscle cells.

Expectations and Role of Student:
Project 1. The successful student will be expected to bring enthusiasm, inquisitiveness, hard work, and passion. The student will be expected to learn and perform cell culture, oligo-treatment to the cells, tissue dissection, cryosectioning, immunostaining and other related techniques. He or she will also learn how to frame and refine an important hypothesis; and to design and carry out experiments designed to confirm or refute the key hypothesis. The student will present oral and written summaries of research and will be required to prepare and present an abstract and paper summarizing findings.

Project 2. Effect of calcium antiresorptive drugs on intracellular calcium concentration and oxidative stress in skeletal muscle cells. The successful student will be expected to bring enthusiasm, inquisitiveness, hard work, and passion. The student will be expected to learn and perform cell culture, calcium assay, evaluation of cellular oxidative stress and apoptosis. By involving lab research activities, the student will learn how to frame and refine an important hypothesis; and to design and carry out experiments designed to confirm or refute the key hypothesis. The student will present oral and written summaries of research and will be required to prepare abstract and paper summarizing findings.