The NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS) recently announced a major U01 grant award to Principle Investigator Dr. Qi Lu, Ph.D, Director of The McColl-Lockwood Laboratory for Muscular Dystrophy Research at Carolinas Medical Center. The grant is called “Antisense therapy for DMD” with the aim to develop a novel experimental therapy into clinic trials, and ultimately into treatment for one common type of muscular dystrophy, Duchenne Muscular dystrophy (DMD).

DMD, which affects one in every 3,500 male babies, is caused by mutations in the gene for dystrophin, a protein that is critical for proper muscle functioning. If the protein is defective, muscle wasting and eventually paralysis of muscles occurs. Such muscle degradation occurs in heart muscles and muscles for breathing as well as skeletal muscles performing body movement. Survival is rare beyond the early 30s and currently no effective treatment exists.

Exon skipping is a novel approach for treating DMD. It differs from the conventional gene therapy which aims to deliver a copy of normal or near normal dystrophin gene into the patients to replace the defect dystrophin gene. Exon skipping aims to repair the patient own defected dystrophin gene to make a functional dystrophin protein again. In this instance, a specifically designed piece of material called “oligomer” is used to recognize the defect part of the gene. The therapy called exon skipping came from the fact that binding of the oligomer forces the muscle cells to remove (thus called to skip) the defected part (called exon) of the gene. As a result, the normal parts of the gene joint together to make a shorter, but functional protein.

The potential of exon skipping for treating DMD was raised about 12 years. In 2003, Dr. Lu and his research team demonstrated for the first time that exon skipping can achieve production of therapeutic levels of dystrophin in dystrophic muscles in model of DMD. This result was published in the journal ***Nature Medicine*** and laid a corner stone for the current enthusiasms for clinic development of the therapy. Shortly afterwards, Dr Lu’s group further showed that oligonucleotide as drug can be delivered via blood system to produce dystrophin in body-wide muscle (Published in ***Nature Medicine and Proccedings of the National Academy of Sciences*** . Currently, two clinic trials conducted in Europe has provided evidence as proof of principle that specific oligomers can repair the defected dystrophin gene in the DMD boys in a similar fashion as in the animal models.

One limitation of this potential therapy for DMD has been the failure to effectively deliver the oligonucleotide molecules into heart muscle. Restoration of skeletal but not cardiac muscle function may actually increase the burden of heart, causing harm to the heart of the treated DMD patients. To address this issue, Dr. Lu in collaboration with AVI Biophama modified the structure of the oligomers and demonstrated that systemic delivery of this modified oligomer restored dystrophin levels to almost normal in both skeletal and cardiac muscles in a mouse model of DMD. The restoration of dystrophin was associated with significant improvement of muscle strength and cardiac function. These findings were published in the ***Proccedings of the National Academy of Sciences*** raises hope that exon skipping may be able to rescue the respiratory and heart failure in DMD patients.

With the Funding from the NIH, Dr Lu’s team plans to develop a system by which highly effective oligomers can be selected specifically to skip defected dystrophin exons essential for the rescue of majority of DMD boys. These oligomers will then be further developed into drugs for clinic trials in DMD.