Scientist clears hurdles for muscular dystrophy therapy

October 29 2008

Approximately 250,000 people in the United States have some form of muscular dystrophy. Duchenne muscular dystrophy (DMD) is the most common type of the disease, predominantly affecting males. Boys with DMD will lose the ability to walk by their teens and typically die before the age of 30. For years, scientists have studied the use of gene therapy as a possible way to correct the muscle deterioration, but hurdles such as the need to treat all muscles in the body, including both skeletal muscle and heart muscle, have challenged researchers looking for an effective therapy until now.

In recent studies, published in *Molecular Therapy* and *Human Gene Therapy,* a team of University of Missouri researchers, led by Dongsheng Duan, associate professor of molecular microbiology and immunology, has found not only a delivery method that can reach every muscle of the body in a large animal model, but a therapy that will work on both skeletal muscle, the type found in arms and legs, and cardiac muscle, such as the heart.

"The difficult challenge with treating Duchenne muscular dystrophy, and other types of muscle-related diseases, is that the therapy must reach almost every muscle throughout the body," Duan said. "We have found that our new therapy, which uses a particular virus to deliver the gene therapy, reaches all of the muscles in large animals. This development raises the hope of whole body correction of Duchenne muscular dystrophy."

Patients with Duchnne muscular dystrophy have a gene mutation that disrupts the production of a protein known as dystrophin. Absence of this protein starts a chain reaction that eventually leads to muscle cell degeneration and death. Eventually, the damaged muscle tissue is replaced by fibrous, bony or fatty tissue and loses function. In the heart, this leads to severe heart disease and can place severe limitations on individuals afflicted with the disease.

In gene therapy, mutated genes are replaced with healthy genes. However, even with gene therapy, the healthy genes must reach every muscle in the body. Previously, scientists, including Duan's team, have experimented using viruses to deliver the healthy genes. However, these earlier studies were conducted in mice. Duan's team has now proven that this delivery system will reach every muscle in larger animals, such as dogs.

"Between 40 percent and 60 percent of the body weight is muscle, so it's vital that we find a way to deliver the therapy to every muscle in the body," Duan said. "Since dogs are 250 times the size of mice, but only nine times smaller than a human on average, we have taken a significant step in understanding if this therapy can work."

Duan's team has not stopped with just that discovery. In gene therapy, it is not feasible to fix every cell in the heart. Previously, scientists were uncertain whether partial correction could benefit patients. In an earlier study, Duan's research team demonstrated that heart tissue could be corrected enough to sustain a healthy life if only 50 percent of the tissue was affected by the therapy. Following the success with heart tissue, Duan's team has demonstrated for the first time that this result also is true with live heart muscle.

The Mizzou researchers delivered the therapy to the hearts of newborn mice with muscular dystrophy and found that gene therapy corrected

many of the electrocardiogram abnormalities in these mice.

New tests have been developed to screen newborns with a high risk of muscular dystrophy. With few treatments available, the screening has not been widely accepted, but that may change if Duan's therapy proves to be effective.

"If you can treat an infant before they develop symptoms, you can treat the patient before they experience muscle loss," Duan said. "If you wait until symptoms start to appear, the muscle has already started to deteriorate. It's very difficult to treat when there is no muscle there."

Source: University of Missouri-Columbia