Clinical trial of molecular therapy for muscular dystrophy yields significant positive results

July 25 2011

A molecular technique originally developed at the University of North Carolina at Chapel Hill has taken one step closer to becoming a treatment for the devastating genetic disease Duchenne muscular dystrophy.

The novel treatment uses strips of genetic code – called antisense oligonucleotides – to restore the function of a defective dystrophin gene. In a study published July 25, 2011 in the journal *The Lancet*, researchers from the U.K., U.S. and Australia demonstrated that a phase Ib/IIa trial of the approach restored production of the critical muscle protein missing in patients with the progressive neuromuscular condition.

"When I first tried my approach in a test tube some twenty years ago, a reviewer of my manuscript commented that it was 'molecular gymnastics that will never amount to anything,'" said study author Ryszard Kole, PhD, a professor of pharmacology who has taken a leave of absence from UNC to develop the technology with AVI Biopharma, in Bellevue, Washington. "Now we have evidence that it works, and in an illness that has no other good therapeutic options."

Duchenne muscular dystrophy is a lethal disease that affects 1 in 3500 newborn boys. In the disease, omissions or misprints in the letters of the dystrophin gene cause its "reading frame" to shift, abbreviating the instructions for making the dystrophin protein. As a result, the cells fail

to make a functional muscle protein and patients eventually lose their ability to walk and breathe. In a milder form of the disease, called Becker muscular dystrophy, the genetic defect leads to one missed component but leaves the rest intact, resulting in a muscle protein that is largely functional and patients that can have a normal lifespan.

In the current study, the researchers tested a way to turn the lethal to the livable form of the illness by using antisense oligonucleotides, strings of genetic lettering that can stick to and mask sections of code. The oligonucleotides cause the cell's "splicing" machinery – responsible for cutting and pasting the instructions together – to skip a few paragraphs so the reading frame is back on track and the rest of the dystrophin protein can be made as instructed.

To prove this concept, the scientists administered the treatment intraveneously (IV) to 19 Duchenne muscular dystrophy patients over the course of 12 weeks. They found that the drug was well tolerated and appeared to increase the levels of dystrophin protein in a statistically significant dose-dependent manner. The best 3 responders showed an increase following treatment of protein levels from 2 percent to 18 percent, from 0.9 percent to17 percent and from 0 percent to 7.7 percent of normal muscle, respectively.

They now plan to expand their studies in a next trial, increasing both the dose and the duration of the treatment to see if the approach has clinical impact. In the future the researchers would like to develop alternative formulations of the drug that can be administered subcutaneously, like for diabetes, or perhaps even in pill form. But Kole says even the current approach holds great promise for the over 30,000 people who have the illness worldwide.

"If I get to see one child benefit from this treatment, it will be a life as a scientist well spent," said Kole.