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Scientists find drug that may help fight duchenne muscular dystrophy

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Drugs are currently being tested that show promise in treating patients with Duchenne muscular dystrophy (DMD), an inherited disease that affects about one in 3,600 boys and results in muscle degeneration and, eventually, death.

Now, scientists at UCLA have found a drug, already approved by the U.S. Food &Drug Administration and being used in humans, that provides a powerful boost to the therapy currently being tested in clinical trials. They hope this one-two punch used in combination will overcome the genetic mutations that cause DMD, restore a missing protein needed for proper muscle function and allow those affected by the disease to lead relatively normal lives.

The drug, dantrolene, was found after researchers examined thousands of small molecules using a high through-put molecular screening technique that allows them to scrutinize many molecules at the same time, said study senior authors Dr. Stan Nelson, a professor of human genetics, and Carrie Miceli, a professor of microbiology, immunology and molecular genetics.

"Dantrolene is such an attractive candidate to test in this disease as it's already approved, has been used safely in humans for decades and we won't have to go through the lengthy and costly drug development process," Nelson said. "We were very pleased to find out that this drug seems to work synergistically with the drugs being tested now on boys with DMD."

The study appears Dec. 12, 2012, in the peer-reviewed journal *Science Translational Medicine*.

The research by Miceli and Nelson is driven by more than just scientific curiosity. Their youngest son, Dylan, 11, was diagnosed with DMD in 2004. While he's still ambulatory – many DMD patients require the use of wheelchairs by about age 10 – Dylan can no longer run or climb stairs and he can't shoot a basketball over his head like other boys his age. Despite these challenges, Miceli said Dylan remains a happy, funny and engaged boy, full of life and passion.

"We entered into this field because of the diagnosis of our son, but we hope our research can help many others," she said. "There are drugs that can help manage the symptoms of the disease, but nothing that changes its course dramatically. We're trying to correct the defect that causes DMD with highly personalized genetic medicine."

DMD is caused by mutations in the Duchene gene, located on the X chromosome and necessary for correct muscle cell function. The mutations prohibit production of the protein dystrophin, causing the muscles, as well as the heart and respiratory system, to deteriorate. An exon or exons are deleted in the mutant gene, causing the cellular machinery to "skip over" the exon and making what was once a readable genetic instruction unreadable.

The drugs being tested in DMD boys now use small pieces of DNA called antisense oligonucleotides to act as molecular patches that allow for the production of dystrophin. The trials thus far have shown that the exon skipping therapy is working, however not enough dystrophin is being produced for fully normal muscle function. Nelson and Miceli sought out molecules that could give a boost to the exon skipping drugs so DMD patients can produce enough dystrophin for more normal muscle function.

Miceli and Nelson, members of the Broad Stem Cell Research Center at UCLA, used DMD patient-specific stem cells and reprogrammed them into muscle cells and then treated them with the exon skipping drugs. The molecular screening technique then added the thousands of small molecules to the cells and the results were analyzed by studying the treated cells to see which cells responded to what molecule. Dantrolene showed promise, Nelson said.

In collaboration with Melissa Spencer, a professor of neurology at UCLA, the scientists tested the combination in a DMD mouse model. The animals were treated with dantrolene in combination with the exon skipping drugs. The treated mice produced more dystrophin and showed improved muscle function. Tests showed the DMD mice treated with the combination therapy were significantly stronger than those that weren't.

DMD, the most common of childhood's deadly DNA-linked diseases, generally leads to death by respiratory or heart failure in the teens or early 20s. Miceli and Nelson hope that their one-two punch could lead to longer life spans for boys with DMD.

"Our hope is that these boys won't have to die so young and suffer from the progressive muscle degeneration and the loss of mobility that they do now," Miceli said. "We hope to find a therapy that at the least results in much more mild symptoms and delays by many years the on-set of this disease."

Going forward, Nelson and Miceli will further their research with the goal of translating their findings from the bench to the bedside. The pair has received a $6 million grant from the California Institute of Regenerative Medicine to do longer term studies of their drug combination therapy in mouse models to ensure it can restore dystrophin levels to normal or near normal levels. They also will explore whether DMD patients with other mutations can benefit from the combination

therapy. They hope their work will result in clinical trials testing the exon skipping drugs with dantrolene or dantrolene-like drugs together in boys with DMD.

"These findings highlight the value of combination therapies and the repurposing of FDA-approved medications as powerful translational strategies," the study states.

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