Scientists exploring new compounds to target muscular dystrophy

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Scientists have identified a promising set of new compounds in the fight against muscular dystrophy. Using a drug-discovery technique in which molecules compete against each other for access to the target – the strand of toxic RNA that causes the most common form of muscular dystrophy in adults – a team at the University of Rochester Medical Center has identified several compounds that, in the laboratory, block the unwanted coupling of two molecules that is at the root of the disease.

The work was published online November 7 by the *Journal of the American Chemical Society*.

"This discovery gives us, for the first time, a molecule that targets the wayward RNA at the root of myotonic muscular dystrophy," said Benjamin Miller, Ph.D., the chemist who led the study. "This is a first step toward developing a drug-like molecule that perhaps could be used someday to treat the disease. This lead molecule provides a framework for moving forward."

Miller leads a team that is developing small molecules that target small strands of RNA. He notes that drugs more commonly target proteins or DNA, but that RNA offers an alluring target for some diseases.

"The drug discovery field really is wide open when it comes to RNA, which is a very difficult molecule to target," said Miller, who is an associate professor in the departments of Dermatology, Biomedical Engineering, and Biochemistry and Biophysics.

The work is the latest in a series of developments in which a Rochester team led by neurologist Charles Thornton, M.D., has shown how a genetic flaw creates the symptoms of myotonic dystrophy, which affects about 35,000 Americans.

"This is an important first step toward developing a drug treatment for myotonic dystrophy. The message from our patients is loud and clear – push this forward as fast as possible," said Thornton, who is co-director of University's Neuromuscular Disease Center.

The disease is marked by progressive muscle weakness, and eventually many patients have difficulty walking, swallowing, and breathing. The disease also affects the eyes, the heart, and the brain. Currently there is no treatment.

The genetic mistake involves a repeated sequence of three chemical bases. Healthy people have anywhere from five to 30 copies of the "triplet repeat" known as CUG on chromosome 19, but people with the disease typically have hundreds or thousands of copies, a kind of molecular stutter. These extra copies become part of large, faulty messenger RNA molecules that can mistakenly glom onto proteins and knockout their normal function.

Earlier this decade, Thornton's team discovered that the faulty messenger RNA has a toxic effect on muscle and heart tissue. The team found that the toxic RNA binds tightly to a crucial protein known as "muscle blind" or MBNL1 and prevents that protein from performing its usual function, ultimately leading to the muscle symptoms of muscular dystrophy.

The goal for doctors is to free up MBNL1 in cells so that it can go about its normal activities, which include building proper chloride channels that are central to normal muscle function.

So Miller set out to free MBNL1 by designing an experiment to search for a small molecule that would sop up extra CUG copies. Using a technique known as dynamic combinatorial chemistry, Miller mixed two sets of 150 compounds, one on polymer beads and the other in solution, and let the components link up with each other in a kind of molecular dance, amid a sea of CUG "triplet repeat" RNA strands. The technique, which Miller helped to pioneer more than a decade ago, allowed him to simultaneously analyze how effectively more than 11,000 molecular combinations could bind to the target CUG RNA strand.

Miller's team sorted out which combinations muscled out the others for access to RNA strands and held most tightly onto them. The team then took the best performers and put them in a solution containing both CUG repeat RNA and MBNL1. Miller's molecules were able to break up the interaction between the two, with the best molecules freeing up to half the MBNL1 – the precise step that needs to be taken in patients with the disease.

The team is continuing its work, further refining the molecules in an attempt to find one that frees MBNL1 even more effectively.

Source: University of Rochester Medical Center