Scientists create potent molecules aimed at treating muscular dystrophy

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While RNA is an appealing drug target, small molecules that can actually affect its function have rarely been found. But now scientists from the Florida campus of The Scripps Research Institute have for the first time designed a series of small molecules that act against an RNA defect directly responsible for the most common form of adult-onset muscular dystrophy.

In two related studies published recently in online-before-print editions of Journal of the American Chemical Society and *ACS* Chemical Biology, the scientists show that these novel compounds significantly improve a number of biological defects associated with myotonic dystrophy type 1 in both cell culture and animal models.

"Our compounds attack the root cause of the disease and they improve defects in animal models," said Scripps Research Associate Professor Matthew Disney, PhD. "This represents a significant advance in rational design of compounds targeting RNA. The work not only opens up potential therapies for this type of muscular dystrophy, but also paves the way for RNA-targeted therapeutics in general."

Myotonic dystrophy type 1 involves a type of RNA defect known as a "triplet repeat," a series of three nucleotides repeated more times than normal in an individual's genetic code. In this case, the repetition of the cytosine-uracil-guanine (CUG) in RNA sequence leads to disease by binding to a particular protein, MBNL1, rendering it inactive. This results in a number of protein splicing abnormalities. Symptoms of this

variable disease can include wasting of the muscles and other muscle problems, cataracts, heart defects, and hormone changes.

To find compounds that acted against the problematic RNA in the disease, Disney and his colleagues used information contained in an RNA motif-small molecule database that the group has been developing. By querying the database against the secondary structure of the triplet repeat that causes myotonic dystrophy type 1, a lead compound targeting this RNA was quickly identified. The lead compounds were then custom-assembled to target the expanded repeat or further optimized using computational chemistry. In animal models, one of these compounds improved protein-splicing defects by more than 40 percent.

"There are limitless RNA targets involved in disease; the question is how to find small molecules that bind to them," Disney said. "We've answered that question by rationally designing these compounds that target this RNA. There's no reason that other bioactive small molecules targeting other RNAs couldn't be developed using a similar approach."

More information: "Design of a Bioactive Small Molecule that Targets the Myotonic Dystrophy Type 1 RNA via an RNA Motif-Ligand Database & Chemical Similarity Searching", pubs.acs.org/doi/abs/10.1021/ja210088v

"Rationally Designed Small Molecules Targeting the RNA That Causes Myotonic Dystrophy Type 1 Are Potently Bioactive", pubs.acs.org/doi/abs/10.1021/cb200408a

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