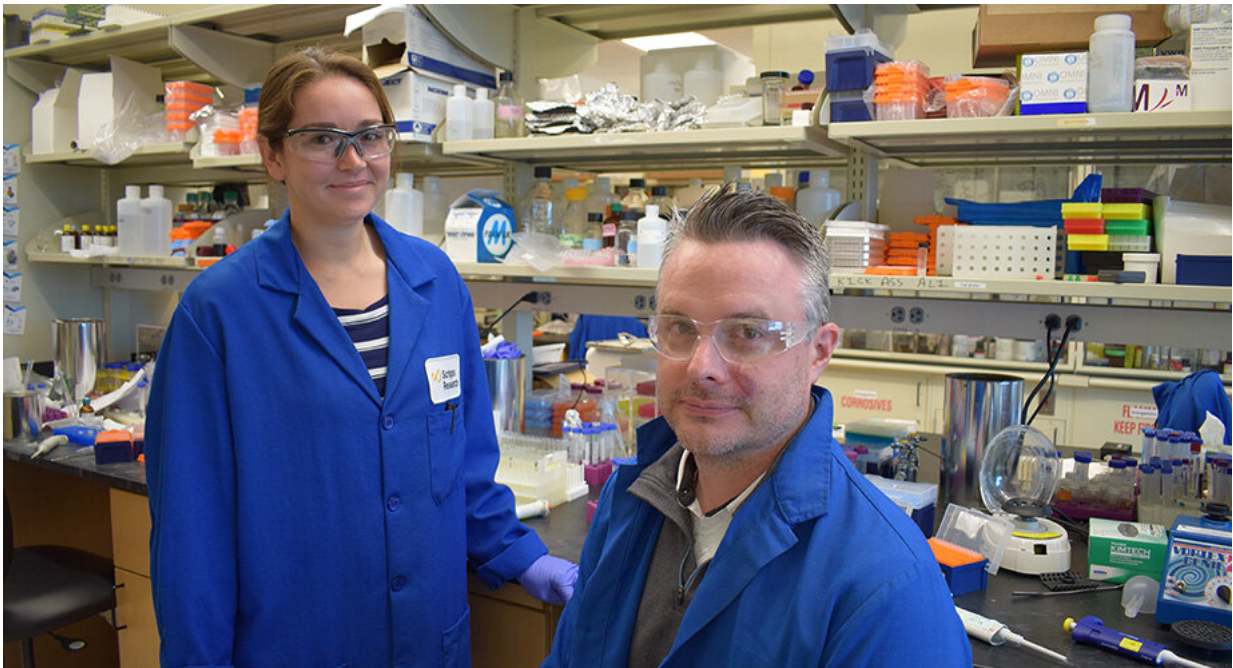


# Two-birds-one-stone strategy shows promise in RNA-repeat expansion diseases

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Alicia Angelbello and Matthew Disney, PhD, in the Disney lab on Scripps Research's Jupiter, Florida, campus. Credit: The Scripps Research Institute

A new strategy for treating a variety of diseases known as RNA-repeat expansion disorders, which affect millions of people, has shown promise in proof-of-principle tests conducted by scientists at Scripps Research.

The results suggest that someday, a handful of well-targeted drugs might

be able to treat the more than 40 human disorders—including Huntington's [disease](#) and variants of amyotrophic lateral sclerosis (ALS)—that arise from RNA-repeat expansions.

"This study lays a foundation for the development of drugs that can address multiple repeat-expansion diseases by targeting shared abnormal structures on their RNAs," says the study's principal investigator Matthew Disney, Ph.D., professor of chemistry at Scripps Research.

In RNA-repeat expansion diseases, [mutant genes](#) contain excess DNA in the form of dozens or even hundreds of repeating short strings of DNA "letters." In [cells](#) where these mutant genes are active, that DNA is copied out into RNA [molecules](#) on the way to being translated into proteins. The resulting abnormal RNAs can cause trouble in a variety of ways, such as by folding up into structures that are toxic to cells.

In the study, published in *Cell Chemical Biology*, the scientists showed that a potential drug molecule they developed can neutralize the toxic RNA that causes two distinct repeat-expansion disorders, myotonic dystrophy 1 (DM1) and Fuchs endothelial corneal dystrophy (FECD). In the latter case, it can do so by an unexpected but powerful mechanism.

## **Genetic diseases in dire need of a treatment**

DM1 is estimated to affect about 140,000 people in the United States. It can manifest anywhere from infancy to adulthood. And while it doesn't always shorten lifespan, it often brings a debilitating set of symptoms including muscle weakness and pain, cataracts, and respiratory and gastrointestinal problems. The disorder is caused by a mutant copy of a gene called DMPK, whose RNAs contain dozens to hundreds of repeats of the RNA letters "CUG."

FECD, which causes progressive damage to the cornea of the eye that

often necessitates corneal transplantation, has a relatively high prevalence; studies suggest it manifests in at least several percent of Caucasian people older than 50. The disorder is caused by a mutant version of a gene called TCF4, whose RNAs also contain abnormally long CUG repeats.

These disorders arise from different mutant genes, and consequently appear in different cell types, but involve virtually the same toxic mechanism: In each case, the inclusion of an abnormally long sequence of CUG repeats causes the RNA copied from the gene to form structures that are "sticky" to certain other proteins in the cell, and effectively capture them—preventing them from doing their jobs in the cell. The depletion of one of these captured proteins, MBNL1, is a particularly important cause of cell damage and symptoms in DM1 and FECD.

## **Encouraging results in pre-clinical tests**

For the new study, Disney and his team used advanced computational methods to design a small organic molecule that selectively binds to the abnormal CUG-expansion RNAs found in MD1- and FECD-affected cells, preventing these RNAs from capturing MBNL1.

To evaluate and improve the molecule, the team used a unique tool they had developed previously, Competitive Chem-CLIP, which allowed them to test their molecule's ability to selectively recognize toxic CUG-expansion structures.

The team showed that in cultured cells derived from patients with DM1, as well as in an animal model of the disease, their improved designer molecule successfully reduced the depletion of MBNL1 and the loss of its function.

In FECD cells, the drug molecule also worked to prevent signs of

disease, but this time by a different and potentially more powerful mechanism. In FECD cells, the disease-causing gene mutation occurs in a non-coding part of the gene called an intron. Normally, introns when copied into RNA are cut out of the RNA almost immediately and degraded by disposal systems in the cell. In FECD, the presence of the CUG-repeat expansion prevents the affected intron from being excised. However, Disney and his team found that their molecule allows that excision to take place, so that the abnormal RNA element is not just blocked but destroyed.

Targeting toxic RNAs with small organic molecules that can be put into pill form has generally been very challenging, so far, Disney notes, but the finding in this study points to the promising possibility of using such molecules not just to block bad RNAs but to trigger their destruction.

"If a drug causes a toxic RNA to be destroyed instead of merely blocking it, then the effect should be longer lasting," he says.

Having performed their proof-of-principle demonstration, he and his team, which includes a startup biotech company, Expansion Therapeutics, are continuing to develop the molecule tested in the study as a potential drug treatment for DM1 and FECD.

The researchers also are taking a similar approach in developing potential drug treatments for RNA repeat-expansion diseases involving CAG repeats, which include the progressive and fatal neurological disorder known as Huntington's disease.

Disney notes that his group's computational approach to drug discovery, versus traditional methods involving the screening of large sets, or libraries, of molecules, gives them a big advantage: "Our ability to do computation-aided design allows us to get initial compounds quickly, and quickly test them," Disney says.

**More information:** Alicia J. Angelbello et al, A Small Molecule that Binds an RNA Repeat Expansion Stimulates Its Decay via the Exosome Complex, *Cell Chemical Biology* (2020). [DOI: 10.1016/j.chembiol.2020.10.007](https://doi.org/10.1016/j.chembiol.2020.10.007)

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