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# Scientists devise new way to dramatically raise RNA treatment potency

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Scientists from the Jupiter campus of The Scripps Research Institute (TSRI) have shown a novel way to dramatically raise the potency of drug candidates targeting RNA, resulting in a 2,500-fold improvement in potency and significantly increasing their potential as therapeutic agents.

The new study, published recently online ahead of print by the journal *Angewandte Chemie*, confirms for the first time that a small molecule actually binds to a disease-causing RNA target—a breakthrough that should help scientists identify precise RNA targets within living cells, profile their interactions, and predict drug candidates' side effects.

"We're trying to make tools that can target any RNA motif," said Matthew Disney, a TSRI associate professor who authored the research with a research associate in his lab, Lirui Guan. "This study completely validates our design—it validates that our compound targets the desired RNA sequence in a complex cellular environment that contains many hundreds of thousands of RNAs."

While targeting DNA has been used as a therapeutic strategy against cancer, few similar approaches have been attempted for disease-associated RNAs.

In the new study, the scientists created a small molecule that binds to the genetic defect in RNA that causes myotonic dystrophy type 1 and improves associated defects in cell culture.

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 the RNA sequence leads to disease by binding to a particular protein, MBNL1, rendering it inactive and resulting in a number of protein-splicing abnormalities.

To achieve the increase in the drug candidate's potency, Disney and his colleagues attached a reactive molecule (a derivative of chlorambucil, a chemotherapy drug that has been used to treatment a form of leukemia) to the small molecule they had identified. As a result, the new compound not only binds to the target, it becomes a permanent part of the target—as if it were super glued to it, Disney said. Once attached, it switches off the CUG defect and prevents the cell from turning it back on.

Disney was surprised at the approximately 2,500-fold improvement in potency with the new approach.

"I was shocked by the increase," he said. "This takes the potency into the realm where one would like to see if the compound were to have real therapeutic potential."

As a result, the new compound, known as 2H-4-CA, is the most potent compound known to date that improves DM1-associated splicing defects. Importantly, 2H-4-CA does not affect the alternative splicing of a transcript not regulated by MBNL1, demonstrating selectivity for the CUG repeat and suggesting that it might have minimal side effects.

"We can now use this approach to attach reactive molecules to other RNA targeted small molecules," Disney said.

The reactive molecule model also provides a potentially general method

to identify cellular targets of RNA-directed small molecules. Such probes could also identify unintended targets, information that could be used to design and identify compounds with improved selectivity in an approach similar to activity-based profiling, Disney said.

**More information:** onlinelibrary.wiley.com/doi/10 … /anie.201301639/full

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