Breaking COVID-19's 'clutch' to stop its spread

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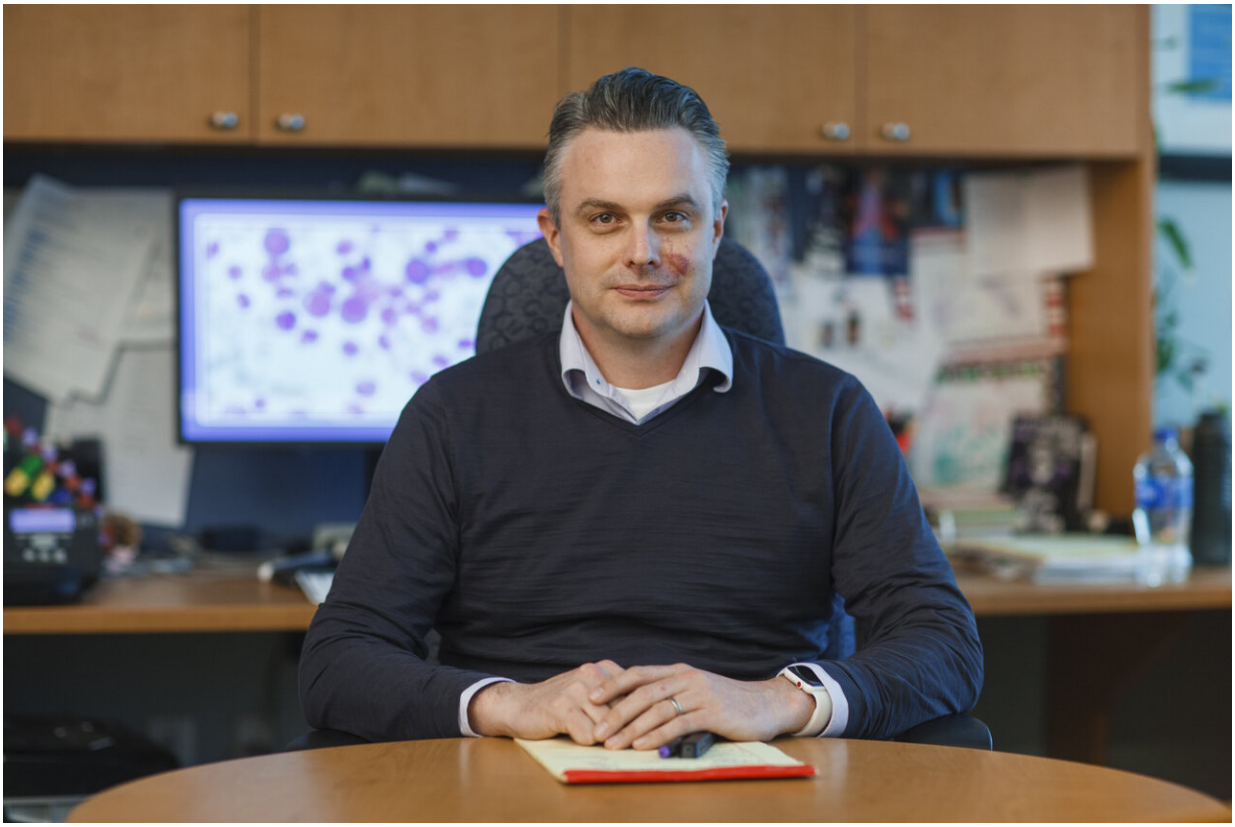

Matthew Disney, PhD, of Scripps Research in Jupiter, Florida, has spent over a decade developing tools to make RNA a druggable target for curing diseases. His lab's latest target is COVID-19, which is caused by a RNA virus. Credit: Scott Wiseman for Scripps Research

Scripps Research chemist Matthew Disney, Ph.D., and colleagues have

created drug-like compounds that, in human cell studies, bind and destroy the pandemic coronavirus' so-called "frameshifting element" to stop the virus from replicating. The frameshifter is a clutch-like device the virus needs to generate new copies of itself after infecting cells.

"Our concept was to develop lead medicines capable of breaking COVID-19's clutch," Disney says. "It doesn't allow the shifting of gears."

Viruses spread by entering cells and then using the cells' protein-building machinery to churn out new infectious copies. Their genetic material must be compact and efficient to make it into the cells.

The pandemic coronavirus stays small by having one string of genetic material encode multiple proteins needed to assemble new virus. A clutch-like frameshifting element forces the cells' protein-building engines, called ribosomes, to pause, slip to a different gear, or reading frame, and then restart protein assembly anew, thus producing different protein from the same sequence.

But making a medicine able to stop the process is far from simple. The virus that causes COVID-19 encodes its genetic sequence in RNA, chemical cousin of DNA. It has historically been very difficult to bind RNA with orally administered medicines, but Disney's group has been developing and refining tools to do so over more than a decade.

The scientists' report, titled "Targeting the SARS-CoV-2 RNA Genome with Small Molecule Binders and Ribonuclease Targeting Chimera (RIBOTAC) Degraders," appears Sept. 30 in the journal *ACS Central Science*.

Disney emphasizes this is a first step in a long process of refinement and research that lies ahead. Even so, the results demonstrate the feasibility of directly targeting viral RNA with small-molecule drugs, Disney says.

Their study suggests other RNA viral diseases may eventually be treated through this strategy, he adds.

"This is a proof-of-concept study," Disney says. "We put the frameshifting element into cells and showed that our compound binds the element and degrades it. The next step will be to do this with the whole COVID virus, and then optimize the compound."

Disney's team collaborated with Iowa State University Assistant Professor Walter Moss, Ph.D., to analyze and predict the structure of molecules encoded by the viral genome, in search of its vulnerabilities.

"By coupling our predictive modeling approaches to the tools and technologies developed in the Disney lab, we can rapidly discover druggable elements in RNA," Moss says. "We're using these tools not only to accelerate progress toward treatments for COVID-19, but a host of other diseases, as well."

The scientists zeroed in on the virus' frameshifting element, in part, because it features a stable hairpin-shaped segment, one that acts like a joystick to control protein-building. Binding the joystick with a drug-like compound should disable its ability to control frameshifting, they predicted. The virus needs all of its proteins to make complete copies, so disturbing the shifter and distorting even one of the proteins should, in theory, stop the virus altogether.

Using a database of RNA-binding chemical entities developed by Disney, they found 26 candidate compounds. Further testing with different variants of the frameshifting structure revealed three candidates that bound them all well, Disney says.

Disney's team in Jupiter, Florida quickly set about testing the compounds in human cells carrying COVID-19's frameshifting element. Those tests

revealed that one, C5, had the most pronounced effect, in a dose-dependent manner, and did not bind unintended RNA.

They then went further, engineering the C5 compound to carry an RNA editing signal that causes the cell to specifically destroy the viral RNA. With the addition of the RNA editor, "these compounds are designed to basically remove the virus," Disney says.

Cells need RNA to read DNA and build proteins. Cells have natural process to rid cells of RNA after they are done using them. Disney has chemically harnessed this waste-disposal system to chew up COVID-19 RNA. His system is called RIBOTAC, short for "Ribonuclease Targeting Chimera."

Adding a RIBOTAC to the C5 anti-COVID compound increases its potency by tenfold, Disney says. Much more work lies ahead for this to become a medicine that makes it to clinical trials. Because it's a totally new way of attacking a virus, there remains much to learn, he says.

"We wanted to publish it as soon as possible to show the scientific community that the COVID RNA genome is a druggable target. We have encountered many skeptics who thought one cannot target any RNA with a small molecule," Disney says. "This is another example that we hope puts RNA at the forefront of modern medicinal science as a drug target."

More information: "Targeting the SARS-CoV-2 RNA Genome with Small Molecule Binders and Ribonuclease Targeting Chimera (RIBOTAC) Degraders" *ACS Central Science* (2020). pubs.acs.org/doi/abs/10.1021/acscentsci.0c00984

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