Climbing a new path allows chemists to ascend cancer's steepest research challenge, a gene called MYC

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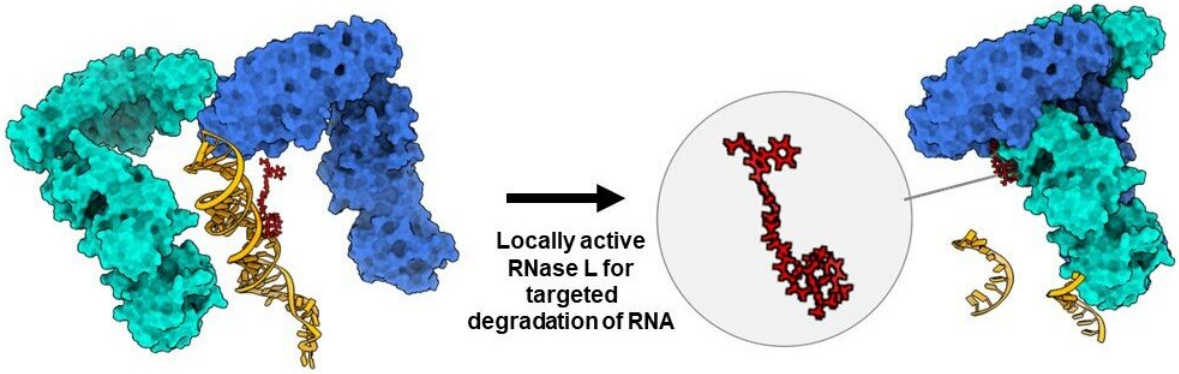

A "fishing hook" molecule in red is added to a drug-like compound to catch enzymes that chop up RNA, yellow, for recycling by cells. The strategy has been used to break up oncogenes known for causing some of the most dangerous, untreatable cancers. Credit: Disney lab at The Wertheim UF Scripps Institute. By Yuquan Tong

The cancer gene MYC has been called the "Mount Everest" of cancer

research because of the difficulty of designing medications that can disable it and the expectation that an effective MYC drug could help so many cancer patients. A collaboration among RNA scientists, chemists and cancer biologists in Florida and Germany has climbed that peak, while opening new routes to summit other similarly hard-to-treat diseases.

The researchers describe their strategy May 24 in the journal *Nature*.

The scientists' approach directs cells' recycling enzymes to cancer genes' RNA and cuts up key segments to prevent them from doing harm. The tactic worked against the MYC cancer gene, and also two other challenging cancer genes, JUN and MIR155. All three of the cancer genes regulate the transcription of other genes, igniting rapid tumor growth.

"For cancer patients whose disease is driven by these common but challenging oncogenes, the RNA degrader approach may offer new hope," said Herbert Waldmann, Ph.D., director of the Max Planck Institute of Molecular Physiology in Dortmund, Germany.

Their study also opens new possibilities for targeting RNA with medicines, opening potentially many other genetic diseases to this treatment approach, said chemist and institute professor Matthew D. Disney, Ph.D., of The Herbert Wertheim UF Scripps Institute for Biomedical Innovation & Technology and the UF Health Cancer Center.

"We discovered around 2,000 new RNA structures that are able to bind drug-like small molecules, and identified six new chemotypes able to bind RNA," Disney said. "We basically have created an encyclopedia of druggable RNA folds."

Among the most challenging of drug targets, MYC is also one of the

most important. Its activation may affect 70% or more of all human cancers. It can direct many other genes to be built or silenced. It affects cell growth, and even a cell suicide program that leads damaged cells to self-destruct, a vital process called apoptosis. It also affects the repair process of damaged DNA, and the growth of blood vessels. In many cancers MYC is overexpressed, leading cells to grow and divide too rapidly.

Activation of another cancer gene, JUN, has been seen in more than 20 different cancer types, including glioblastoma, breast, prostate, lung, colorectal cancer and more.

A small RNA gene called MIR155, meanwhile, drives inflammation and the growth and spread of many cancers. Researchers have found it activated in breast, kidney, gastric and other cancers.

Efforts to make drugs that prevent the three oncogenes from doing harm have largely failed, due to their complex structural challenges.

International collaboration

Surmounting these challenges involved the efforts of an international team of three laboratories.

In Florida, Disney's group brought insights about drug discovery for RNA structures, and new RNA degradation technologies.

At the Max Planck Institute of Molecular Physiology, Waldmann's group designs compounds inspired by natural substances, such as those that have inspired many antibiotics and cancer drugs.

Organic chemist Frank Glorius, Ph.D., of the Organic Chemistry Institute at the University of Münster in Germany, has developed

innovative methods to build new drug-like molecules. Some of his compounds, housed in Waldmann's collection, were specifically designed to influence biology in cell membranes. Compounds derived from imidazole, a molecule common in natural products and drugs, modified with carbon-based chains, ultimately proved to be the most effective at binding to the cancer-linked RNAs.

"The compounds look a bit like a TV on two long, thin legs," Glorius said.

"It was a true collaboration," Waldmann added. "All three of us and our groups were needed to arrive at these insights."

The idea for the partnership first arose in 2016 during a scientific conference in Spain, when Waldmann and Disney compared notes after a talk. Both agreed that targeting RNA with drugs presented an exciting possible way to target incurable diseases, but it was early days. Nothing like that existed in the market.

Targeting RNA to stop cancer

RNA represented a difficult drug-targeting challenge. Comprising just four nucleotides, RNA has many jobs. It reads genes, assembles proteins and is recycled to carry out other work in the cell. Its structures are so diverse and changeable that many in the pharmaceutical industry wrote off trying to make RNA-directed medicines as a pointless exercise.

But over the course of 15 years, Disney and his group have identified many conserved, druggable RNA structures. Disney's team built their own compound collections and showed in mice that targeting RNAs can wipe out cancer tumors and improve other diseases, including ALS and myotonic dystrophy. RNA offered an alternate route to tackle diseases whose key protein structures couldn't be reached by medications.

Following that initial conversation, in 2018 Disney sent two members of his lab, then-graduate students Matthew Costales, Ph.D., and Hafeez Hanif, Ph.D., to Dortmund to use their screening methods to hunt for potential RNA-binding candidates. Disney said the results surpassed his expectations. In all, they probed more than 61 million interactions between the compound collections and human RNA. When they looked at their results, they found the universe of known, druggable RNA structures had expanded dramatically.

But it would take several more years of work to connect those structures and compounds they found to the difficult cancer targets MYC, c-JUN and MIR155.

Senior Staff Scientist Jessica Childs-Disney, Ph.D., and graduate student Yuquan Tong, from Disney's lab at The Wertheim UF Scripps Institute, conducted many of those crucial experiments.

"We found it wasn't enough to bind these targets' RNA. That alone didn't make enough of an impact. We had to also modify the compounds so that they could recruit targeted small-molecule RNA degradation enzymes," Tong said.

Disney had devised an innovative method for editing out these disease-causing RNA segments. He did so by attaching a chemical fishing hook to the molecules, one designed to catch the cell's RNA recycling enzymes. It worked as planned. The RNA recycling enzyme chopped up the RNA that the drug molecule was attached to, preventing the disease-causing proteins from being built. They called their hybrid molecule a RiboTAC, short for "ribonuclease targeting chimera."

"With the degrader added, we started seeing these 'undruggable' cancer RNAs reduced by 35%, 40%, 50% or more. This caused cancer cells to die and cleared tumors in mouse-based studies of breast cancer that

spread to lungs," Disney said.

Disney reached out to a former colleague, a leading expert on the role of MYC in cancer, John Cleveland, Ph.D. Cleveland is the executive vice president, center director and chief scientific officer at Moffitt Cancer Center in Tampa.

"Our lab tested the efficacy of the RiboTAC compounds designed to destroy MYC RNA and showed that they effectively kill B-cell lymphomas that are driven by MYC, which are very aggressive and difficult-to-treat tumors," Cleveland said. "In sum, these results—that one can now design specific RNA degraders to disable many oncogenic RNAs—represents a truly transformative step in anti-cancer therapeutics."

Waldmann said the study shows that compound classes inspired by natural products provide a rich, new source for targeting RNA disease targets in general.

"Of course, we are developing them further, following our concept of pseudo natural products, thereby broadening coverage of the chemical space defined by this unique chemical matter," Waldmann said.

Because the strategy is so novel, it will take several years of additional work before the innovations reach patients via a clinical trial, he added.

"This is a long road to take, a marathon run, actually," Waldmann said.

The compounds are showing the scientists where to go to make more and better drugs to fight these once-impossible cancer targets, and providing a banquet of new RNA structures to test in other disease settings, Disney said. His team at The Wertheim UF Scripps Institute is especially focused on cancer and other hard-to-treat diseases.

"This is a starting point. It's showing us where to go to build small molecule, RNA-targeting medicines that could eventually treat patients with diseases like aggressive cancers that currently have poor or no options," Disney said. "This new data also shows us that this approach could have many other disease applications."

More information: Matthew Disney, Programming inactive RNA-binding small molecules into bioactive degraders, *Nature* (2023). DOI: 10.1038/s41586-023-06091-8.
www.nature.com/articles/s41586-023-06091-8

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