

Attacking RNA with small-molecule drugs

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The RNA synthesizer used to prepare short, fluorescently-labeled RNA substrates for the new study. Credit: Olga Fedorova/Yale University

Yale researchers have developed a way to target RNA with small-molecule drugs, creating a new method for tapping into a vast number of

biological mechanisms critical to metabolism and gene expression.

"There is tremendous interest in targeting RNA with [small molecules](#)," said Yale biochemist Anna Pyle, whose lab conducted the research.

"Despite this potential, there has been limited progress on the development of small-molecule drugs that bind RNA, and a pervasive view that RNA is not a viable therapeutic target."

Pyle and her colleagues focused on RNA targets within pathogenic yeasts, opportunistic fungal organisms that are especially problematic for patients with compromised immune systems, including patients with implanted devices, neonatal patients, and cancer patients.

Pyle's team identified small molecules that would inhibit a particular group of large, self-splicing ribozymes found in bacteria, plants, and fungi—but not found in mammals. These RNA molecules have an elaborate structure that contains tiny, solvent-accessible pockets for a small molecule drug to bind with the larger molecule.

The researchers also chose this group of RNA molecules because of their crucial role in fungal metabolism.

"Our work establishes that RNA is 'druggable,' and that refractory pathogens such as pathogenic fungi and drug-resistant bacteria can be attacked by targeting their unique RNA repertoire," Pyle said. "It demonstrates that the burgeoning landscape of functional RNA elements contains a wealth of potential targets that can be modulated by small [molecules](#), opening a new frontier in molecular pharmacology."

The study appears Oct. 15 in the journal *Nature Chemical Biology*. The co-first authors of the study are Olga Fedorova of Yale and G. Erik Jagdmann Jr. of New England Discovery Partners. Additional authors are Rebecca Adams of Yale, and Lin Yuan and Michael Van Zandt of

New England Discovery Partners.

Pyle is a Yale professor of molecular, cellular, and developmental biology, and of chemistry, and a Howard Hughes Medical Institute investigator. Fedorova is a research specialist at Yale and the Howard Hughes Medical Institute.

More information: Small molecules that target group II introns are potent antifungal agents, *Nature Chemical Biology* (2018). [DOI: 10.1038/s41589-018-0142-0](https://doi.org/10.1038/s41589-018-0142-0) , www.nature.com/articles/s41589-018-0142-0

Provided by Yale University

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