Study shows that RNA can be targeted by small molecule drugs, creating new possibilities for disease treatment

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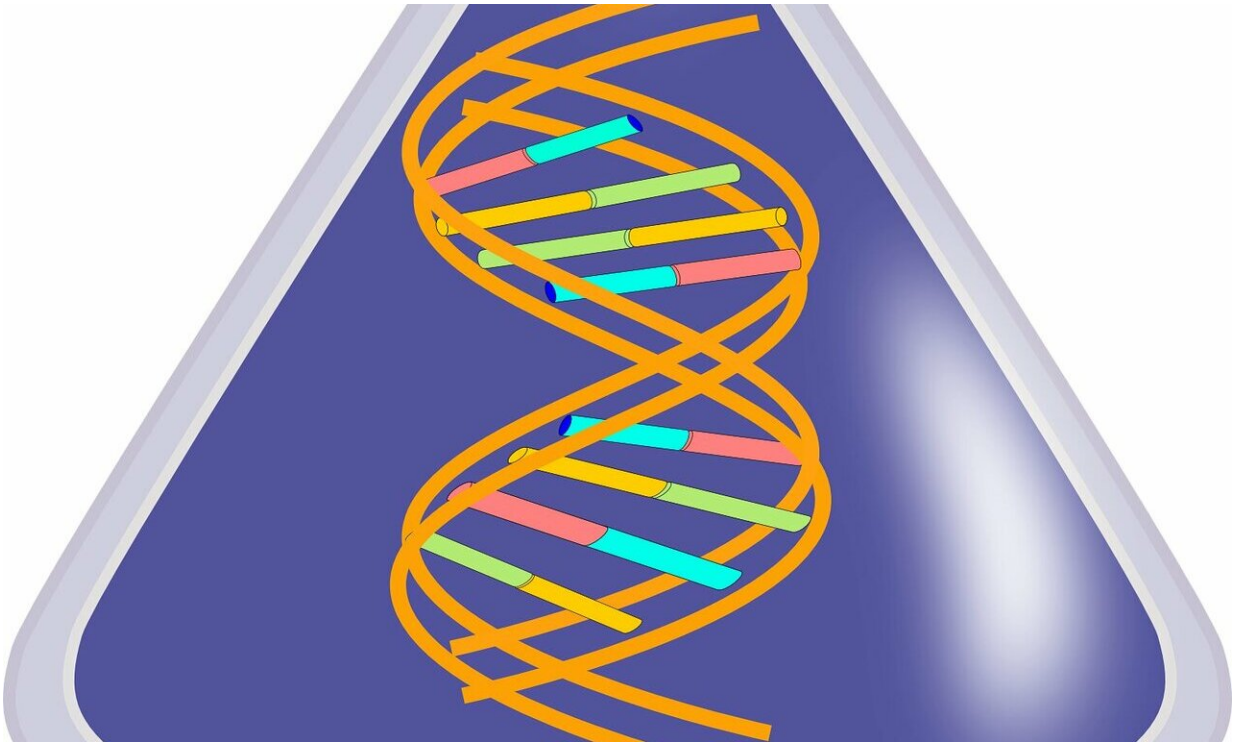

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RNA (ribonucleic acid) plays many roles in human health, and now a study in the journal *Nature* offers powerful evidence that RNA could also be a viable target for drug development. This work, led by

researchers at Massachusetts General Hospital (MGH), suggests that a new class of biological factors numbering in the thousands can be targeted and thereby heralds a new era in drug development.

Nearly all drugs currently available target one of approximately 700 disease-related proteins among the roughly 20,000 human proteins identified by the Human Genome Project. However, in recent years there has been growing interest in expanding the list of "druggable" targets to include RNA. In cells, DNA (deoxyribonucleic acid) carries the genetic code for forming proteins. A segment of DNA is copied, or transcribed, into a "coding" RNA, which is in turn translated into protein. However, the vast majority of RNA in the human genome—98 percent—is "noncoding."

"These noncoding RNAs play very important roles in the genome, and we now understand that mutations in this noncoding space can result in disease," says the senior author of the *Nature* paper, Jeannie Lee, MD, Ph.D., of the Department of Molecular Biology at MGH. "And there may be far more of these RNA genes than there are protein-coding genes. If we could target these RNAs, we would hugely increase the universe in which we can find drugs to treat patients."

However, the pharmaceutical industry has historically been hesitant to pursue RNA as a drug target. Proteins tend to have stable shapes, or conformations, which make them optimal targets: Drugs bind to proteins like a key in a lock. By contrast, explains Lee, RNA tends to be highly flexible, or "floppy," and capable of assuming multiple conformations. "If a lock is constantly changing shape, your key is not going to work," says Lee. Noncoding RNA's unstable nature has made companies reluctant to invest in trying to develop medications that target it. However, it's known that some regions on RNA retain stable conformations, despite all of that shape-shifting, but finding such regions has been a challenge.

Lee directs a molecular biology lab at MGH, where she and her team study RNA and its role in a biological process called X-chromosome inactivation (XCI), which deactivates one copy of the X chromosome in female mammals and is necessary for normal development. In a study led by postdoctoral fellow Rodrigo Aguilar, Ph.D., Lee's group collaborated with colleagues at Merck Research Laboratories to find out if RNA could be a viable drug target. The focus of the study was a form of noncoding RNA called Xist, which silences genes on the X chromosome. Finding a way to interfere with this process and reactivate a dormant X chromosome could help guide development of treatments for genetic disorders caused by mutations on the X chromosome (known as X-linked disorders), such as Rett syndrome and Fragile X syndrome.

Together with Merck scientists Kerrie Spencer and Elliott Nickbarg, the MGH team screened Xist against a library of 50,000 small molecule compounds and found several that bind to a region called Repeat A (RepA) on Xist. One compound, which Lee's team named X1, had particularly interesting qualities: It prevented several key proteins, PRC2 and SPEN, from binding to RepA, which is necessary for Xist to silence the X chromosome. "As a result, X inactivation cannot take place," says Lee. To understand why, the team collaborated with structural biologists led by Trushar Patel of the University of Lethbridge in Canada. Normally, Xist's RepA can assume 16 different conformations, but X1 caused it to adopt a more uniform shape. This structural change prevented RepA from binding with PRC2 and SPEN.

The approach employed in this study could be used to identify other RNA-targeting drugs. "This really opens up a large universe for new drug development," says Lee. "Now we don't just have 700 proteins to target using small molecules. In the future, we may have tens and possibly hundreds of thousands of RNAs to target to cure disease."

More information: Jeannie Lee, Targeting Xist with compounds that

disrupt RNA structure and X inactivation, *Nature* (2022). DOI: 10.1038/s41586-022-04537-z.
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