

## The Scientist: NewsBlog:

RNA in control

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An ancient RNA molecule is the answer to a bacterial mystery, according to a study published in [Science](#) tomorrow (July 18). Researchers have identified the binding molecule of a key messenger in bacteria, but to their surprise, the molecule was not a protein -- traditionally thought of as regulators of cellular processes -- but a unique RNA trigger.

In the last six years, RNA triggers, called [riboswitches](#), have emerged as surprising regulators of gene expression -- a role previously ascribed almost exclusively to proteins. "I think if in 2001 you were proposing that bacteria were loaded with flavors of riboswitches" that manipulate genetic expression, said [Ron Breaker](#) of Yale University and senior author of the paper, "you'd lose all scientific credibility."

The riboswitch his group identified, which binds the bacterial second messenger cyclic di-GMP, is the newest addition to a string of [recent riboswitch discoveries](#). But it is especially interesting, said [Sebastian Doniach](#), a biophysicist at Stanford studying the structure of riboswitches, because "cyclic di-GMP is a more general substrate than those of previous riboswitches." It regulates many different pathways in a variety of cells, something not seen in other classes of riboswitches, said Doniach, who was not involved in the study.

Cyclic di-GMP, a circular molecule made of two RNA nucleotides, is ubiquitous in bacteria and involved in a range of various functions including motility, morphology, and virulence. But how it regulates gene expression was not known until Breaker's lab stumbled upon the answer.

[Breaker](#), a Howard Hughes Medical Institute investigator, and colleague Zasha Weinberg designed a computational pipeline of computer algorithms to sift through bacterial genomes for the signature of riboswitches, bits of RNA that function by binding single, specific ligands to alter gene expression. [Last year](#), their technique produced a riboswitch candidate called the GEMM motif (Genes for the Environment, for Membranes and for Motility), but they were having trouble identifying the associated ligand. GEMM is implicated in multiple pathways, as its name suggests, and the two biologists knew of no single ligand that was involved in them all.

One day in a game of "guess the ligand," Breaker and Weinberg began listing the multiple pathways to each other while arguing that no connection amongst them made sense. That's when research scientist Narasimhan Sudarsan strode into the room, Breaker recalled. Sudarsan held up a finger, quieting the two men, and said, "I know what the ligand is." Sudarsan, who was familiar with cyclic di-GMP, knew the small molecule had been detected in many of the same pathways as GEMM. Three days later, he came back with proof that the ligand was cyclic di-GMP, said Breaker. "He knew a lot of the literature," said Breaker, "and he drew the connection."

The team performed both biochemical and genetic analyses of GEMM regions in *Vibrio cholerae*, *Bacillus cereus* and *Clostridium difficile* to determine that cyclic di-GMP was indeed the ligand for the riboswitch. In *V. cholerae*, the two RNA molecules tag-team to control expression of a protein critical for the bacteria's ability to infect mammals. That new information raises the possibility that these RNA mechanisms may hold clinical potential, but "we're a long way from the leap to make analogs to trick the riboswitch," said Breaker.

His team hypothesizes that riboswitches are ancient genetic regulators that emerged early on; although proteins eventually took over the show, today the RNA molecules remain highly conserved. At this point, more than 20 classes of metabolite-sensing riboswitches have been discovered in all three domains of life, and the search for more continues. "I think there's a lot more out there nobody has found yet," said Doniach.