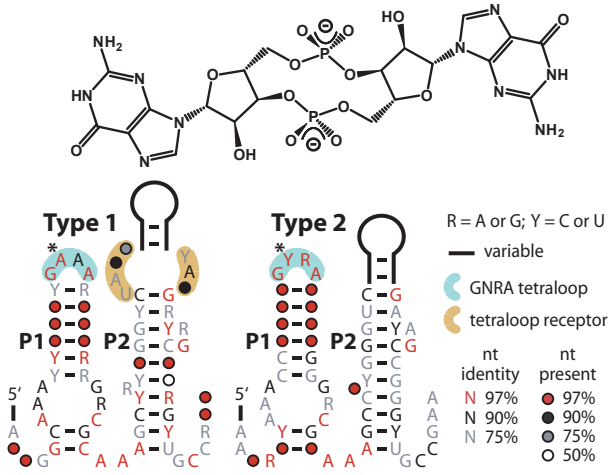
Breaker Laboratory

Molecule of the Year 2008

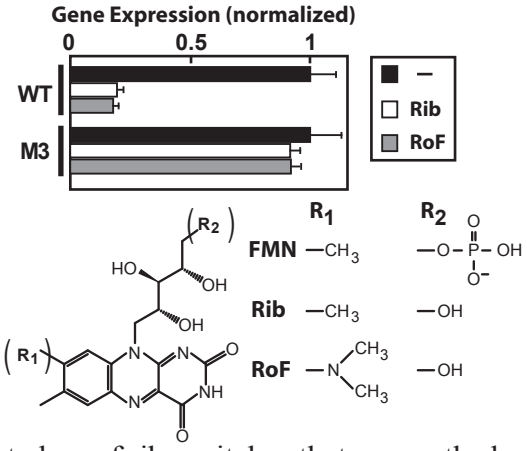
Cyclic di-GMP Riboswitches

Fig. 1. Top: The chemical structure of cyclic di-guanosine monophosphate (c-di-GMP). Bottom: Consensus sequences and structures of Type 1 and Type 2 aptamers for c-di-GMP.



Roseoflavin

Fig. 2. Top: The chemical structure of roseoflavin (Rof), the coenzyme flavin mononucleotide (FMN) and its precursor riboflavin (Rib). WT and M3 represent wild-type and binding-defective mutant aptamers, respectively. Bottom: Suppression of FMN riboswitch-mediated gene expression by roseoflavin.



In recognition of the discovery and validation of the first class of riboswitches that senses the bacterial second messenger c-di-GMP[1], and in recognition of the discovery that the natural antibiotic compound roseoflavin binds to FMN riboswitches and represses gene expression[2], the status of Breaker Laboratory "Molecule of the Year" is conferred upon these findings.

C-di-GMP is a widespread second messenger in bacteria whose concentration changes trigger major changes in cell physiology, including bacterial motility, biofilm formation, and changes between infectious and non-infectious forms of pathogens. The discovery of a riboswitch class that senses c-di-GMP helps explain how this second messenger brings about widespread changes in gene expression, and offers insight for those who wish to exploit analogs of c-di-GMP to disregulate bacterial signalling. Possible opportunities to target riboswitches with new antibacterial compounds are highlighted by the finding that roseoflavin, a natural antibiotic pigment produced by the bacterium *Streptomyces davawensis*, binds to FMN riboswitches and suppressed expression of genes that are essential for FMN biosynthesis. This is the first natural compound shown to bind riboswitches, and likely inhibits bacterial growth by this mechanism.

Yale University Investigators: Dr. Narasimhan Sudarsan, Ph.D.; Elaine R. Lee, Dr. Zasha Weinberg, Ph.D.; Ryan H. Moy; Jane N. Kim; Dr. Kristian H. Link, Ph.D.; Dr. Kenneth F. Blount, Ph.D.; Dr. Ronald R. Breaker, Ph.D.

1. *N. Sudarsan, E. R. Lee, Z. Weinberg, R. H. Moy, J. N. Kim, K. H. Link and R. R. Breaker (2008) Riboswitches in eubacteria sense the second messenger cyclic di-GMP. Science 321:411-413.*

2. *E. R. Lee, K. F. Blount, R. R. Breaker. Roseoflavin is a natural antibacterial compound that binds to FMN riboswitches and regulates gene expression. RNA Biol. (in press).*