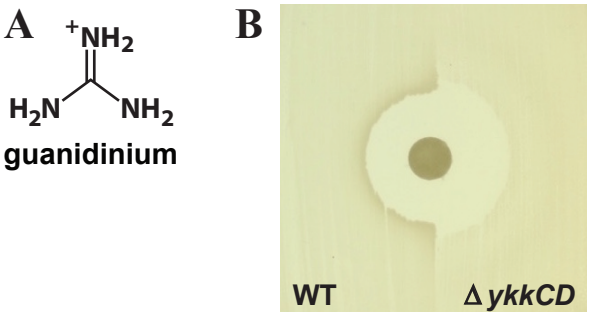
Breaker Laboratory

Molecule of the Year 2016

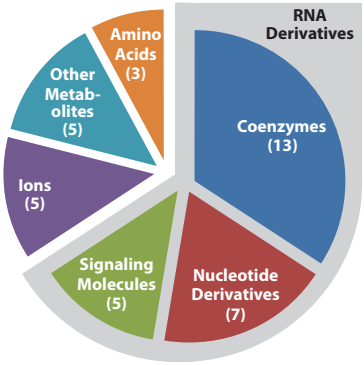
Guanidine and its Many Riboswitches

Fig. 1. (**A**) Chemical structure of guanidinium ion, the natural ligand for guanidine-I, -II, and -III riboswitch classes. (**B**) Agar diffusion assay revealing that a KO of a guanine-I riboswitch controlled transporter gene in *Bacillus subtilis* causes increased guanine sensitivity. Disk spotted with 10 µL 6 M guanidine.



Riboswitches and RNA World Compounds

Fig. 2. A summary of the types of compounds sensed by ~40 known riboswitch classes experimentally validated since the first in 2002. The majority of ligands are RNA-derived compounds, suggesting ancient origins for riboswitches.



In recognition of the discovery of guanidine riboswitches,[1,2] and in recognition of the predominance of RNA-like compounds as riboswtch ligands,[3] the status of Breaker Laboratory "Molecule of the Year" is conferred upon these findings.

Guanidine (or its positively charged guanidinium ion form (Fig. 1A) is typically thought of as a chemical moiety of metabolites such as arginine and guanine, as a laboratory reagent for denaturing proteins, or as an explosive chemical propellant for air bags or weapons. However, the validation of three distinct classes of riboswitches for this compound[1,2] reveal that bacteria naturally encounter this molecule and that they have evolved genes whose protein products overcome guanidine toxicity.

RNA World relics in modern cells, such as certain ribozymes and coenzymes, help reveal the true nature of life before the evolutionary emergence of proteins. Certain characteristics of modern riboswitches suggest that some of these gene regulation molecules might also represent relics of ancient signaling processes. For example, it is striking that 25 of the 33 known ligands for riboswitches respond to compounds derived from RNA (Fig. 2).[3] This strong bias for RNA-like ligands among the most common riboswitches is consistent with the hypothesis that RNA World organisms exploited similar RNA switches, and that some modern riboswitches represent relics from these earliest forms of life.

Yale University Investigators: Ruben Atilho, James Nelson, Ph.D.; Madeline Sherlock, Sarah Malkowski, Ronald R. Breaker, Ph.D.

1. *J. W. Nelson, et al. (2016) Metabolism of free guanidine in bacteria is regulated by a widespread riboswitch class. Mol. Cell (in press).*

2. *M. E. Sherlock, S. Malkowski and R. R. Breaker (unpublished results).*

3. *R. R. Breaker (2016) Prospects for ribozyme discovery and analysis. Paper presented to the Solvey Conference on Chemical Catalysis .*