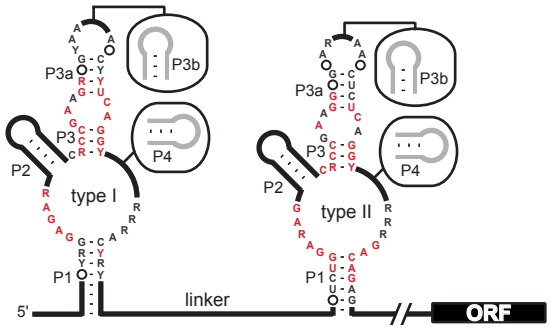
Breaker Laboratory

Molecule of the Year 2004

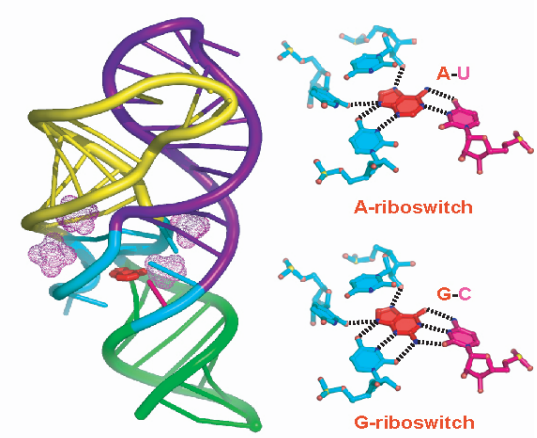
Tandem Glycine Riboswitch

Fig. 1. Consensus sequence and structure of the *gcvT* riboswitch found in many bacteria. The riboswitch carries two glycine-specific aptamers that operate cooperatively to trigger expression of genes encoding the glycine cleavage system. This provides a more digital genetic response to changing glycine concentrations.



Riboswitch Structure Models

Fig. 2. Atomic-resolution structure model of an adenine-specific aptamer from *Vibrio vulnificus* (left) and the ligand-binding sites of riboswitches that selectively bind adenine or guanine (right). The models confirm biochemical results indicating that a three-stem junction folds in the absence of protein factors to form a highly-selective pocket for its target metabolite, and that a single nucleotide defines base specificity.



In recognition of the discovery of the first cooperative riboswitch[1] and in recognition of the establishment of the first high-resolution structural models for riboswitch-ligand interactions,[2] the status of Breaker Laboratory "Molecule of the Year" is conferred upon these two advances.

Riboswitches most frequently carry a single aptamer domain for metabolite sensing. However, more complex functions that demand more sophisticated RNA structural arrangements are needed if RNA is to challenge proteins for carrying out higher-ordered tasks. The glycine riboswitch class is the first natural example of an allosteric RNA that harnesses cooperative interactions between tandem aptamers to achieve digital switching - wherein small changes in ligand concentration lead to greater changes in gene expression. The structural complexity of riboswitch RNAs was further demonstrated by the work of two separate teams* who solved structures of purine-sensing riboswitch aptamers using x-ray crystallography technichniques. This work confirms that riboswiches form complex-folded receptors for metabolites without the need for proteins.

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**Batey Lab: U. Colorado and Patel Lab: Sloan-Kettering (with collaboration from the Breaker Lab).*

1. Mandal, M., Lee, M., Barrick, J.E., Weinberg, Z., Emilsson, G.M., Ruzzo, W.L. and Breaker, R.R. 2004. A glycine-dependent riboswitch that uses cooperative binding to control gene expression. *Science* **306:** 275-279.
2. Serganov, A., Yuan, Y.-R., Pikovskaya, O., Polonskaia, A., Malinina, L., Phan, A.T., Hobartner, C.,Micura, R., Breaker, R.R. and Patel, D. 2004. Structural basis for discriminattive regulation of gene expression by adenine- and guanine-sensing mRNAs. *Chem. Biol.* **11:** 1729-1741.