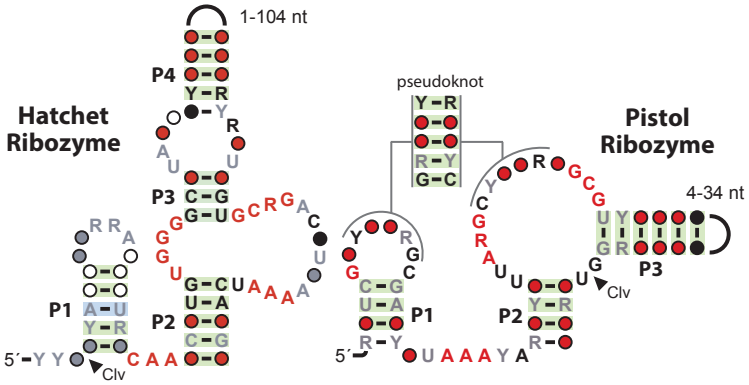
Breaker Laboratory

Molecule of the Year 2014

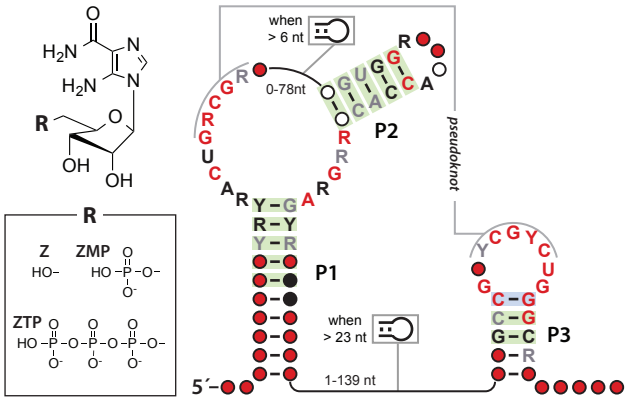
Hatchet and Pistol Self-cleaving Ribozymes

Fig. 1. Consensus sequence and secondary-structure models of hatchet and pistol ribozymes. Arrowheads marks the sites of RNA cleavage. Red, black, and gray nucleotides are conserved at >97%, 90% and 75%.



ZTP Riboswitches

Fig. 2. (Left) ZTP and its natural derivatives. **(Right)** Consensus sequence and secondary-structure model for ZTP riboswitch aptamers. Annotations are as described for Fig. 1.



In recognition of the discovery[1] of hatchet and pistol ribozymes, which are the 13th and 14th natural classes of of catalytic RNAs known, and in recognition of the validation[2] of *pfl* motif RNAs as ZTP riboswiches, the status of Breaker Laboratory "Molecule of the Year" is conferred upon these findings.

Hatchet and pistol ribozymes were discovered by searching for novel structured noncoding RNA motifs in the vicinity of certain genes that are commonly located near to known self-cleaving ribozyme classes. This search strategy has created a burst of ribozyme discoveries after an era where only one novel ribozyme class was being reported per decade.

Recent research efforts have led to the validation of a number of orphan riboswitches, which have revealed important aspects of microbial physiology. One very common orphan riboswitch, called *pfl*, regulates genes associated with folate and purine metabolism. Its ligand was speculated to be ZTP, an "alarmone" described more than 30 years ago that that signals folate distress. By overcoming RNA folding problems, researchers[2] proved that ZTP and its precursor ZMP (also called AICAR) indeed are selectively recognized by members of this riboswitch class. A construct based on this riboswitch can be used as a tool to screen for antibacterial compounds that cause floate distress.

Yale University Investigators: Zasha Weinberg, Ph.D.; Peter Kim; Tony H. Chen; James N. Nelson, Ph.D.; Kimberley A. Harris, Ph.D.; Christina E. Luense, Ph.D.; Sanshu Li, Ph.D.; Ronald R. Breaker, Ph.D.

1. *Z. Weinberg, P. B. Kim, T. H. Chen, S. Li, K. A. Harris, C. E. Luense, R. R. Breaker. New classes of self-cleaving ribozymes revealed by comparative genomics analysis. (in preparation).*

2. *P. B. Kim, J. W. Nelson, R. R. Breaker. An ancient riboswitch class in bacteria regulates purine biosynthesis and one-carbon metabolism. Mol. Cell (in press).*