

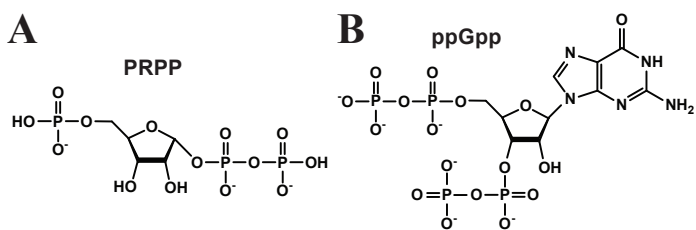
Breaker Laboratory

Molecule of the Year

2017

Riboswitch Classes for PRPP and ppGpp

Fig. 1. Newly validated ligands for riboswitch classes identified among variant *ykkC* motif RNAs. (A) Chemical structure of the RNA nucleotide precursor PRPP (phosphoribosyl pyrophosphate). (B) Chemical structure of the nucleotide-based alarmone ppGpp.



Lost Language of the RNA World

Fig. 2. Table of the possible types cyclic dinucleotides derived from the four common ribonucleotides that could serve as molecular words in an RNA World language. Red compounds are known to exist in modern biology.

		Position 2			
		G	A	C	U
Position 1	G	G_p^DG <i>i, iii</i>	G_p^DA <i>i, ii, iii</i>	G_p^DC <i>i, ii, iii</i>	G_p^DU <i>i, ii, iii</i>
	A		A_p^DA <i>i, iii</i>	A_p^DC <i>i, ii, iii</i>	A_p^DU <i>i, ii, iii</i>
	C			C_p^DC <i>i, iii</i>	C_p^DU <i>i, ii, iii</i>
	U				U_p^DU <i>i, iii</i>

i. 2',5' linkage following position 1
ii. 2',5' linkage following position 2
iii. 2',5' linkages following positions 1 and 2

In recognition of the discovery of two riboswitch classes that selectively respond to PRPP¹ and ppGpp², and in recognition of the hypothesis that certain common RNA-derived signaling molecules might be relics of the chemical ‘language’ of RNA World organisms³, the status of Breaker Laboratory “Molecule of the Year” is conferred upon these findings.

Many known riboswitch classes are triggered by RNA-derived metabolites, suggesting that some riboswitches might be of ancient origin. This hypothesis is further supported by the discovery¹ of riboswitches for PRPP (Fig. 1A), which is the first committed step in the biosynthesis of RNA nucleotides. PRPP riboswitches therefore sense the key first step for the production of their own building blocks. Similarly, the discovery² of riboswitches for ppGpp (Fig. 1B) reveal another link between RNA-based signaling molecules and RNA-based sensors.

Ancient RNA World organisms would have likely used derivatives of RNA building blocks to serve as signaling molecules³. Such compounds still exist in modern cells in the form of common alarmones such as ppGpp and ZTP, and second messengers such as c-di-GMP and c-di-AMP. It seems probable that the common RNA-based signaling molecules in extant biological systems first emerged as a form of RNA World ‘language’.

Yale University Investigators: James Nelson, Ph.D.; Madeline Sherlock; Shira Stav, Ph.D.; Narasimhan Sudarsan, Ph.D.;
 Ronald R. Breaker, Ph.D.

1. M. E. Sherlock, SN. Sudarsan, S. Stav, R. R. Breaker (2018) Tandem riboswitches form a natural Boolean logic gate to control purine metabolism in bacteria. (submitted)
2. M. E. Sherlock, SN. Sudarsan, R. R. Breaker (2018) Riboswitches for the alarmone ppGpp expand the collection of RNA-based signaling systems. (submitted)
3. J. W. Nelson, R. R. Breaker (2017) The lost language of the RNA World. *Sci. Signal.* 10, pii:eaam8812.