299e Programmable, Ligand-Controlled Riboregulators of Gene Expression

Travis S. Bayer and Christina Smolke

In recent years, cis and trans RNA elements have become well recognized as important regulators of gene expression. In addition, many interesting and advanced nucleic acid activities have been identified including catalysis, in the form of ribozymes, ligand binding, in the form of aptamers, and targeted expression, in the form of antisense, siRNAs, and miRNAs. Nucleic acids offer a unique platform for biomolecule design in that there is currently a relatively greater understanding of how the linear sequence of these molecules relates to their structure and function. In addition, interactions between nucleic acids and other molecules can be designed with relative ease through both antisense-based and aptamer-based design strategies.

We present here recent advances made in the design of ligand-controlled RNA molecules for regulating gene expression in various cell types. Platforms will be described that function both in cis and in trans to regulate target protein levels in vivo. These molecules are generated through rational, modular design strategies and present a flexible platform for the design of application-specific regulator molecules. In particular, we will focus discussion on the description of regulator molecules that take different inputs, such as biomolecule concentration levels and heat, and translate these inputs into regulated gene expression events. Both small molecule- and protein-controlled platforms will be discussed. Tuning strategies based on both modulating the binding affinities of the incorporated sensor domains of these molecules and the energetics of the different domains of these molecules will be presented. Recent results exploring the mechanistic basis of the response properties of these regulator molecules will also be discussed. Finally, the design of signal integration schemes comprised of interacting riboregulator molecules will be discussed as initial progress into cellular biocomputation and ‘smart' programming of cellular behavior in vivo.