Programming Cellular Behavior with RNA Controllers

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Synthetic biology is an emerging field of interdisciplinary research that seeks to transform our ability to probe, manipulate, and interface with living systems by combining the knowledge and techniques of biology, chemistry, computer science, and engineering. Advances in synthetic biology are transforming our ability to design, build, and characterize biological systems, thereby advancing biological frontiers by expanding biomanufacturing capabilities, developing next-generation therapeutic approaches, and providing new insights into natural biological systems. While progress has been made in the design of genetic circuits encoding computational operations, communication channels, and dynamic behaviors, capabilities for constructing large-scale genetic systems currently surpass our ability to design such systems. This growing 'design gap' has highlighted the need to develop methods that support the generation of new functional biological components and scalable design strategies for complex genetic circuits that will lay the foundation for integrated biological devices and systems.

The vast majority of genetic systems engineered to-date utilize protein-based transcriptional control strategies. However, as the examples of functional RNA molecules playing key roles in the behavior of natural biological systems have grown over the past decade, there has been growing interest in the design and implementation of synthetic counterparts. Researchers are taking advantage of the relative ease with which RNA molecules can be modeled and designed to engineer diverse functional RNA molecules that act as sensors, regulators, controllers (ligand-responsive RNA regulators), and scaffolds. These synthetic regulatory RNAs are providing new tools for temporal and spatial control in biological systems.

I will describe recent work in the design of synthetic RNA controllers that can detect changes in molecular and environmental inputs and link those changes to gene expression events, and thus new cellular behaviors. A number of design strategies have been developed for assembling RNA-based information processing and control devices from modular genetic components encoding sensing, gene regulatory, and computational activities. These design strategies have recently been extended to the programming of higher-order information processing schemes, highlighting the potential of synthetic biology strategies to support the rapid engineering of cellular behavior. More recently, the development of high-throughput technologies are enabling the rapid tailoring of RNA devices to new molecular inputs and genetic outputs, providing a scalable platform for constructing user-programmed control systems in living cells. The application of synthetic regulatory RNAs as controllers in different biological systems are advancing next-generation therapeutic and diagnostic strategies and transforming our ability to engineering biomanufacturing platforms. In particular, I will discuss the application of this class of genetic devices to advancing the development of safer and more effective cellular therapies.