ENGINEERING NUCLEIC ACID-BASED MOLECULAR SENSORS FOR PROBING AND PROGRAMMING CELLULAR SYSTEMS

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Information flow through cellular networks is responsible for regulating cellular function at both the single cell and multi-cellular systems levels. One of the key limitations to understanding dynamic fluctuations in intracellular biomolecule concentrations is the lack of enabling technologies that allow for user-specified probing and programming of these cellular events. I will discuss our work in developing the molecular design and cellular engineering strategies for the construction of tailor-made sensor platforms that can temporally and spatially monitor and regulate information flow through diverse cellular networks. The construction of sensor platforms based on allosteric regulation of non-coding RNA (ncRNA) activity will be presented, where molecular recognition of a ligand-binding event is coupled to a conformational change in the RNA molecule. This regulated conformational change may be linked to an appropriate readout signal by controlling a diverse set of ncRNA gene regulatory activities. Our research has demonstrated the modularity, design predictability, and specificity inherent in these molecules for cellular control. In addition, the flexibility of these sensor platforms enables these molecules to be incorporated into larger circuits based on molecular computation strategies to construct sensor sets that will perform higher-level signal processing toward complex systems analysis and cellular programming strategies. In particular, the application of these molecular sensors to the following downstream research areas will be discussed: metabolic engineering of microbial alkaloid synthesis and ‘intelligent’ therapeutic strategies.