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2019 Seminars

Deciphering patterns in selective small molecule: RNA interactions

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While small molecules offer a unique opportunity to target structural and regulatory elements in therapeutically relevant RNAs, selectivity has been a recurrent challenge in small molecule:RNA recognition. In particular, RNAs tend to be more dynamic and offer less chemical functionality than proteins, and biologically active ligands must compete with the highly abundant and highly structured RNA of the ribosome. Indeed, no small molecule drugs targeting RNAs other than the ribosome are currently available, and our recent survey of the literature revealed little more than one hundred reported chemical probes that target non-ribosomal RNA in biological systems. As part of our efforts to improve small molecule targeting strategies and gain fundamental insights into small molecule:RNA recognition, we are analyzing patterns in both RNA-biased small molecule chemical space and RNA topological space privileged for differentiation. To begin, we identified physicochemical, structural, and spatial properties of biologically active RNA ligands that are distinct from those of protein-targeted ligands. Elaboration of four RNA binding scaffolds into a library enriched with these properties has led to improved recognition of medicinally relevant RNA targets, including viral and long noncoding RNA structures. At the same time, we used pattern recognition protocols to identify RNA topologies that can be differentially recognized by small molecules and have elaborated this technique to visualize conformational changes in RNA secondary structure. We are currently expanding these studies with the ultimate goal of applying these insights to the rapid development of ligands with high affinity and specificity for a wide range of RNA targets, particularly those critical to cancer progression.