

**P041** Choosy RNAs: an RNA-centric view of small-molecule–RNA binding selectivity

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As a central biomolecule of life, RNA facilitates information storage and transfer, catalysis, protein synthesis, and viral replication. As such, attempts to modulate RNA function have become a central thrust in modern therapeutic efforts. Low molecular weight RNA-binding compounds have often been employed for this task, dating to the advent of aminoglycoside antibiotics. Due to its functional ubiquity and cellular abundance, however, RNA is difficult to selectively target. To elicit a desired phenotype while minimizing spurious effects, a therapeutic must selectively differentiate the RNA target from other cellular RNAs. Classically, target selectivity has focused on the small-molecule, identifying components that mediate specific recognition of RNA structural elements. The principles thus derived should presumably facilitate the de novo design of novel, target-selective binders. We suggest a complementary paradigm, in which selectivity is also determined by features inherent to the particular RNA target. By measuring the binding of several different classes of systematically derivatized aminoglycosides to both the prokaryotic ribosomal A-site and the HIV TAR, we reveal that the A-site is the more selective target. That is, the A-site is more discriminatory of subtle aminoglycoside changes than the TAR. This difference can be understood in the context of the RNA:aminoglycoside complex structures. Thus, RNA target choice directly impacts the resultant binding selectivity.