Sequence-Based Design of Small Molecules Targeting RNA

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One of the major biomolecules that is considered to be a challenge to recognize with small molecules is RNA. We have taken a non-traditional approach to define small molecules targeting RNA. Most chemical probe discovery efforts focus on a screen to identify lead compounds targeting a single biomolecule. A high throughput library-versus-library screening approach termed two-dimensional combinatorial screening (2DCS) studies the binding of small molecules to libraries of RNA motifs. This results in an annotated library of druggable RNA motifs and small molecules to drug them. This information is mined against the human transcriptome to identify disease-causing RNAs that have RNA motifs that are bound by small molecules by using an approach termed Inforna. This approach has defined precise small molecules that target a host of RNAs involved in various incurable or difficult to treat diseases and have helped to show that RNA – indeed – is druggable with small molecules. Furthermore, these studies also show that sequence-based design can be used take a disease-causing biomolecule's sequence and quickly design a lead medicine to target it. In this talk, we describe results of this stagey to bind RNAs and to facilitate their elimination from cells by using various methods including targeted degradation