Single Molecule Study of the CUG Repeat·MBNL1 Interaction and Its Inhibition by Small Molecules

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Effective drug discovery and optimization can be accelerated by techniques able to deconvolute the complexities often present in targeted biological systems. We report a single-molecule approach to study the binding of the alternative splicing regulator MBNL1 to $(CUG)_{n=4,6}$ and the effect of small molecules on this interaction. Expanded CUG repeats (CUG^{exp}) are the causative agent of myotonic dystrophy type 1 by sequestering MBNL1. Unexpectedly, MBNL1 is able to bind to the $(CUG)_n$·inhibitor complex indicating that the inhibition is not a simple competitive process. A simple ligand, highly selective for CUG^{exp} was used to design a new dimeric ligand that binds to $(CUG)_n$ almost two orders of magnitude more tightly and is more effective in destabilizing MBNL1·$(CUG)_4$. The single-molecule method and the analysis framework we developed should be generalizable to the study of a broad range of biomolecular interactions.