Toward Efficient Identification of Small Molecule Inhibitors of RNA-Protein Interactions in Myotonic Dystrophy Type 1

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Myotonic dystrophy is a dominant genetic disorder affecting 1 out of 8000 adults. Patients experience multiple symptoms including cataracts, heart conduction defects, and loss of muscle strength. An RNA gain-of-function model proposes that the poly(CUG) expansions in non-coding RNA can sequester RNA-binding proteins involved in mRNA splicing, with MBNL1 being the major protein affected. The loss of mRNA splicing regulation through the aggregation of MBNL1 with poly(CUG) RNA is believed to cause the majority of the symptoms associated with the disorder. There is evidence that an inhibition of this MBNL1-RNA complex will rescue misregulated splicing.

We have utilized molecular dynamics simulations to screen the NCI, Chembridge, Marvel, and HTSF libraries, identifying several possible inhibitors. Currently we are employing electrophoretic mobility shift assay (EMSA) to confirm and quantify their activity. We aim to optimize the assay for the identification of strong inhibitors which can act as lead compounds for a treatment for myotonic dystrophy.