Discovery and Study of Small Molecule Inhibitors of MBNL·RNA Complexation as Therapeutic Agents to Treat Myotonic Dystrophy

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Myotonic dystrophy (DM) is currently an incurable genetic disease that affects 1 in 8,000 humans worldwide. Although extensive efforts have been made to understand its pathogenesis, the mechanism by which DM1 causes its symptoms is not fully understood. Nevertheless, it is known that the splicing protein – MBNL1 is sequestered by two types of abnormally long RNAs (CUG and CCUG repeats). This key discovery inspired the development of ligands that inhibit MBNL1-RNA complex formation, allowing MBNL1 to resume its biological functions.

Our group has synthesized ligands that recognize the base mismatches in CUG and CCUG repeats. Although little is known about the binding mode, these ligands disrupt the MBNL1-RNA complex *in vitro*. We utilized synthesis, gel shift assays, and molecular modeling to elucidate the binding modes of these ligands potentially allowing for the design of ligands with better inhibitory activity.