Bis-amidinium Based Ligands as Potential Therapeutics for DM

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Myotonic dystrophy (DM) is a multisystemic disease, affecting 1 in 8000 people worldwide. There are two types of DM: DM1 and DM2. A DM1 diagnosis is made when a patient has from between 50 and several thousands of CTG repeats in the 3'-untranslated region of *DMPK* gene on chromosome 19. DM2 is caused by an expansion of CCTG with more than 75 repeats in intron 1 of *ZNF9* gene on chromosome 3 indicating the disease state. The length of the repeat sequence in both disease types is directly related to the severity and onset of the disease. Transcribed CUG and CCUG repeats sequester the muscleblind-like (MBNL) protein family including MBNL1, a regulator for alternative splicing. The depletion of MBNL1 in nucleus causes mis-splicing of more than 100 pre-mRNAs, which leads the disease symptoms of myotonia, muscle weakness, cataract and heart hypertrophy. To date, there is no cure for DM.

One approach to treat DM is to target toxic RNAs with small molecules. Based on the reported crystal structures of $(CUG)_{12}$, our group rationally designed a ligand with a recognition unit, melamine, covalently linked to an acridine intercalator. The melamine unit is proposed to bind to UU mismatches through Janus-Wedge recognition. The conjugate of melamine and acridine was found to disrupt the MBNL1-$(CUG)_{12}$ complex *in vitro*. Herein, we report a bis-amidinium-based ligand, which has low micromolar inhibition potency and much less cytotoxicity in comparison to acridine-based ligands. The bis-amidinium ligand partially dissolved the RNA-MBNL1 foci and partially rescued IR and cTNT splicing defects in DM1 cell model. By replacing the melamine unit by triaminopyrimidine, which has been proposed to bind selectively to CU mismatches, a set of ligands that targets DM2 was synthesized. The study of their biological activities shows that these ligands disrupt the MBNL1-$(CCUG)_8$ complex *in vitro* and dissolve the disease foci in DM2 cell model.