Rational design of potent dimeric ligands as potential theraputic agents for myotonic dystrophy type I (DM1)

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It is known that expanded CUG repeats arising from the DMPK gene sequester the splicing protein MBNL1 and that this leads to myotonic dystrophy type I (DM1). Herein, we describe the rational design and synthesis of a library of dimers that bind with high affinity to CUG repeats. Our goal is to disrupt MBNL1-CUG repeat complex formation. Previously a CUG binding ligand, containing a 1,3,5-triazine-2,4,6-triamine recognition unit linked to an acridine, showed promising MBNL1-$(CUG)_{12}$ inhibition potency.

The repeating nature of the aberrant RNA, prompted us to follow a bivalent approach through ligand dimerization in order to increase the affinity and selectivity of the ligand. A small library of dimeric ligands was synthesized using linkers with different lengths and functionality.

The most potent dimer, AJ8, contained *N,N′*-bis(3-aminopropyl)-1,3-propanediamine, as the linker and was found to inhibit the MBNL1-$(CUG)_{12}$ complex formation with an IC_{50} of 1.09 μM in the presence of excess tRNA as a competitor. The inhibition potency is more than 200-fold greater than the corresponding monomer leading to a bivalent effect that is greater than 100-fold. Another advantage of AJ8 is improved drugability profile as it is not cell cytotoxic and unlike the corresponding monomer is aqueous soluble.

This study suggests a general approach by taking advantage of multivalent effect for targeting disorders with repeating causative agents.