Pharmacophore Modeling and Identification of Molecular Scaffolds Capable of Inhibiting the Interaction Between $(CUG)_n$ RNA and the MBNL1 Protein as Potential Therapeutic Agents for Myotonic Dystrophy

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Trinucleotide repeat expansions are the result of slippage during DNA replication and are involved in a number of genetic disorders, including Huntington's disease, fragile X mental retardation, and myotonic dystrophy. Mytonic dystrophy type 1 (DM1) is an autosomal dominant neuromuscular disorder associated with a $(CTG)_n$ expansion in the 3'-untranslated region of the dystrophia myotonica protein kinase (DMPK) gene and is characterized by muscular atrophy, dysphagia (difficulty swallowing) and myotonia. In DM1, the $(CUG)_n$ RNA sequesters a key splicosomal protein, muscleblind-like protein 1 (MBNL1), preventing mediation of proper splicing of two pre-mRNAs, cardiac troponin T (cTNT) and insulin receptor (IR). The severity of DM1 correlates with the length of the CTG repeat tract. Currently there is no cure for myotonic dystrophy. We are investigating the inhibition of the $(CUG)_n$-MBNL1 complex by small molecules to identify scaffolds which could be further developed into therapeutic agents for DM1. In order to select a more focused library for screening, we designed two pharmacophore models based on a major groove binder and a minor groove binder, respectively. In the case of the minor groove binder, no crystal structure of RNA-bound molecule was available, so molecular dynamic (MD) simulations were utilized to elucidate the potential binding mode. The top 120 hits were selected from the pharmacophore screen for further analysis. A model system of $(CUG)_{12}$ RNA and a truncated MBNL1 protein (MBNL1N) will be used to determine inhibitory activity by electrophoretic mobility shift assay (EMSA), and positive hits will be analyzed for RNA binding activity by isothermal calorimetry (ITC). Progress in screening and identifying ligands will be discussed.