Drug-functionalized Cell-penetrating Peptides for Enhanced Delivery and Binding in Myotonic Dystrophy Type 1 Treatment

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Recent development in (CUG)n-RNA small molecule binders showed potential for treatment of myotonic dystrophy type 1 (DM1). However, many difficulties exist before the drug could be used in in vitro and in vivo studies, such as low water solubility, high cytotoxicity at effective dosage, and cell membrane penetrability. In addition, as a mere RNA binder, the drug molecules only occupies the binding sites of (CUG)n instead of removing it. As a rational design to solve these problems, small molecules that were known to bind to (CUG)n repeat were conjugated onto the side chains of cell-penetrating peptides (CPPs) by click-chemistry. The CPPs greatly improved the water-solubility of the hydrophobic drug, preventing aggregation, and effectively transporting them into the cells. In addition, the resulting multi-valent drug polymers could have dramatically improved binding affinity towards (CUG)n repeat, as well as reduced cellular toxicity. Peptides with different length, drug loading and helicity were evaluated using model cells. Overall, the exceptionally high binding affinity and efficient drug delivery allowed full function recovery in splicing reversal studies. Short RNA-cleaving peptide could also be conjugated onto the CPPs, granting the conjugates the ability to degrade the toxic RNA upon binding.