SESSION I: SPEAKER ABSTRACTS

Discovery of Multivalent, Bidirectional Transcription Inhibitors for Myotonic Dystrophy Type 1 (DM1)

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Early investigation into the pathobiology of myotonic dystrophy type 1 (DM1), an incurable neuromuscular disease, led to an understanding that DNA containing expanded d(CTG•CAG) repeats form stable secondary structures and undergo bidirectional transcription to yield toxic gain-of-function RNA and further repeat-associated non-ATG (RAN) translation to form homopolymeric proteins. Herein, we report small molecule ligands capable of inhibiting transcription bidirectionally, binding to $d(CTG)^{exp}$ hairpins and halting the production of $r(CUG)^{exp}$ and $r(CAG)^{exp}$. Using fragment-based drug discovery and target-guided synthesis, we developed an azide-alkyne clickable fragment library of nucleic acid-binding ligands and performed a pairwise screen for reactivity on $d(CTG)^{exp}$ hairpins. Using MALDI-TOF mass spectroscopy to detect click products, we found several ligands undergo a template-assisted click reaction only on the target DNA, reflecting the binding affinity and proximity of the reactive groups. Hit compounds were able to inhibit the *in vitro* transcription of $d(CTG•CAG)_{90}$ bidirectionally at low concentrations and qualitatively decrease RNA levels and downstream effects in confocal experiments. Thus, target-guided drug discovery can be used to find inhibitors for DM1 and potentially serve as a therapeutic strategy in cells to mitigate low cell permeability. Further, this approach may be broadly applicable to other trinucleotide repeats and other diseases that undergo bidirectional expression.