Dynamic RNA-Templated Drug Discovery. On-Target Synthesis and Selection of Modular Therapeutic Agents for Myotonic Dystrophy

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The development of on-target, self-assembling therapeutic agents has gained renewed interest lately. Herein, r(CUG)16, a model for the toxic expanded CUG RNA that causes myotonic dystrophy type 1 (DM1), is used as a template to selectively couple small molecules. A library of alkyne- and azide-containing ligands, capable of producing more than 5000 compounds, was incubated in the presence of r(CUG)16 under physiological conditions. The r(CUG)16 accelerates the alkyne-azide [3+2]-cycloaddition by bringing suitable clickable partner in proximity, whereas other RNA sequences, such as r(CCUG)8 and tRNA, are inactive. The limited number of click products formed indicates a dynamic selection useful for the discovery of therapeutic agents that target the DM1 toxic RNA. Beyond being a powerful strategy for discovering tighter binding leads, in situ target-guided synthesis also can itself be a therapeutic approach. The self-assembly approach can avoid the poor uptake of higher molecular weight agents.