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Making Stable Aptamers as ALS Drug Candidates

Excessive activation of the \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) subtype of ionotropic glutamate receptors has been hypothesized as one of the leading pathogenic mechanisms for amyotrophic lateral sclerosis (ALS). Developing powerful inhibitors to control the excessive receptor activity is thus a logical therapeutic strategy. In a proof of concept experiment, we have successfully identified a class of AMPA receptor-selective RNA aptamers or RNA inhibitors. The potency of one aptamer rivals any existing AMPA receptor inhibitors ever reported thus far. Unmodified, however, these RNA aptamers are limited in therapeutic applications in vivo by their inherent sensitivity towards ribonucleases, the enzymes that catalyze the degradation of RNA into smaller pieces so that the biological function of the RNA as inhibitors is lost. However, chemical modifications of RNA molecules can turn them into ribonuclease-resistant or biostable aptamers. Thus, making ribonuclease-resistant aptamers is required, as the first step, to translate these aptamers from powerful AMPA receptor antagonists into clinically useful drugs. The specific goal of this proposal is to develop high-affinity, chemically modified aptamers. These chemically modified aptamers will be immediately suitable for testing their neuroprotective effectiveness in ALS cellular and animal models.