Li Niu  
Chemistry

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**Characterization of Chemically Modified Aptamers as New ALS Drug Candidates**

Excessive activation of the α-amino-e-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) subtype of ionotropic glutamate receptors is an important pathogenic mechanism for ALS. Finding inhibitors to control the excessive receptor activity has been a long-pursued strategy for developing ALS drugs. We previously showed that nanomolar affinity RNA inhibitors or RNA aptamers selectively targeting AMPA receptors can be identified. These aptamers are superior to traditional, small-molecule inhibitors, because these traditional inhibitors are organic compounds and generally have poor water solubility, low affinity and cross activity. However, unmodified, these RNA aptamers are limited in therapeutic applications in vivo by their inherent sensitivity towards ribonucleases, the enzymes that catalyze RNA degradation. In contrast, chemical modifications of RNA molecules can turn them into ribonuclease-resistant or biostable aptamers. Thus, making biostable aptamers is the first step to translate these powerful AMPA receptor aptamers into clinically useful drugs. Thus far, we have successfully developed several high-affinity, chemically modified aptamers for AMPA receptors. The goal of this proposal is to characterize these chemically modified RNA aptamers for their neuroprotective effectiveness on glutamate-induced neurotoxicity in ALS cellular and animal models. These studies are key preclinical experiments to advance these RNA inhibitors as a new ALS drug.