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**Discovery of AMPA Receptor Potentiating Aptamers as Cognitive Enhancers**

Potentiators of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamate receptors are chemical molecules capable of enhancing the receptor response to glutamate, the neurotransmitter in the brain. AMPA receptors are indispensable for brain activities such as memory and learning. Clinical studies have shown that AMPA receptor potentiators are cognitive enhancers since the use of these potentiators is beneficial to memory and to the treatment of some cognitive disorders and diseases, such as depression and memory loss, which are two of the most common symptoms for the veterans who have the Gulf War Illness.

Therefore developing better potentiators contributes to the health and the treatment of the Gulf War Illness. Currently, however, virtually all of the existing, chemically synthesized AMPA receptor potentiators are small organic molecules. They are poorly water soluble, have low affinity and are not known to have any receptor subunit selectivity. Furthermore, how these potentiators affect the channel-opening rate process of AMPA receptors, which occurs in the microsecond time domain, is poorly understood.

Here we propose to use a combination of two novel techniques to produce subunit-selective, water soluble, and nanomolar affinity potentiators, a goal that remains elusive in the field of drug design. Specifically, we propose to identify *RNA molecules or aptamers* as potentiators that are selective to GluR2, a key AMPA receptor subunit involved in memory and a number of neurological disorders and diseases. The hypothesis to be tested is that the use of an *in vitro* iteration procedure, known as *systematic evolution of ligands by exponential enrichment* (SELEX), to discover aptamers from a RNA library, combined with a laser-pulse photolysis technique to characterize the aptamers with the *functional* (i.e., non-desensitized) receptor states that only exist in the microsecond time domain, will yield nanomolar affinity potentiators selective to the GluR2 AMPA receptor subunit.

The use of GluR2-selective potentiating aptamers/aptamer drugs will enable us to uniquely probe whether the GluR2 subunit is functionally involved in various diseases, and if so, it will allow us to achieve a more quantitative potentiation of this subunit so that the therapeutic intervention is more tightly regulated. For now, however, the specific goal or the interim outcome of this research is to identify potentiating aptamers that exclusively act on the GluR2 AMPA receptor subunit without any unwanted activity on any other kinds of glutamate receptor subunits.

It should be emphasized that the approach we have described in this proposal, which is to discover RNAbased, subunit-selective potentiating aptamers, offers both a novel drug design strategy and a new class of drug candidates potentially for a new therapy for a number of cognitive disorders, such as memory loss and depression. The ultimate goal of our research is to

bring these aptamers from “bench side to bedside”. As potentiating drugs, they will be clinically useful not only for Gulf War veterans who have memory loss and depression, for instance, but also for patients from civilian populations. Aptamers are generally considered safe and have minimal toxicity and immunogenic response. If all goes well, we anticipate in five years or so, we might be able to bring an aptamer drug to clinical trials.