Novel Aminoadamantane Nitrates for the Treatment of Neurological Diseases

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Country

USA

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Novel Aminoadamantane Nitrates for the Treatment of Neurological Diseases

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Research Abstract

? DESCRIPTION (provided by applicant): Memantine, an aminoadamantane, is approved to treat moderate-to-severe Alzheimer’s disease in the US and Europe. Memantine selectively inhibits abnormally active N-methyl-D-aspartate-type glutamate receptor (NMDAR) channels, while preserving normal glutamate activity and physiological neuronal function (Lipton, 2006;

Lipton, 2007a,b). Pathological NMDA receptor activity is further down-regulated by S-nitrosylation of cysteine residues located on the N-terminus or extracellular domain. Taking advantage of these insights, we have developed a series of bifunctional antagonists, nitromemantines, that not only preferentially bind to the open-channel state but also selectively target NO to a second modulatory site using the memantine pharmacophore as a homing motif. Our data suggest that some of these memantine analogs have good potency, while maintaining selectivity for persistently open NMDAR channels. Most importantly, they appear to have greater neuroprotective properties than memantine in both in vitro and in vivo animal models. Our results provide structural guidance to further optimize, and then identify, a potential development candidate with an optimal profile to maximize neuroprotective effects. PRI owns, and the PI is a co-inventor on the original nitromemantine patents (Wang, 2002, 2003, 2008). Recent work from the laboratory of our collaborator (and co-inventor), Prof. Stuart Lipton, demonstrates the unique superiority of one of our nitromemantines (YQW- 036, 1-amino-3,5-diethyl-7-nitrateadamantane) versus memantine to rescue/protect synapses (Talantova, 2013). This compound preferentially and uniquely modulates pathogenic extrasynaptic NMDARs versus synaptic NMDARs. Phase I seeks to identify a development candidate based on our promising dual-targeted lead compound. Phase II will support translational, IND-enabling studies. The achievement of this milestone will generate a proprietary first-in-class, disease-modifying drug for Alzheimer’s disease.

Further information available at:

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