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Title: NSI- 189, a neurogenic, pro-cognitive, antidepressant compound, reverses synaptic plasticity deficits in adult mouse model of Angelman syndrome

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ABSTRACT

NSI-189 is a new chemical entity discovered on the basis of its neurogenic activities on human hippocampal neural stem cells in vitro and in vivo on young normal mouse hippocampus. Additionally, it has been found to increase hippocampal volume in normal healthy adult mouse, stimulate synaptic remodeling of hippocampus in an ischemic stroke model, reverse peripheral neuropathy in mouse diabetic models, and ameliorate cognitive impairment in radiation-induced brain injury model. In humans, the compound has been tested in patients diagnosed with recurrent major depressive disorder in phase 1b and 2 studies. In both studies, patient-reported outcome of depression, SDQ (symptoms of depression questionnaire), and of cognition, CPFQ (cognitive physical functioning questionnaire), were statistically significant against placebo. Especially, in the phase 2 study, NSI-189 showed statistically significant advantages on certain objective cognitive measures of attention and memory in CogScreen battery. These effects of NSI-189 are seen from chronic administration (4-16 weeks) at low doses of 10-30 mg/kg in animal studies and 40-80 mg daily in humans. At concentrations of 1-3 μ M in vitro, and after about 3 hours of incubation, NSI-189 enhances long-term potentiation (LTP), a cellular model of learning and memory, to supra-normal levels in hippocampal slices from normal mice and restores LTP in slices from mice with a maternal deletion of UBE3A, a model for Angelman Syndrome, which lack LTP. We also find that within 7 days of systemic administration in adult Angelman mice at doses that result in brain drug concentrations of 1-3 μ M, NSI-189 reverses motor and cognitive deficits in vivo and restores LTP, measured ex vivo in hippocampal slices. These results suggest that NSI-189 may be used at much higher doses to induce fast onset of treatment effects by mechanisms enhancing synaptic plasticity and at lower doses to maintain the treatment effects chronically by mechanisms enhancing neurogenesis.