

Development of Novel Therapy for Angelman syndrome

Haidun Yan^{1*}, Zhe Pei^{1*}, Ramona M. Rodriguiz², Xiaoming Wang¹, Mike Lewis⁵, Mike Ackley⁵, Frank Salituro⁵, Al Robichaud⁵, Jim Doherty⁵, William C. Wetzel^{2,3,4}, Yong-hui Jiang^{1,3}

¹Departments of Pediatrics, ²Department of Psychiatry and Behavioral Science, ³Neurobiology, and ⁴Cell Biology, Duke University School of Medicine, Durham, NC 27710 USA; ⁵Sage Therapeutics, Cambridge, MA 02026 (*Equal contribution)

Despite substantial progress in understanding the molecular basis of AS, it remains a significant challenge to develop effective pharmacological therapies for the disorder. A recent study has shown that tonic inhibition is specifically decreased in cerebellar granule cells of Ube3a^{m-/p+} mice and this impairment is believed to contribute to impaired motor function. 1) We recently reported that treatment of lovastatin can suppress the seizure activity in AS brain slices and animal model. 2) Recently, novel synthetic neurosteroid positive allosteric modulators (PAMs) of GABA_A receptors have been described that have potent effects on both synaptic and extrasynaptic receptors and preferential effects on extrasynaptic receptors. We hypothesized that these compounds would enhance tonic currents in cerebellar granule cells and correct the motor dysfunction in an AS mouse model. We will present these data in the meeting