Synaptic Vesicle glycoprotein 2A (SV2A) levels as a translatable measure of synaptic density following HDAC inhibition

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Disruptions of dendritic spines are reported for many CNS diseases and are closely related to cognitive impairment. In patients with Alzheimer's disease (AD), synapse loss in the hippocampus is strongly correlated with cognitive deficits. There is a growing realization that epigenetic regulation plays a role in neuronal function and dysfunction. A class of epigenetic regulatory enzymes known as histone deacetylases (HDACs) remove acetyl groups on lysine residues on histones, selectively decreasing expression of certain genes. Acetylation and deacetylation of these lysine residues is important in regulating gene expression of neuronal proteins critically needed for synaptic function and plasticity. HDAC2 overexpression in mice has been shown to decrease spines, synapses and cause cognitive impairment; the opposite is observed in HDAC2 knockout mice. In addition, cognitive deficits have been shown to be attenuated following treatment with HDAC inhibitors. Safe and well tolerated HDAC inhibitors that improve synaptic density in AD patients would provide a complementary treatment approach to the current amyloid and tau modifying therapies.

One principle challenge in understanding any potential beneficial role of improving synaptic density in neurological disorders has been the lack of tools to quantify changes in synaptic density in a clinical setting. Synaptic vesicle glycoprotein 2A (SV2A) is a membrane protein found in presynaptic terminals and is essential for synaptic function. Recently, Finnema and colleagues (2016) have demonstrated that you can quantify synaptic density in human subjects by PET imaging of SV2A using [^{11}C]UCB-J, which would make this an important tool for translational studies of synaptic function. Rodin has demonstrated that the prototypic Class I selective HDAC inhibitor, CI-994, significantly increased dendritic spine numbers in the hippocampus in wild type mice following 14 days of oral administration. The increase in spine density was accompanied by a significant increase in the synaptic levels of SV2A. We have also shown that sub-chronic CI-994 administration improves Long Term Potentiation (LTP)-deficits in the 5xFAD mouse model of AD.

Together these findings strongly support that SV2A measurements would be a viable translational approach to study the pro-synaptic effects of HDAC inhibitors in a clinical setting.