Testing potential regulators of BDNF expression to identify candidate Rett syndrome therapeutics

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Enhancement of Brain-Derived Neurotrophic Factor (BDNF) signaling has been shown to have potential therapeutic benefit in animal models of Rett syndrome. BDNF is a secreted protein known to act through two different receptors, the TrkB receptor tyrosine kinase and the p75NTR receptor. Multiple therapeutic strategies to increase BDNF signaling are currently under investigation because there are impediments to delivery of the BDNF polypeptide itself to the brain in a manner that would be efficacious. With the prior support of IRSF (now Rettsyndrome.org), we developed and optimized a gene-targeted reporter-based assay for BDNF expression suitable for High Throughput Screening using primary cortical neurons, a cell type thought to be important in aspects of the cognitive impairments of Rett syndrome. We then screened the Prestwick2 library, comprising over 1100 known bioactives and FDA-approved drugs, identifying a number of hits that upregulate reporter expression. These hits include compounds previously demonstrated to stimulate Bdnf expression, as well as compounds not previously described as having this activity.
The objectives of this proposal are to determine the properties of several of these compounds, analyzing their effects on the expression of different BDNF mRNAs as well as enhancer RNAs in vitro. These studies will help define the mechanisms by which these compounds influence BDNF expression and their expression-regulating properties. We will also test compounds for their ability to regulate BDNF expression in vivo, quantitatively determining their effects in different brain regions in order to help assess their therapeutic potential. The goal is to identify one or more compounds that show promise for further development as a therapeutic treatment for Rett syndrome. We intend to submit promising compounds for further testing in Rett models by the Rettsyndrome.org Scout Program. Because the compounds we are studying have a history of use in humans, they could be re-purposed as therapeutics for Rett syndrome in the near future.