High Throughput AD Drug Screening of Alpha-Secretase Activity Modulators as a Novel Model for Alzheimer's Disease

Modi, Morni

Due to the increasing prevalence of Alzheimer’s Disease (AD) and currently the absence of effective disease modifying drugs, there is a need for improved drug screens to identify plausible AD disease drugs. Amyloid Precursor Protein (APP) can be converted to sAPP a, a harmless form of APP metabolism and is a competing pathway for the generation of beta-amyloid. a -Secretases can be activated by several pathways involving receptor mediated activation and direct PKC modulation of a –secretase activity. The present study investigates a way to inhibit the formation of ß –amyloid (Aß) plaques which results in the progressive form of dementia known as Alzheimer’s Disease. This study suggests the use of modified HEK293e cells and SH-SY5Y neuroblastoma cells as a novel method for the screening of a candidate drug, Bryostatin, under the Aß hypothesis. By treating models of brain cells (HEK293e) and SH-SY5Y neuroblstoma cells with drugs such as Bryostatin, which is derived from the sea moss Bugula Neritina, a-secretase can be upregulated through Protein Kinase Chain (PKC) modulation. Therefore, the non-toxic form of APP (sAPPa) can be produced and a method to treat AD may be achieved. Upon treatment, it was found that Bryostatin isoforms 1,2,3,10,12,14b, and 16 are potent activators of a-secretase expression in both concentrations tested. (10^-7 and 10^-8 M). These results suggest that Bryostatin could be a promising and novel drug to be used as a low-dose therapy for AD and may help move this drug towards clinical trials for the treatment for AD.

Awards Won:
Third Award of $1,000