expected that further studies will provide some lead candidates as potential agents to treat AD.

P3-041 DRUG REPOSITIONING OF XHC FOR ALZHEIMER'S DISEASE: BACE1 PROMOTER REPRESSING ACTIVITY OF XHC

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Background: Amyloid hypothesis postulated that exceed extracellular amyloid beta deposits are the fundamental cause of Alzheimer's disease. Amyloid beta is produced by sequential proteolysis to amyloid beta precursor protein (APP) by beta-secretase (BACE1) and gamma-secretase. Another important phenomenon in AD patient is increased BACE1 expression. **Methods:** Our strategy is to find specific drugs reducing BACE1 expression rather than direct inhibition of BACE1. Using USA FDA approved drug library (Prestwick Chemical Library), we could discover putative therapeutic chemicals by cell based assay. **Results:** Among those candidates, XHC reduced the levels of BACE1 protein and mRNA in SH-SY5Y cells. A soluble APPb and C99 which are the products of BACE1 protease, were also decreased by treatment of XHC. We also confirmed that XHC could improve cognitive functions of 3XTg-AD mice. Decreased level of amyloid beta deposition and BACE1 expression also observed in XHC-treated AD mice. **Conclusions:** The fact that XHC is orally efficacious in AD animal models and is clinically safe to use make XHC an excellent candidate for advancement to clinical AD trials.

P3-042 ENCAPSULATION OF AMYLOID-BETA SCAVENGING COMPOUNDS INTO BBB PERMEABLE NANOPARTICLES

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Background: Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by a progressive decline in memory as a result of neuronal cell death. One of the pathological hallmarks of AD includes the accumulation of amyloid-beta (Aβ) toxic oligomers. Many developed small molecule drugs demonstrating neutralizing activity towards toxic Aβ oligomers under in *vitro* conditions, were shown to fail in clinical trials. We hypothesize that one of the major challenges in the development of therapeutic strategies in AD is presented by the limited ability of the therapeutic compounds to penetrate the blood-brain barrier (BBB). **Methods:** Our approach consists of the encapsulation of small molecules neutralizing toxic Aβ oligomers into BBB permeable nanocarriers. We evaluated the effect of drug loading on the nanoparticles and their ability to cross the BBB using a BBB on a chip technology. **Results:** We developed up to 24 nm diameter reversible single chain polymer nanoparticles (AFM, SEC, DLS) that are non-toxic to neuroblastoma cell line. NMR shows they are crosslinked to encapsulate selected small molecule drugs which inhibit aggregation of Aβ and toxicity. **Conclusions:** Blood-brain barrier perimable single polymer chains can be used to encapsulate small molecule drugs with anti-toxic aggregant behavior.

P3-043 INVESTIGATING MULTI-THERAPEUTIC AMYLOID STRATEGIES FOR TREATING ALZHEIMER'S DISEASE

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Background: In Alzheimer's disease (AD), the pathological accumulation of Beta-amyloid peptide (Abeta) and the formation of Abeta plaques have been associated with neurotoxicity. Presently, two promising strategies in reducing Abeta have been reported; *scyllo*-Inositol (SI), an inositol stereoisomer that enters the brain and inhibits plaque formation (McLaurin et al., 2006) and MRI-guided focused ultrasound (MRIgFUS) to transiently open the blood brain barrier, allowing for the delivery of BAM-10, an Abeta antibody (Jordão et al., 2010). In the present study, we evaluate the effects of SI treatment alone, a combination treatment of SI/BAM-10 versus no treatment in TgAD mice. **Methods:** TgAD mice were aged to 5 months, prior to SI treatment or a combination of BAM-10, followed by SI treatment for 1 month or no treatment, and sacrificed at 6 months of age. SI was given ad libitum in drinking water and BAM-10 was delivered to the brain using MRIgFUS. Immunohistochemical staining for Abeta and immunofluorescent staining for astrocytes (GFAP) and microglia (Iba-1) were conducted on 40μm coronal sections spanning the brain. Triple stains of Thio-S for neuritic plaques, Iba-1 and GFAP were conducted and analysed using Imaris to determine the percentage of phagocytosed Abeta compared to extracellular plaques. **Results:** SI and SI/BAM-10 treatments showed significant reduction in Abeta plaques in both the cortex and hippocampus when compared to the non-treated, but negligible differences between SI and SI/BAM-10. A trend for increased Abeta phagocytosis by activated microglia was also observed in SI and SI/BAM-10 treatment groups when compared to non-treated. Furthermore, GFAP staining showed decreased astrogliosis in SI and SI/BAM-10 treatment groups when compared to non-treated. Through analysis of the triple stain, SI and SI/BAM-10 treatment groups also showed increasing trends in percentage of plaque phagocytosed when compared to non-treated. However, no significant differences were observed between the SI and SI/BAM-10 treatment paradigms in these stains. **Conclusions:** Previous studies show that BAM-10 remains bound to ABeta up to 4 days after MRIgFUS delivery (Jordão et al., 2010). In the SI/BAM10 treatment, the SI likely provides the prevailing therapeutic effect at the end of the treatment period, similar to SI treatment alone.

P3-044 MILD BETA-AMYLOID PRECONDITIONING HAS A NEUROPROTECTIVE EFFECT BY ENHANCING CELLULAR TOLERANCE VIA BDNF PATHWAY

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Background: Since Janoff introduced novel strategy in 1964, preconditioning has been an attractive strategy for protecting neurons by enhancing cellular tolerance. Abundant studies have shown