

**Edward N. and Della L. Thome Memorial Foundation, Bank of America, N.A. Trustee,
Awards Program in Alzheimer's Disease Drug Discovery Research
2010 Award Recipient**

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*Histone Acetyltransferase (HAT) Activators as Chromatin Remodelers for the Treatment of Memory Loss
in Alzheimer's Disease*

Amyloid-beta, a peptide that is present in high amounts in Alzheimer's Disease (AD), has been found to inhibit memory and its electrophysiological model, long-term potentiation (LTP). Amyloid-beta was also found to reduce histone acetylation, a chromatin modification that is important for the formation of memory. The main strategy that is currently used to up-regulate histone acetylation involves HDAC inhibitors. However, the pleiotropic effect of nonspecific HDAC inhibition may hamper their therapeutic potential. Activators of histone acetyltransferase (HAT) might constitute an alternative avenue to enhance histone acetylation. To this end, in preliminary experiments, hippocampal levels of two HATs, CBP and PCAF, were found to be reduced following amyloid-beta elevation. Most importantly, a newly-designed HAT activator, YF2, which is soluble, membrane permeable and blood-brain barrier permeant, was found to i) enhance enzymatic activity of PCAF and CBP in an in vitro assay; ii) increase specific histone acetylation of H3, H4 and H2B in hippocampal lysates, iii) rescue deficits in LTP as well as fear and reference memory induced by amyloid-beta. A course of investigation involving the design of selective HAT activators that target specifically CBP and PCAF, downstream of amyloid-beta is proposed in this application. The aims of our proposal are: 1) to design and synthesize novel HAT activators which are optimized for AD; 2) to identify new HAT activators with high affinity and good selectivity for CBP and/or PCAF; 3) to determine if new HAT activators have good pharmacokinetic profile and are safe; 4) to select HAT activators that rescue synaptic dysfunction in a mouse model of amyloid-beta elevation; 5) further screen HAT activators to determine if they are beneficial against cognitive abnormalities in a mouse model of amyloid-beta elevation. On the completion of these studies we will identify a new drug for the treatment of cognitive loss in AD.

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Translation of BRI2 Derived Peptides into Therapeutic Candidates

Alzheimer's Disease is the most common cause of dementia in the world and the 6th leading cause of death in our nation. It increases exponentially with age, afflicting an estimated 1% of individuals aged 60-64 years and nearly 50% of those 85 years or older. Longer life spans coupled with the changing demography of the aging baby boomers renders AD a pressing public-health issue. However current treatments only modestly retard the progression of the illness because they treat the symptoms rather than the cause of the disease. Genetic data indicate that APP processing and APP metabolites play a pivotal role in AD. A possible approach to develop therapeutic strategies for AD involves the characterization of the biological pathways/molecules that regulate APP processing. Understanding how APP cleavage is physiologically regulated might suggest therapeutic interventions that are otherwise unimaginable. Recently, we found that BRI2 is a ligand of APP that regulates APP cleavage. BRI2 hides the cleavage site of APP from BACE and the γ -secretase and reduces APP cleavage by secretases. In doing so, BRI2 selectively reduces APP processing while leaving the secretases undisturbed to act on other substrates. To take advantage of this function we have produced BRI2-derived peptides that mimic its role. These BRI2-peptides inhibit APP cleavage by BACE and also interfere with the toxicity of A β 42 oligomers that are derived by APP processing. Thus, we will refer to these peptides as IAPT (Inhibitor of APP Processing and Toxicity). This grant aims to perform lead optimization on the parent peptides in terms of absorption, distribution, metabolism, excretion, toxicity (ADMET) and general pharmacokinetics. We will also seek to identify small-molecules that retain BRI2-like biological activity but have ADMET properties suitable for oral-administration as therapeutics to treat AD in patients. Advanced leads will be qualified by evaluation in animal models of dementia.

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Amyloid Vaccines and Human Anti-Amyloid Antibodies

There is compelling evidence that aggregation and accumulation of the amyloid beta protein (Abeta) in the brain plays a pivotal role in Alzheimer's Disease (AD), "triggering" a complex neurodegenerative cascade. Thus, numerous therapeutic modalities targeting Abeta and Abeta aggregates are in the developmental pipeline. Among the most promising of the anti-Abeta based therapeutic approaches for AD are Abeta vaccines and humanized anti-Abeta monoclonal antibodies. For reasons discussed more extensively below, it is highly likely that the clinical efficacy of disease modifying effects of these and other anti-Abeta therapies will be highly dependent on the extent of underlying pathology present at the time of initiation of treatment. Indeed, a therapy which fails to show efficacy in the symptomatic patient might show remarkable efficacy with respect to preventing the development of AD or slowing the conversion from preclinical AD to symptomatic AD.

The implementation of prophylactic or very early intervention trials with anti-Abeta therapeutics will likely require the development of therapies that are as safe as possible. Here, we propose to develop novel active and passive AD immunotherapies that have potential to be safer, more efficacious, and possibly more cost-effective, than current approaches. The overall rationale is that Abeta aggregates, not monomeric Abeta, are the ideal targets of immunotherapy. Specifically, we propose two complementary and synergistic aims:

1. Optimization and pre-clinical validation in AD mouse models of heterologous amyloid (HAPs) vaccines that result in robust humoral immune responses to Abeta amyloid (as well as other potentially pathogenic amyloids), but not monomeric Abeta or other APP derivatives.
2. Identification and characterization of human (as opposed to humanized) anti-amyloid antibodies that target Abeta aggregates with minimal targeting of Abeta or APP derivatives and validation of their efficacy.

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ApoE-directed Therapeutics for the Treatment of Alzheimer's Disease

We propose to develop new drugs that promote Abeta clearance from the brain by targeting the transcriptional machinery regulating the expression of ApoE and its incorporation into HDL particles. Lipidated forms of ApoE act normally to promote the proteolytic degradation of Abeta. Importantly, elevation of ApoE levels in the brain is associated with reduction in Abeta levels and plaque burden and improved cognition in animal models of AD. We propose to investigate drugs that target the ligand-activated transcription factors, retinoid X receptors (RXRs), which regulate the synthesis of ApoE and the formation of HDL.

We show that the retinoid, bexarotene, stimulates the expression of ApoE and highly lipidated HDLs. Elevation of ApoE levels promote the degradation of Abeta in the brain. We provide preliminary data demonstrating that oral treatment of APP/PS1 mice for 7 days with the FDA approved RXR agonist, bexarotene (Targretin™), increases the levels of ApoE in the brain leading to a reduction in plaque load and A β levels by 65% and improved cognition. In vivo microdialysis demonstrated that within 24 hrs of drug administration there was a 30% decrease in interstitial Abeta levels owing to a 70% reduction in Abeta half life. Bexarotene freely passes the blood-brain barrier.

Aim 1 will establish if bexarotene is a viable candidate for clinical development. We propose to determine optimal drug dosage and scheduling of its administration that result in reduced amyloid pathology and improved behavior.

Aim 2 is directed at the development of new chemical entities that act as selective modulators of RXRs. The principal side effect of bexarotene is triglyceridosis, owing to stimulation of SREBP1c expression. Selective RXR modulators act to differentially promote receptor activity at individual target gene promoters. We will modify the bexarotene scaffold to minimize SREBP1c activity and maximize activity at the ApoE and ABCA1 promoters.

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Chien-liang Glenn Lin, Ph.D.

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Glial Glutamate Transporter EAAT2 as a Therapeutic Target for Alzheimer's Disease

Glutamate-mediated excitotoxicity is involved in the pathogenesis of Alzheimer's Disease (AD). Excitotoxicity is defined as excessive exposure to the neurotransmitter glutamate or overstimulation of its membrane receptors such as NMDA receptors. This overstimulation can lead to neuronal injury or death. A therapeutic target has been to reduce excitotoxicity through modulation of the glutamate neurotransmitter system. Memantine, an uncompetitive NMDA-receptor antagonist that inhibits pathological functions of NMDA receptors, has been approved for treating the advanced stages of AD. Memantine is a relatively safe drug with few side effects but only small clinically relevant effects on cognition, global functioning, and activities of daily living. The major factor causing excitotoxicity in AD is the impairment of glutamate reuptake function. It is primarily due to the loss of glial glutamate transporter EAAT2, the major glutamate transporter in the central nervous system. One potential therapeutic approach to prevent excitotoxicity is to activate EAAT2 protein expression and boost glutamate uptake function. In collaboration with the Laboratory of Drug Discovery in Neurodegeneration (LDDN) at the Harvard Medical School, we executed high-throughput screen to identify compounds that can activate EAAT2 expression. This screen resulted in the discovery of two promising classes of EAAT2 translational activators. The goals of this study are to optimize and characterize these two lead series and to assess whether these EAAT2 expression activators can ameliorate Alzheimer's-like pathology and behavior in APPSw/Ind mice.

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Optimization of Neuroprotective, Pro-Neurogenic Small Molecules for Treatment of Alzheimer's Disease

Alzheimer's Disease (AD) is characterized by neurodegeneration, so drugs that improve neural structure and function may represent valuable treatments. Specifically, we have targeted neurogenesis in the hippocampus. The hippocampus is involved in learning and memory, and is one of the first regions to be damaged in AD. This region uniquely generates new neurons throughout adulthood, and is critical for learning and memory. AD patients display altered patterns of neurogenesis, and might benefit from agents that normalize this activity. Enhancement of neurogenesis in mouse models of AD can ameliorate cognitive deficits. We hypothesize that the cognitive deficits in AD can be treated with small molecules that promote the formation and survival of functional neurons within the hippocampus. Accordingly, we aim to develop neuroprotective, pro-neurogenic small molecules that will prevent or reverse cognitive decline associated with Alzheimer's Disease. Compounds will be optimized for efficacy, bioavailability, metabolic stability and absence of toxicity. We have identified a small molecule named P7C3 that promotes hippocampal neurogenesis in mice and rats. This drug-like substance repairs the structure and function of malformed hippocampuses, and prevents age-associated cognitive decline in rats. It protects newborn neurons from cell death and allows them to differentiate into fully integrated mature neurons. It distributes into the CNS, is non-toxic to embryonic, weaning or adult mice, and is active at 5 mg/kg oral dose. We plan to mount a medicinal chemistry campaign to optimize the potency and CNS-penetration of P7C3. Simultaneously, we will optimize compounds for metabolic stability and the absence of toxicity or off-target interactions. Compounds will be tested in mice and rats for bioavailability, half-life, ability to promote neurogenesis, and capacity to improve cognition and memory in mice models of AD. Our objective is to identify small molecules suitable for advancement to IND-enabling studies by the end of this project.

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Screening for New Drugs to Treat Alzheimer's Disease

Alzheimer's Disease (AD) is a neurodegenerative disorder that leads to dementia. There is increasing evidence of a vascular contribution in AD. Many AD patients suffer from altered cerebral blood flow, damaged cerebral vasculature, and abnormal hemostasis. Circulatory deficiencies could therefore play an important role in this disease. However, a mechanism underlying a vascular contribution in AD is unclear. We have found that the deposition of fibrin(ogen), the primary protein component of blood clots, plays a role in exacerbating pathology and cerebrovascular dysfunction in AD mouse models. We also found that the beta-amyloid peptide binds specifically to fibrinogen and that fibrin clots formed in the presence of beta-amyloid have an abnormal structure, making them resistant to degradation by fibrinolytic enzymes. These results indicate that in the presence of beta-amyloid, any fibrin clots formed are more persistent and exacerbate blood brain barrier damage, neuroinflammation, and neuronal death. Therefore, molecules that block this interaction could restore the normal structure of fibrin clots and could be used as therapeutic agents.

We have designed a high throughput screen to identify small molecules that inhibit the interaction between beta-amyloid and fibrinogen. We have screened compounds using two complementary assays: fluorescence polarization and AlphaLISA. We have identified three candidate compounds, and their half-maximal inhibition (IC₅₀) ranges between 1 μ M and 20 μ M. These results suggest that our screening strategy is effective for identification of small molecules that inhibit the interaction between beta-amyloid and fibrinogen. We hope to expand our screening with a wide range compound library to find the most potent compounds and improve upon our candidate compounds using structure-activity relationships and pharmacokinetic studies. In addition, we will validate our hit compounds using functional studies such as intravital microscopy and mouse behavior. We hope our candidate inhibitors will become effective drug therapies for treating AD patients.

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Linda Van Eldik, Ph.D.

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Refinement of p38alpha MAPK inhibitors for Alzheimer's Disease

This project's goal is to de-risk a novel, CNS-penetrant, efficacious, small molecule in order to identify a new therapeutic candidate for Alzheimer's Disease (AD). The initial lead compound and its more refined analog were developed through structure-assisted, selective ligand targeting of p38alphaMAPK, a key protein kinase that drives stressor-induced proinflammatory cytokine overproduction and is involved in neuronal homeostasis. The p38alphaMAPK isoform is a validated therapeutic target for peripheral tissue disorders, but extension to CNS disorders was limited by the need for adequate CNS penetrance with retention of selective inhibitory activity. To address this problem, we used our discovery engine that integrates informatics and computational biology with pharmacology experimental filters, providing a recursive, drug discovery focused effort. The initial small molecule, cmpd069A, is a selective p38alphaMAPK inhibitor that is brain penetrant and shows efficacy in an AD-relevant animal model that exhibits the targeted mechanism of pathology progression. The recursive nature of the discovery engine yielded several second-generation inhibitors, with cmpd181 exhibiting promising pharmacology profiles with retention of p38alphaMAPK inhibitor activity.

Growing evidence has implicated p38alphaMAPK in CNS disorders, including AD. Activation of p38alphaMAPK is an early event in AD, is linked to cytokine overproduction and synaptic dysfunction, and correlates with pathology progression. This project is an early step in testing the hypothesis that orally bioavailable, brain-penetrant, small molecule p38alphaMAPK inhibitors can be developed into effective future AD therapeutics.

Our specific aims are:

Aim 1. Subject cmpd181 to pharmacological screens that de-risk the potential for failure in later-stage preclinical, IND-enabling investigations. As needed, perform medicinal chemistry refinement in an effort to identify the best candidate(s) for follow-on development with industrial partners.

Aim 2. Determine dose-dependent efficacy in AD-relevant animal models as a selection criterion among refined candidate compounds.

The deliverable will be identification of at least one candidate for future clinical development.