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**Conference Consensus**

# Proceedings of the Harvard-Shanghai Conference on Brain Health - A Special Meeting for Understanding and Intervention of Alzheimer's Disease

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This article describes the proceedings of the 2018 Harvard-Shanghai Conference on Brain Health - a special meeting for understanding and intervention of Alzheimer's disease (AD), which took place October 12-13, 2018 at the Harvard Center in Shanghai, China. AD is a worldwide disease and an irreversible and progressive neurodegenerative disorder. Genetics have identified not only mutations in specific genes that are linked to the inherited early onset form of AD, but also the cause(s) of the more typical late onset form of the disease. Over the past years, studies have identified new molecular mechanisms and modifiable risk factors of AD. Understanding the mechanisms and risks of AD enables the development of effective interventions to prevent or cure the disease. Recent research has shown that the disease can be prevented; and an increasing number of researchers are developing therapies that can modify disease pathology or reduce risk. This conference highlighted some of these mechanisms and approaches in translational AD medicine.

*Key Words: Alzheimer's disease, translational medicine, mechanisms, prevention, therapeutics*

## Background of Alzheimer's disease (AD)

Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disorder and the most common cause of dementia in the elderly. It is a global disease, affecting over 5 million Americans and approximately 50 million people worldwide. In addition to affecting brain health, well-being, and quality of life, the care for people with AD as well as other related dementias causes a tremendous financial burden, presently costing approximately $226 billion in the United States. [1] If the disease prevalence trajectory goes unaltered, the number of AD patients may nearly triple to 13.8 million, with the associated costs rising to as high as $1.1 trillion by 2050 in the United States. [2, 3]

Risks for developing AD include age, family history, and other various factors. Given that aging is the main risk factor, it is not surprising that nearly 50% of the population over 85 years old are



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affected by AD. Indeed, everyone is susceptible to AD if one lives long enough. AD is a genetically complex and heterogeneous disorder that has two primary forms: early- and late-onset, based on age at the time of disease occurrence. [4-7] Early-onset familial AD (FAD) (<60 years old; 5-10% cases) is usually caused by mutations in the amyloid-β protein precursor (*APP*), presenilin 1 (or *PSEN1*), and presenilin 2 (*PSEN2*). [8-10] The majority of AD, up to 90-95% of all cases, are late-onset AD (>60 years old) associated with a variant (ε4) of the gene encoding apolipoprotein E (*APOE*), several other risk genes, and numerous environmental factors.

The etiology of AD has not been completely elucidated. The pathology of AD is characterized by two hallmarks: β-amyloid plaques primarily comprised of a small protein, amyloid-β (Aβ), and neurofibrillary tangles composed of hyper-phosphorylated and aggregated tau protein. [8, 11, 12] It is noteworthy that both of these hallmarks have been used as biomarkers in the brain and blood for AD as well as in the elderly with normal cognition. [13-17] Elucidating the mechanisms by which changes in Aβ and tau proteins accompany the progress of AD will have a major impact on our understanding of its pathogenesis. Considerable genetic, biochemical, molecular biological, and pathological evidence supports the "*Aβ hypothesis*, " which posits that excessive accumulation of Aβ is the primary pathological event, leading to increased levels of phosphorylated tau (p-tau) and the formation of neurofibrillary tangles, followed by synaptic dysfunction, neuro-inflammation, neurodegeneration, and ultimately, dementia. [8, 11, 12, 18-20] Translational studies that target these specific AD-pathologic processes at different disease stages may be helpful to effectively prevent and generate therapeutics for AD. [8, 21]

## Overarching goals: a collaborative consortium for AD prevention and treatment

Building on recent research advances in AD worldwide including China, the overarching goal of the conference was to strengthen international academic exchange and inter-disciplinary communication and cooperation through mutual understanding and shared effort. The Chinese population is aging dramatically at an unprecedented pace, such that AD will soon be an emerging public health crisis in China. However, AD awareness among Chinese people still remains low and AD research in China would benefit from tighter integration with institutions overseas. Thus, the goal of this conference was to convene scientists from China, Harvard University, and other leading institutions in the United States and Europe to foster communication regarding a variety of frontiers in the field of AD, and to jointly promote awareness and empower its research in China. By so doing, we can collaboratively find solutions for pressing global healthcare challenges.

Research by faculty at Harvard Medical School, Massachusetts General Hospital, and other leading institutions in Shanghai, China, and beyond has greatly advanced our understanding of potential treatments for AD, which were presented in this conference. It is believed that the blending, enhancing, and absorbing of research results from Harvard, Shanghai, and other institutions can promote the comprehensive development of AD and will shed light on its contributions to health and wellness. Furthermore, this conference may bring in intimate dialogues among investigators from different fields, including scientists, clinicians, or traditional Chinese Medicine practitioners. The discussion would potentially help identify and establish future collaborative research efforts on an national or international level that can carry forward the study and intervention of AD, ultimately better serving humanity worldwide. Using the overarching goal, we collectively believe that the meeting should promote scientists from Harvard University and other institutions, including those in China, to come together to share the frontiers of their research, and encourage scientists to work together to find effective solutions for any problems in the future.

The specific objectives for the conference are 1) to have a clearer and more integrative understanding of how to manage AD, 2) to facilitate the cross-talk of colleagues from Harvard, Shanghai, and others to enhance translational studies, including prevention and therapeutic potentials of AD, 3) to strengthen the international academic exchange, cross-disciplinary communications, and cooperation through mutual understanding and shared effort, and 4) to bring intimate dialogues between investigators from different fields, including scientists, clinicians, and traditional Chinese Medicine practitioners. As a result, the investigators from Harvard, Shanghai, and other institutions have gained tremendous knowledge and improved the understanding, as well as potential preventions and treatments, of AD, some of which will be presented below.

## Modifying factors of AD

Guided by the overarching goal of advancing the prevention and treatment of AD, the conference agenda was organized into the following four tracks: Track 1 - Understanding the pathogenesis of AD, Track 2 - Exploring new materials and technologies for AD, Track 3 - Understanding and exploring AD therapeutics, and Track 4 - Exploring the prevention of AD. Each half-day track fostered inspirational dialogue among research scholars, clinicians, traditional Chinese and Tibetan medical doctors, research scholars, and investigators.

An underlying theme–and common key research finding-throughout all four tracks is that AD can be understood and prevented by focusing on managing modifiable risk factors. As with many other complex diseases (e.g. cancer, stroke), AD has to be evaluated in an integrative way. Several modifiable risk factors have been identified and characterized for AD, including sleep, diet, medications, psychological well-being, and co-morbidities (e.g. diabetes). [22-26] For example, certain medical exposures (non-steroidal anti-inflammatory drugs) and dietary exposures (folate, vitamin E and C, and coffee) were discovered to be protective factors of AD in a recent meta-analysis. [26] The underlying mechanisms of these modifiable components are starting to be better understood. Importantly, these findings may be used to help manage these modifiable factors by maintaining healthy everyday activities in order to lower AD risk. Moreover, deeper knowledge of these risk factors will be important for finding a successful treatment and/or a cure. [27, 28]

## Developing the second generation imaging probes for amyloid beta

Aβ deposits and tau tangles are the two characteristic biomarkers for AD. In the progression of AD, various Aβ subtypes co-exist, including soluble and insoluble Aβs, but soluble Aβs are the dominant species at the pre-symptomatic stage. Studies show that soluble Aβs, such as oligomers, are more neurotoxic than insoluble deposits (fibrils and plaques) and can serve as biomarkers for the pre-symptomatic stages of AD. [13, 14] Notably, recent evidence

indicates that Aβ species are the key initiator for AD pathology. Therefore, for early/pre-symptomatic imaging, Aβs are the ideal targets. Additionally, it is well-established that abnormal levels of Aβs in the brain appear 30 years before symptoms start in humans. However, the current or the first generation (1$^{st}$G) PET probes can only detect abnormal Aβ deposits approximately 5 years before the clinical syndrome, leaving a 25-year gap between pathogenesis and imaging detection. In recent years, the focus has shifted to developing the 2$^{nd}$G (second generation) imaging probes, which are highly sensitive for both soluble and insoluble Aβs, and can be used to fill this 25-year gap. Most 1$^{st}$G PET tracers are based on the scaffold of thioflavin and styrene, whose intrinsic limitations are their insensitivity to soluble Aβs, the high toxicity species, and likely biomarkers for the pre-symptomatic stage.

To overcome this intrinsic limitation of the 1$^{st}$G probe, investigators from Dr. Chongzhao Ran's group at MGH and from other institutions have begun to systematically explore fluorescent half-curcuminoids as the new scaffold for detecting Aβs. [29-33] Recently, after numerous failed attempts, Dr. Ran's group successfully adapted half-curcuminoid into PET probes for Aβs. During the conference, Dr. Ran discussed the tracer design and optimization of the scaffold of half-curcuminoids as the novel 2$^{nd}$G of PET tracers for Aβs. [34] These PET tracers are currently optimized in animal models, with the long-term aim to advance them for future translational studies (contributed by Dr. Chongzhao Ran).

**Modulation of amyloid deposition and neuroinflammation by microbiome**

Animal models of AD recapitulate the severe amyloidosis and neuroinflammation that is evident in the human disease. It is now well-established that inflammation associated with amyloid deposition reflects the activation of astrocytes and microglia in response to injury. However, the role of peripheral tissues, and more importantly, the microbiota in regulating innate immunity that leads to CNS dysfunction, has not been defined.

Dr. Sangram S. Sisodia led a series of studies to test the hypothesis that the composition of the intestinal microbiome plays a key role in modulating neuro-inflammation that will ultimately influence amyloid deposition in two established mouse models of β-amyloidosis. [35, 36] Specifically, a combination of antibiotics was orally administered in AD animals to induce rapid and sustained alterations in gut microbial populations. The antibiotic cocktail was administered either postnatally or throughout the lifetime of the animal prior to cull. We then employed IHC, biochemical, and molecular assays to evaluate amyloid deposition and neuroinflammation in two mouse models. The studies indicate that alterations in the microbiome parallel changes in plasma cytokines and chemokines, reductions in amyloid deposition, and modulation of morphological and transcriptional landscapes of microglia. Thus, the results of these studies reveal an unexpected, but significant, alteration in amyloid deposition and microglial phenotypes in the brains of transgenic mice upon treatment with orally administered antibiotics (contributed by Dr. Sangram S. Sisodia). [35, 36]

**Harnessing the vascular protective and lipidation power of HDL mimetic peptides to defeat AD**

Pathological hallmarks of AD include cerebral amyloid angiopathy (CAA), as well as Aβ plaques and neurofibrillary tangles in the brain parenchyma. Inheritance of the APOE4-encoding gene is the strongest genetic risk factor identified to date for late onset AD. The presence of APOE4 is associated with an elevated level of CAA. Although the mechanisms by which APOE4 affects the development of AD are not completely understood, compelling evidence indicate that the pathogenic effects of APOE4 are mediated by lipid-related pathways. Compared with the more common APOE3 isoform, APOE4 exhibits deficiency in lipidation and formation of high-density lipoproteins (HDL) in the brain. Genetic and pharmacological manipulations of APOE lipidation/HDL formation pathways have been shown to modulate cognitive function and neuropathology in animal models of AD. However, adverse side effects associated with those treatments are of significant concern.

Dr. Ling Li's group have shown that overexpression of human apoA-I rescues cognitive function in AD mice by attenuating CAA and neuroinflammation. [37] The recent subsequent study showed that a unique HDL/APOA-I mimetic peptide, known as 4F that has advanced into clinical trials for cardiovascular disease, could enhance apoE secretion and lipidation from astrocytes and microglia, and counteract Aβ-induced suppression on apoE secretion and lipidation by glial cells. In addition, this peptide effectively inhibits Aβ aggregation, protects cultured neurons against Aβ-induced cytotoxicity, efficiently penetrates the BBB, and promotes the efflux of Aβ across the BBB. These findings suggest that HDL mimetic peptides may serve as effective agents to reverse apoE4 lipidation deficiency, as well as enhancing neurovascular function and cerebrovascular Aβ clearance, which thus, represents a promising new approach to combat CAA/AD (contributed by Dr. Ling Li). [38]

**Decoding the ubiquitin signaling in protein degradation**

The ubiquitin-proteasome system (UPS) is central in the regulation of protein degradation and plays a key role in most cellular functions. Disruption of normal protein degradation is frequently reported in neurodegenerations, including AD. The regulatory potency of the protein degradation machinery depends on its high specificity for substrates and the ability to processively unfold and degrade its targets, which is bestowed by the exquisite structures of the 26S proteasome holoenzyme. Specificity of ubiquitin-mediated protein degradation was thought to be simply determined by the ~600 E3 enzymes in humans. However, statistical analysis on published datasets show insignificant correlation between the steady-state ubiquitylation levels and protein stability in all comparisons. To understand how conjugated ubiquitins on substrates control the key steps in the degradation process in order to determine the degradation rate, Dr. Ying Lu's group has developed single-molecule detection methods to analyze its kinetics and used cryo-EM to resolve proteasomal states during substrate degradation. In this conference, the results from these efforts and important unsolved issues were presented and discussed (contributed by Dr. Ying Lu).

**Nutrition and cognitive impairment: novel findings from the Singapore Chinese Health Study**

Diet plays an important role in achieving optimal cognitive function. Many studies in Western populations have reported that nutrient deficiency and unhealthy dietary patterns are related to

cognitive decline, but few studies were done in Chinese populations. We analyzed the relations of various dietary factors and risk of cognitive impairment in a large cohort study over a span of 20 years. The Singapore Chinese Health Study recruited 63, 257 Chinese adults living in Singapore ages 45-74 years of age during 1993-1998. Diet was measured by a 165-item semi-quantitative food-frequency questionnaire at baseline. Cognitive impairment was assessed using a modified Singapore version of Mini-Mental State Examination among 16, 948 alive participants during 3 follow-up visits (2014-2016), when participants were 61-96 years old. Multivariable logistic regression models were used to estimate the associations. Cognitive impairment was present in 2, 443 (14.4%) participants. We found that higher dietary intakes of red meat, preserved fish/shellfish, and dairy products were associated with a higher risk of cognitive impairment, while higher intakes of fresh fish/shellfish, tea, riboflavin and folic acid, vitamin C and E, and monounsaturated and omega-6 polyunsaturated fatty acids were associated with a lower risk of cognitive impairment. Overall, adherence to healthy dietary patterns (including Alternative Healthy Eating Index-2010, Alternate Mediterranean Diet score, Dietary Approaches to Stop Hypertension, and healthful plant-based diet index) were all associated with lower risk. In conclusion, our study identified a number of dietary factors related to cognitive impairment in Chinese adults, indicating the importance of healthy dietary patterns in optimal cognitive performance (contributed by Dr. An Pan).

**A randomized controlled trial on cognitive decline and aging: a choral singing versus health education study**

Health benefits of music have been extensively studied in the medical field, but it is unknown if group-based musical intervention, such as choral singing, can delay cognitive decline. This study led by Dr. Lei Feng assessed the efficacy and underlying biological mechanisms of choral singing in the prevention of cognitive decline among at-risk individuals living in the community. Specifically, a randomized controlled trial (RCT) was designed. Community-living elderly aged 60 and above were recruited into the clinical trial if they fulfilled the pre-specified criteria of having high risk of future dementia. Participants received weekly choral singing interventions or health education for two years. The primary outcome measure is the change in cognitive performance measured using a composite cognitive test score (CCTS). Brain magnetic resonance imaging (MRI) as well as blood and urine based markers were used to examine biological changes before and after the intervention.

The results showed that two-year interventions had been completed for 93 trial participants. The average age was 70 (SD 5.5) years and 73 out of 93 (79%) were female. The between-group difference on the absolute change of CCTS from baseline to 24 months was statistically significant ($P<0.05$) and was in favor of choral singing. There was no between-group difference on global measures of brain aging derived from MRI or markers of immunosenescence and oxidative damage.

In summary, the interim analysis suggest that choral singing improves cognitive health in aging. Results from this set of interim analyses did not support a beneficial effect of choral singing on biological aging in comparison to a structured health education program. However, it is possible that the imaging and biological markers analyzed in this interim analysis may not be sensitive enough. The study team are currently working on more sensitive biomarkers, such as brain connectivity and epigenome-wide DNA methylation profiles (contributed by Dr. Lei Feng).

**Opportunity of natural products in treating AD**

AD is the most common form of dementia in the elderly. It is characterized by progressive neurodegeneration, which damages memory and cognitive function. In view of the limitations of a handful of FDA approved drugs and the lack of efficacious therapeutic agents for the treatment of AD, it has long been a challenging and attractive task to discover new anti-AD drugs. Natural products offer many therapeutic advantages to reduce the progress and symptoms of AD. For instance, natural products including lignans, flavonoids, tannins, poly-phenols, triterpenes, sterols, and alkaloids, have anti-inflammatory, antioxidant, anti-amyloidogenic, and anticholinesterase activities. Considering the multifactorial nature of AD, the concept of Multi-Target-Directed Ligands (MTDLs) has emerged as a new strategy for designing therapeutic agents for AD. MTDLs are believed to exert their effects by simultaneously affecting multiple AD targets, which contribute to etiology of AD through combination of natural products (Ligands). Therefore, MTDLs are conceivably to be more efficacious than mono-target agents or a single chemical entity. In this presentation, we have focused on the potential of an herbal formula (NPI-AD-001) with proven anti-inflammatory and immuno-modulatory activities for preventing and reducing symptoms of AD (contributed by Dr. David Lee).

**The use of Chinese Herbal Medicine to treat AD: potentials to identify advantageous features and novel mechanisms**

Currently, almost all chemical compounds or biological reagents to reverse or slow down the AD process have failed in clinical trials.[39-41] An integrative and multi-targeted strategy is becoming increasingly more attractive and appreciated to effectively combat this devastating disease. Traditional Chinese Medicine (TCM) has been historically widely used for treatment of dementia in China. Thus, studies on the potential advantageous features of TCM treatment and underlying mechanisms are urgently needed. The Amnesia Remedy Formula (ARF) was invented by one of the most influential Masters of TCM, Sun Simiao, who lived for about 100 years. Dr. Qiang Zhou's group has found improved cognitive functions with the administration of ARF by mechanisms including up-regulation of cerebral blood flow, enhancement of neural plasticity and clearance of the amyloid plaque.

Specifically, the study tested the efficacy of ARF on two animal models of AD, and examined the central role of PKA signaling in the enhancement of neural plasticity via the PKA/CREB/BDNF pathway, as well as clearance of toxic p-tau via PKA/GSK3β/p-tau pathway. In the scopolamine model, ARF effectively reversed memory in the Morris water maze (MWM) test, with some features superior to the anti-AD drug, donepezil. In a battery test of MWM, novel object recognition or T maze in 5-month-old senescence-accelerated mouse prone 8 (SAMP8) strain mice, two weeks of ARF administration showed overall memory improvement better than donepezil. The effect lasted over 1 week following the last administration. Furthermore, ARF increased expression of PKA/CREB/BDNF and synaptic proteins PSD95, as well as enhanced Ser9 phosphorylation of glycogen synthase

kinase-3β (GSK3β), which was related to reduced p-tau in the hippocampus. Blockade of PKA signaling blunted the anti-AD-like effect of ARF, with reversal of CREB/BDNF signaling. Transcriptomic analysis indicated that some changes of novel molecules along this pathway may be part of the pathological and therapeutic mechanism, which warrants further investigation. In summary, these preliminary studies support that ARF may display some advantageous features in treating AD, via a multi-targeted manner, including enhancement of neural plasticity and reduction in tau toxicity (contributed by Dr. Qiang Zhou).

### c-Glycosylflavonoids as glycogen synthase kinase-3β inhibitors to alleviate tau hyperphosphorylation and amyloid neurotoxicity

Hyperphosphorylation of tau proteins in neurons plays a pivotal role in AD pathology. Glycogen synthase kinase-3β (GSK3β) is a key enzyme catalyzing hyperphosphorylation of tau protein. Selective inhibition of GSK3β is a promising therapeutic strategy for AD treatment. It was unexpected that Dr. Qing Li's group found a glycosylflavone, isoorientin, that selectively inhibits GSK3β *in vitro*. Semi-synthesis of isoorientin has led to over 300-fold improved potency. [42, 43]

Furthermore, enzyme kinetic studies and molecular modeling demonstrated that both isoorientin and its synthetic analogs specifically inhibit GSK3β via a substrate competitive, rather than the common ATP competitive mode. Structure-activity relationship analyses and in-silico modeling suggest the mechanism of actions by which the hydrophobic, π-cation and orthogonal multipolar interactions are involved for the GSK-3β inhibition and selectivity. Cellular studies further demonstrated that those c-glycosylflavonoids effectively attenuate GSK3β-catalyzed tau hyperphosphorylation and is neuroprotective against amyloid-induced neurotoxicity in human SH-SY5Y cells. The new inhibitors are valuable chemical probes and drug leads with a therapeutic potential to tackle AD and other GSK-3β relevant diseases (contributed by Dr. Qing X. Li).

### Developing translational programs for precision and multidisciplinary medicine of AD

Understanding the AD modifying factors and underlying mechanisms in this conference has provided the opportunity and future directions to translate this knowledge into manageable strategies to ameliorate AD pathology. This notion is further supported by recent progresses in targeting molecular pathological changes in cell and animal models of AD. [21, 27, 28, 44-48]Furthermore, emerging mechanisms and approaches have been discovered through multidisciplinary efforts in areas of medicine, chemistry, biology, physics and others, which offer an integrative view of AD . These exciting results generated from the collaborative endeavor cannot be achieved in one discipline. There appears to be several more interesting areas that can be further explored. A recent study found that direct modulation of brain activity with electrical stimulation in human led to improved memory outcomes, and suggested the lateral temporal cortex as a target for memory improvement. [49] Furthermore, neuronal stimulation by auditory system and/or light induced γ-oscillations reduced amyloid levels in the brain and improved memory in AD transgenic mice. [50, 51] Moreover, collaboration between conventional pathology and electrophysiology should be able to generate new findings by studying AD pathology, due to neural circuits and hippocampal endophenotype changes. [52] CRISPR/Cas genome editing techniques can provide potentials in correcting the genetic variants responsible for disease and may open a new avenue for disease therapy. [53, 54] These powerful and potentially safe genetic editing approaches may be utilized not only to understand but also to manage human diseases, including AD. Guidelines from a consortium with experts may be generated and followed to address the emerging question of AD. Caution should be advised in performing studies in these new directions.

## Conclusion and perspectives

Research from faculty at the Harvard Medical School, Massachusetts General Hospital, and leading institutions in Shanghai, China, and beyond has generated tremendous knowledge to advance the possible prevention and treatment AD, all of which was presented at this conference and some of which was disseminated in this article. Thus, the goal of the conference—that is, to strengthen international academic exchange, cross-disciplinary communications, and cooperation through mutual understanding and shared effort—was achieved. The presentations demonstrated that blending, enhancing, and absorbing research globally can promote a more comprehensive understanding of AD, and point the way to future studies designed to improve health and wellness worldwide.

In summary, the 2018 Harvard-Shanghai conference was made possible by several Harvard Medical School and Massachusetts General Hospital investigators originally from China and their colleagues from the United States and China, as well as those from several other countries, including Singapore and Germany. The topics of the conference were focused on AD, which is a global neurodegenerative disease without a cure. As a result, this conference brought close dialogue among investigators from different fields and have led to ongoing efforts to establish collaborative research, at both the national and international level, which are advancing therapeutic AD interventions that may ultimately improve health and wellness worldwide.

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## Conflicts of interest

As above.

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