Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD)
12th Annual FDA/Alzheimer's Disease Allies Meeting 2019
Diversifying the Therapeutic Pipeline for Alzheimer's Disease

1. Introduction

At the 2019 annual meeting of the Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) Coalition, Alzheimer’s disease (AD) experts from academia, industry, the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid Services (CMS); as well as members of the AD community; met to explore the current therapeutic landscape for AD—from discovery and validation of novel targets to the clinical testing of novel drug candidates and non-pharmacological interventions.

Amyloid-beta (Aβ) therapies still dominate the landscape for late-stage clinical trials and may have been given a new life with the recent aducanumab results. Aducanumab is a monoclonal antibody in late-stage development that targets aggregated Aβ and has been shown to clear Aβ plaques in patients with prodromal or mild AD.1 In March 2019, the drug’s manufacturer, Biogen, terminated two clinical trials when an interim futility analysis concluded that the drug had failed to meet its prespecified endpoint, the slowing of cognitive decline. Then, seven months later the company reversed itself, saying that in one of the two trials the highest dose of drug slowed cognitive decline by 22%. Biogen now plans to seek regulatory approval to market the drug, which, if approved, would represent the first disease-modifying treatment for AD and the first AD drug of any type approved since 2003.

While the positive results reported for aducanumab have kindled hope in the AD community that an effective treatment may soon be available for patients, the need remains for a deeper understanding of disease complexity and the identification of a more diverse landscape of drug targets. Indeed, the NIA drug development portfolio spans multiple targets including cytoskeleton/tau, ApoE4, α-synuclein, heat shock proteins, neurotransmitters and growth factors receptors, neuroinflammation, oxidative stress, bioenergetics, cell-based therapies, and vasculature factors.

As an example of a non-amyloid or Tau therapy, Chinese regulators recently approved a mannose-based oligosaccharide compound called Oligomannate (GV-971, manufactured by Green Valley Pharmaceuticals) for mild-to-moderate AD. Oligomannate is a natural product derived from brown seaweed that alters the gut microbiome, reduces neuroinflammation, and was shown to improve cognition compared to placebo in a Phase 3 clinical trial. Chinese regulators have granted conditional approval to the drug, and the company is planning to conduct clinical trials in other countries in 2020, including the United States, with eventual plans to seek regulatory approval.

2. Building an open science ecosystem to expand the target landscape and enable predictive drug development for AD


As described by Dr. Suzana Petanceska at the meeting, in addition to a pipeline of NIA and trans-NIH translational research funding initiatives, the NIA has established multiple consortia to accelerate the

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development of AD therapeutics across all stages of development from target identification and validation through late-stage clinical trials. drug approval. These consortia include:

- Accelerated Medicines Partnership for AD (AMP-AD)
- Molecular Mechanisms of the Vascular Etiology of AD (M-OVE-AD) Consortium
- Alzheimer’s Disease Centers for Discovery of New Medicines
- Model Development and Evaluation for Late-Onset AD (MODEL-AD) Consortium
- Resilience AD Consortium
- Alzheimer’s Disease Clinical Trials Consortium (ACTC)
- Alzheimer’s Biomarker Consortium-Down Syndrome (ABC-DS)
- Alzheimer’s Disease Preclinical Efficacy Database (AlzPED)

The AMP-AD program is a public-private partnership among NIA/NIH, pharmaceutical industry and non-profit organizations. This NIA-led partnership is managed by the FNIH and has two components: one focused on biomarkers in clinical trials, and the other on target discovery and preclinical validation. The target discovery component uses a systems biology approach within an open science research model to discover and characterize the next generation of therapeutic targets for AD. The program brings together seven multi-institutional research teams to i) generate high quality, high-dimensional molecular data from human biosamples (brain, CSF and plasma) collected in AD research brain banks and well-phenotyped cognitive aging cohorts ii) develop network models of disease pathways and candidate targets iii) conduct early target validation across multiple experimental models Central to the mission of the program is the rapid and broad sharing of data, methods, and results via centralized big data infrastructure: the AD Knowledge Portal and the Agora open-source platform, both developed and maintained by Sage Bionetworks. Over the first 5 years, the AMP-AD teams discovered over 500 candidate target genes – all of which have been made available through the open-source, web-based interactive platform Agora along with the supporting evidence and data and extensive druggability information (including small-molecule druggability, antibody feasibility, safety, tissue engagement, overall feasibility, and new modality) contributed by the AMP-AD partners.

2.1 Targeting viral genes associated with neuropathology

Building on the work of the first phase of AMP-AD, Ben Readhead, one of the AMP-AD principal investigators, and colleagues are exploring the pathogen hypothesis of AD, which posits that infectious microbes such as herpes simplex virus may play a role in driving the development of AD pathology. An infectious basis for AD was first proposed by Alois Alzheimer more than 100 years ago and has more recently been supported by genomic, neuropathologic, and epidemiological evidence. To begin disentangling whether microbes act as an accelerant, cause, or opportunist, Readhead et al. have applied computational modeling approaches to multi-omic data, generating biomolecular networks comprising genes, metabolites, lipids, and proteins. For example, one of these networks indicates that HSV-1 is significantly and positively associated with the number of copies of the ApoE4 allele, which is associated with an increased risk of developing AD. They have also shown an inverse association between another herpes virus and the number of copies of the ApoE2 allele, which is protective. Other networks they identified have linked HSV to immune regulation and the density of neurofibrillary tangles.

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Meeting participants mentioned other approaches that are being used to explore the relationship of viral infections to AD. Some investigators are exploring claims data to see if treatment with the anti-herpes virus medication valacyclovir is associated with an altered risk of developing AD. Another group is conducting an NIA-funded Phase 2 study of valacyclovir as a possible treatment for slowing or preventing AD.

The second part of Readhead’s project is applying genome-wide screens to three-dimensional cerebral organoids generated from induced pluripotent stem cells derived from AD patients. These organoids enable the researchers to study experimentally the influence of viral genes on neuropathology. Combining the computational and experimental findings will potentially help identify drug targets and test small molecules against these targets.

2.2 Targeting genes that promote resilience

Age-related decline in cognitive and physical function has been well documented but can obscure the fact that some individuals maintain high functioning into late life. Catherine Kaczorowski and her team, supported by the NIA’s Resilience-AD funding initiative, are using a systems genetics approach to understand the nature of resilience and discover and validate resilience-based targets for AD prevention. Understanding the mechanisms of resilience is particularly challenging since resilience to AD involves not only the brain but also the cardiovascular system, microbiome, and other systems in the body.

Approximately 50-70% of the variation in cognitive decline is controlled by genetic factors. Even among patients with familial forms of AD caused by autosomal mutations in the genes for the amyloid precursor protein (APP) or presenilin proteins, there is substantial variability in disease onset and progression, suggesting that additional genetic factors confer protection against dementia. Catherine Kaczorowski and colleagues are creating genetically diverse mouse models of autosomal dominant AD (ADAD) to better understand individual differences in disease susceptibility. These mice have identical high-risk human AD mutations but differ across the remainder of their genome, which allows the scientists to examine the contribution of individual genes on AD susceptibility and resilience. This approach has enabled them to identify candidate genes that promote resilience.

One of the genes identified by Kaczorowski’s team as associated with the risk of cognitive deficit is a variant in the receptor binding domain of the ApoE gene. This finding is consistent with and could help explain recent work showing that an individual carrying the PSEN1 mutation (which confers a nearly 100% risk of developing AD) and who was also homozygous for the ApoE3 Christchurch mutation, did not develop cognitive impairment until her 70’s despite high levels of brain amyloid. These findings also support ApoE as a potential therapeutic target.

These mouse models allow researchers to examine molecular networks that change as a function of genotype and identify genes that drive cognitive outcomes. Among the modules identified are those associated with fatty acid metabolism and immune function. Using the AMP-AD human data, investigators tested the relevance of the mouse predictions and showed that these modules were conserved in humans.

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This demonstrates the feasibility of using mouse models as discovery tools for studying resilience in humans. Meeting participants suggested trying to correlate the transcriptional modules identified in mice with the spectrum of proteins that can be identified in cerebrospinal fluid from individuals with AD and exploring the impact of environmental factors on these molecular networks.

3. Diversifying the AD Therapeutic Landscape

Since 2006 the National Institute on Aging (NIA) has been building an integrated translational research program to diversify the landscape of tractable therapeutic targets and reinvigorate the drug development pipeline. Several promising candidate therapeutics developed through support from NIA’s translational research programs are currently in early clinical drug development were highlighted at the ACT-AD meeting. These drug candidates are targeting multiple aspects of the disease process including proteostasis, synaptic plasticity, and neurotrophic signaling networks. NIA continues to build a robust portfolio of therapeutics programs for a diverse set of targets including targets for molecular mechanisms related to aging and resilience.

3.3 Targeting chaperome networks

Gabriela Chiosis and colleagues are developing new therapeutics, companion diagnostics and chemical biology tools to target the epichaperome-driven dysregulation in protein connectivity associated with neurodegeneration. Her team has shown in cellular and animal models, as well as in human specimens, that AD-related stressors such as aging, genetic factors, and vascular injury mediate global disturbances in connectivity through maladaptive chaperome networks called epichaperomes. The term “chaperome” refers to an ensemble of chaperone and co-chaperone proteins that mediate a cell’s molecular folding machinery to regulate protein degradation and cellular homeostasis. Conversely, epichaperomes provide the backbone upon which proteome-wide connectivity and protein networks become disturbed and ultimately dysfunctional. In cancer and neurodegenerative diseases, many different stressors remodel proteome networks by changing the interactions among protein partners (i.e., by restructuring chaperomes into epichaperomes). In a new study published in *Nature Communications*, her team discovered how stress rewires key connections in the brain through this maladaptive mechanism. Dr. Chiosis and her colleagues, including neuroscientists at Weill Cornell Medicine, the New York University School of Medicine, and the Nathan Kline Institute for Psychiatric Research, developed a term to describe this phenomenon: protein connectivity-based dysfunction (PCBD).

Epichaperomes, and in turn PCBD, may provide targets for drug intervention. Inhibiting epichaperomes with small molecules, for example, has been shown to have anti-tumor activity. In AD, pathways related to synaptic plasticity are especially sensitive to different kinds of stress. Correcting the connectivity dysfunction with epichaperome inhibitors, therefore, may provide a novel therapeutic approach to correct synaptic plasticity.

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dysfunction in AD. Importantly, in mice, epichaperome drugs developed by the Chiosis group repaired network connectivity and functional imbalances, reverting these defects to normal levels. Other pathways disrupted by epichaperomes, such as inflammatory and metabolic pathways, may also be targetable using epichaperome inhibitors. Radiolabeled epichaperome inhibitors are also useful for detecting at-risk patients through molecular imaging and as companion diagnostics for epichaperome inhibitors.

3.4 Targeting neurotrophin receptors

Neurotrophins are essential signaling proteins in a pathway that promotes the survival of neurons; hence, they are also a key part of the degenerative signaling network in AD that when triggered by Aβ, tau, microglia dysfunction, and aging, lead to increased synaptic dysfunction, spine loss, and neurite degeneration. Several labs have shown both in vitro and in vivo that the p75 neurotrophin receptor modulates this degeneration signaling network.

Frank Longo and colleagues have developed LM1 1A-31a as a first-in-class candidate drug for the treatment of AD; his team has shown that this small molecule p75 ligand can counteract multiple neurodegenerative signaling mechanisms and processes associated with AD including tau phosphorylation-misfolding mislocalization- oligomer formation; loss of synaptic function/LTP; loss of spines; degeneration of neurites; and cognitive loss. The development of this novel neurotrophin receptor modulator as a treatment for exemplifies how the NIA has funded research along the entire translational trajectory: from elucidating the molecular mechanism and initial target validation, through all phases of development of first-in-class small molecules including early-stage clinical trials.

Human data suggests that preservation of dendritic spines is a resilience mechanism. These findings support the theory that there are components of AD that are reversible even at late stages of the disease; thus, targeting key hubs and networks with a systems biology approach may provide treatments that are both symptomatic and disease-modifying. Discussants noted the need for new tools for interrogating spine, dendritic, and circuit structure and function to accelerate such studies.

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3.5 Targeting cAMP signaling

Cyclic adenosine 3’-5’ monophosphate (cAMP) is a signaling molecule that regulates many cellular functions including gene transcription, at least in part with the help of phosphodiesterase enzymes (PDEs). One group of these enzymes—the PDE4 family—regulates signaling in neurons and glia and thus have been explored as therapeutic targets for AD.29 Supported by NIA through the NIH Blueprint Neurotherapeutics Program, Mark Gurney and colleagues have developed a small molecule allosteric inhibitor of PDE4 (BPN14770). They have shown that it engages its target and in humanized mice injected with Aβ protein, protects against neuronal damage, prevents behavioral impairment, and prevents the loss of proteins essential for synaptic function.30,31

Now in clinical development, the experimental drug BPN14770 showed positive safety and tolerability in Phase 1 studies with an absence of dose-limiting side effects. The drug is now being tested in the multi-site PICASSO AD trial (NCT03817684), a Phase 2 study for early AD, with topline results expected in March of 2020. An interesting point that emerged during meeting discussions is that in addition to testing a novel compound, this trial was successful in recruiting a diverse group of participants, including many Latinos. This was attributed to a reliance on community-based physicians instead of academic sites for recruitment in locations with large Latino populations, using a simple screening method and a centralized institutional review board (IRB), providing transportation to trial sites, and providing outcome assessment tools in Spanish as well as raters fluent in Spanish. Meeting participants suggested that this trial could serve as a model for designing more efficiently enrolling trials.

Dr. Laurie Ryan discussed NIA’s programs and initiatives in the clinical trial space. Currently, NIA supports more than 230 trials in AD and related dementias. These trials include both pharmacological and non-pharmacological trials implemented through the Alzheimer’s Clinical Trial Consortium (ACTC). Many of these trials test novel pharmaceutical approaches, including next-generation amyloid approaches, neuron regeneration, neuroinflammation, and anti-viral approaches. Drug trials are also underway with repurposed compounds for the treatment of neuropsychiatric symptoms such as agitation. The NIA is also supporting non-pharmacologic clinical trials investigating the benefits of exercise, diet, cognitive training, or a combination of those lifestyle interventions; technological interventions (e.g., neurostimulation); and care management studies.

3.6 Targeting modifiable risk factors for AD treatment and prevention

There is abundant evidence suggesting lifestyle factors can impact the development of dementia in both positive and negative ways. Risk factors including obesity, hypertension, diabetes, smoking, a sedentary lifestyle, and an unhealthy diet may increase the likelihood of cognitive decline; while protective factors such as education, physical activity, and cognitive and social activity may decrease the risk.32

Animal studies, and more recently human clinical studies, have demonstrated the positive effects of exercise on the brain. Possible mechanisms and targets include neuro-repair, oxidative stress, inflammation, glucose metabolism, and clearance of toxic proteins.33 For example, six months of aerobic exercise has been

shown to increase brain volume in healthy but sedentary older adults; and aerobic exercise has also been shown to improve cognitive function in individuals with mild cognitive impairment (MCI). The multi-site EXERT study is testing the effects of exercise alone on progression in individuals with MCI.

Dietary interventions such as the MIND (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay) diet which combines a Mediterranean and Dietary Approach to Systolic Hypertension (DASH) diets have also been shown to slow cognitive decline with age.

Studies also suggest that combining exercise and diet produces a synergistic effect. In 2015, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) showed for the first time in a randomized controlled trial, that a two-year multi-domain intervention targeting lifestyle and vascular risk factors could improve or maintain cognitive functioning in older adults at risk of cognitive decline. The intervention combined dietary guidance, physical activity, cognitive training, social activities, and intensive monitoring and management of metabolic and vascular risk factors and is now being replicated in the Worldwide FINGERS program (WW-FINGERS), an international network of FINGER-like lifestyle intervention studies, which includes the U.S. POINTER study. POINTER will enroll 2,000 cognitively normal older adults in a similar multidomain intervention trial at increased risk for cognitive decline based on a sedentary lifestyle, poor diet, suboptimal cardiovascular health status, and a first-degree family history of memory impairment. Outcome assessments will be harmonized with other WW-FINGER trials. Meeting participants suggested adding assessments of the immune system and inflammatory function.

4. Conclusion

The 12th Annual FDA/Alzheimer's Disease Allies Meeting, Diversifying the Therapeutic Pipeline for Alzheimer's Disease, brought together esteemed members of the AD community including NIH and FDA scientists, leading researchers from academia and biotech/pharmaceutical industry and patient advocates to discuss the growing therapeutic pipeline for AD. The meeting showcased a range of NIH-supported AD research initiatives that are delivering novel therapeutic targets and a diverse portfolio of candidate therapeutics targeting multiple aspects of the disease process. These new interventions span pharmacologic and non-pharmacologic modalities and are aimed at all stages of the disease, from the early presymptomatic stage where prevention may be a realistic goal to late-stage disease where relief of symptoms remains an unmet medical need.