A distinct note of optimism has begun to emerge from recent publications on Alzheimer’s disease (AD), while the repetitive refrain of the past five years—that despite significant investments, the field has been beset by disappointments and setbacks—is growing faint. The optimism stems in part from the slow but steady realization of goals originally set forth by the National Alzheimer’s Project Act (NAPA). Although NAPA was signed into law back in 2011, it was designed to have an enduring impact and to supply a sense of urgency, along with the goal of effectively treating AD by 2025. Among the recent developments that ultimately can be traced to its blueprint are a historic $425-million increase for Alzheimer’s research at the National Institutes of Health (NIH) for fiscal year 2019, and the July 2018 publication of a unifying and transformative research framework jointly developed by the National Institute on Aging (NIA, a division of NIH) and the Alzheimer’s Association (AA). The 2018 research framework, which is intended for observational and interventional research (rather than routine clinical application), addresses the scientific progress that has taken place in the field since 2011. It reflects an understanding of AD as existing along a continuum rather than in stages; a greater focus on disease prevention; an awareness that environmental and lifestyle issues may play significant roles in the development of the disease; and an emphasis on discovering, validating, and properly cataloguing biomarkers that predict, track, and characterize disease pathogenesis and progression. Although the field has long been aware of an extended preclinical phase of AD—a period of 15 to 20 years or more before the development of symptoms—the current emphasis on preventing or delaying the disease also has led to a heightened scrutiny of and exciting discoveries regarding the earliest molecular events that may contribute to AD.

By providing a common language for the AD research community, the 2018 framework will facilitate the generation and testing of new hypotheses, as well as standardized reporting of research results. It also stresses the importance of collaboration, information sharing, and the harmonization of research efforts around the world in today’s era of open-data and team science.

**Arriving at an Accurate Definition of AD**

A key feature of the NIA–AA research framework is a new biological definition of AD that focuses on underlying pathological processes of the disease, which can be documented either during autopsy or, in living people, by means of biomarkers. The authors of the framework emphasize that this updated definition represents a major conceptual shift away from the idea that AD is defined exclusively as a clinical syndrome. “For several decades, most clinicians, and the lay public, really have viewed AD through the lens of a 1984 definition,” says Clifford R. Jack Jr, MD, professor of radiology at the Mayo Clinic and lead author of the 2018 framework paper. “If an individual met clinical criteria that included a progressive loss of abilities, typically with a prominent amnestic component—that is, loss of memory that typically progressed to the point where the person became dependent on others—the individual was classified as having probable AD if other possible causes of symptoms, such as tumor or stroke, could be excluded. The word ‘probable’ was important, because whether someone had AD could be determined definitively only at autopsy.”

Over time, and with increasing frequency, says Dr. Jack, people began to drop the word “probable” and, perhaps more significantly, began to lose sight of its importance. In published papers, investigators would refer simply to AD rather than probable AD. Even when the definition of AD was updated in 2011, based on a growing awareness of the need to focus on the pathophysiology, clinical symptoms were never entirely separated from the diagnosis of AD, and this lack of precision created a number of problems.

“Perhaps the biggest problem was a frequent discrepancy between what clinicians were calling AD and what was actually discovered to be true based on autopsy,” says Dr. Jack.
“Roughly a third of all people given the clinical label of AD turned out not to have Alzheimer’s—either at autopsy or based on a growing number of biomarker studies.”

Awareness that the clinical diagnosis of AD was far from a gold standard grew steadily for more than a decade. As far back as 2008, a paper in *Brain* co-authored by Dr. Jack described a study in which a significant number of participants diagnosed with AD were shown to have negative amyloid positron emission tomography (PET) scans. More recently, the results of phase 3 studies of bapineuzumab and solanezumab, published in the *New England Journal of Medicine* in 2014, revealed that about one-third of people enrolled in those clinical trials, using a clinical definition of AD, also had scans that were negative. Gradually, many in the field reached a logical conclusion: the time had come for a biological definition of AD.

“With the development of reliable biomarkers for beta amyloid and tau, which has allowed us to see in living people what pathologists once could see only at autopsy,” says Dr. Jack, “it became possible to give a definite diagnosis in life, regardless of clinical presentation.”

Although today people are indeed diagnosed with AD before they develop symptoms, the new definition has had its share of critics, many of whom have been reluctant to part with an older perception of the disease.

“I often challenge critics to name just one disease in all of medicine where the disease does not precede the symptoms,” says Dr. Jack. “Diabetes, for example, isn’t defined by symptoms such as blindness or peripheral neuropathy or kidney failure, it’s defined by an A1C biomarker test. The same is true with hypertension, which is not defined by strokes or heart attack but by a *biomarker test*, the measurement of blood pressure. Why should AD require the presence of symptoms, unlike every other disease in medicine?”

### The AT(N) Biomarker Scheme

After a consensus was reached regarding the biological definition of AD—that is, the presence of β-amyloid (Aβ) plaques and neurofibrillary tangle tau s— it became important to create an orderly framework to investigate AD in observational studies and clinical trials. A fundamental goal was to develop a scheme in which various biomarkers (imaging and biofluids) were grouped under the pathophysiology that each one measured. A paper published in 2016 provided a foundation for the new scheme.⁶

“The rationale for this scheme is gradually becoming clear to more people,” says Dr. Jack, “but for a long time there was sort of a hazy group of biomarkers that weren’t organized in any particular way. The formalization of this biomarker grouping promoted a lot of productive thinking and soul searching in the field.”

According to the AT(N) scheme, A represents biomarkers for amyloidosis, currently detected with amyloid PET and cerebrospinal fluid (CSF) Aβ42; T represent biomarkers for tau, detected by means of tau PET and CSF phosphorylated tau (P-tau); and N, which is enclosed in parentheses because these markers are not specific for AD, represents markers of neurodegeneration.

“While biomarkers in the A and T categories are specific for AD, those in the N category are not,” notes Dr. Jack. “Atrophy of the hippocampus on an MRI [magnetic resonance imaging] scan, for example, is not specific for AD—it can be seen with other disorders and conditions. Likewise, hypometabolism on FDG [fluorodeoxyglucose] PET and CSF total tau, which also indicate neurodegeneration or neuronal injury, are not specific for AD. In some circles, this has been controversial because there are entities, for example, that sell software to measure hippocampal volume on MRI as a diagnostic test for AD, even though it can’t be used to diagnose AD. A lot of other disorders can shrink the hippocampus that have nothing to do with AD.”

Dr. Jack points out that the current scheme also helps to underscore important distinctions between different measures of the same biomarker. For example, low CSF Aβ42 and cortical amyloid PET ligand binding both measure amyloidosis, but the CSF measure indicates a propensity to deposit amyloid plaques (i.e., a pathologic state) whereas amyloid PET indicates actual pathologic load. He adds that the development and application of tau PET have helped to increase recognition of this type of distinction, as cortical tau PET ligand binding likewise is an indication of pathologic load, while elevated CSF P-tau is an indication of the propensity to deposit tau.

“This new AT(N) framework has to be and is designed to be modified and expanded over time as new developments occur,” says Dr. Jack. “So, for example, one major new development in recent years has been the development of plasma biomarkers for amyloidosis. The flexibility of the current scheme is such that it fits perfectly underneath the A category. There is no need for a separate plasma-biomarker category.”

### Not Yet Ready for Clinical Care

Concerns about changes in memory that might possibly signal mild cognitive impairment, along with the growing awareness among the general public that AD develops before the emergence of symptoms, are prompting many individuals to ask their clinicians about being tested for the disease. But insurers are not yet convinced of the value of biomarker tests for AD, and many people lack access to such testing.

“We clearly state that the current research framework is not yet ready for clinical practice for some obvious reasons. Most importantly, imaging biomarkers are not universally available throughout the country, and are certainly not available throughout the world,” says Dr. Jack. “The NIA–AA framework is not intended to be used only in the U.S. and Europe and a handful of other countries. It’s a conceptual approach that is intended to be applicable worldwide. But there are areas of the world where PET scanning doesn’t exist or where it’s not possible for people to undergo lumbar punctures or have CSF samples analyzed. Most likely, the eventual validation and approval of plasma biomarkers will make it possible to apply the AT(N) scheme to routine clinical use.”

Although amyloid PET has been approved for use by the FDA, the Centers for Medicare and Medicaid Services (CMS) does not offer coverage for this testing. Tau PET is not yet FDA-approved for use, but the first tau PET ligand has been submitted to the agency for approval. At this time in the U.S., it is possible to be reimbursed only for less expensive but more invasive CSF testing, most of which is processed by a single lab in Cleveland, Ohio.

“The primary reason for lack of coverage for amyloid PET...
is the lack of a disease-modifying treatment,” says Dr. Jack. “Insurers require proof that knowing the result of this test will in some way change medical outcomes for those who undergo it. Currently, PET scans for clinical purposes are available only to those who can pay out of pocket or participate in a research study where people are told the results.”

One promising development has been the Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study, which reported noteworthy results in October 2018. A four-year, $100-million study of more than 16,000 Medicare recipients, IDEAS aimed to discover whether amyloid scanning results would significantly affect treatment decisions and alter the course of treatment. The study found that the scan results did indeed influence decisions about treatment plans in approximately two-thirds of cases. What remains unknown is how amyloid PET results ultimately may affect patients’ health. To date, insurers still do not cover the test.7

Meanwhile, some guidance is available for those people willing to pay out of pocket for amyloid PET. In 2013, an amyloid-imaging taskforce (AIT) convened by AA and the Society of Nuclear Medicine and Molecular Imaging issued guidelines on specific clinical scenarios in which amyloid PET might be used appropriately, despite the lack of insurance coverage for this testing.

“Aiming to those guidelines,” says Dr. Jack, “undergoing amyloid PET testing is appropriate only in symptomatic individuals, and not in asymptomatic [people] seeking testing simply out of curiosity. The guidelines also state that a person seeking testing should be seen by a dementia specialist who recommends the testing, with the expectation that amyloid PET will reveal important information about etiology.”

Basic Research and the Search for New Biomarkers

Achieving greater precision in the design of clinical trials requires an enormous amount of basic research. Such research enables a greater understanding of the sequence of events leading to AD, and of the complex interplay among molecules, systems, and mechanistic processes contributing to its development. NIA/NIH—the world’s largest funder of biomedical research—supports a wide range of studies examining, for example, gene-expression patterns and age-related changes in glial cells (microglia, astrocytes, and oligodendrocytes)8,9,10 that may contribute to neurodegenerative disorders. Also, researchers are using sophisticated technology to examine subcellular mechanisms of neurodegeneration, such as altered endosomal and lysosomal trafficking of molecules within neurons.11 Perhaps one of the most exciting developments has been the use of induced pluripotent stem cells (iPSCs) technology, which allows scientists to investigate potential mechanisms of AD in models with human genetics and physiology. This technology also is being used to identify targets of potential disease-modifying interventions.12

Basic and translational research are critical, too, for the discovery of new biomarkers that will improve our understanding of disease pathogenesis and help predict disease onset. Current research is examining complex interactions among biomarkers, and how a range of risk factors for AD—such as age, apolipoprotein E (APOE) genotype, autoimmune disorders, and neuroinflammation—may influence these to increase the likelihood of developing AD.

“There’s a significant need for longitudinal, natural history studies in which people are seen very early on—in their 30s and 40s—and are subsequently followed with standardized, harmonized biomarkers,” says Eliezer Masliah, MD, director of the Division of Neuroscience at NIA. “These studies will help us predict, for example, the rate at which some individuals are likely to convert clinically to mild cognitive impairment, based on a particular combination of biomarkers and genetics. Among people with an amyloid positive scan in the brain, what’s the rate of conversion at five years? Among people with the ApoE4 allele, what’s the conversion rate at 10 years? Some studies are already beginning to give us answers to these questions, but only in selected populations—for example, in Caucasian women. We need a variety of similar studies in diverse populations. We also need an array of new biomarkers, including vascular biomarkers, and new biomarkers of neurodegeneration. We’re finding that beta amyloid and tau alone are not enough.”

Validated beta amyloid and tau biomarkers, which are used to define AD as a unique disease among other neurodegenerative disorders, provide enormously useful information about the accumulation of toxic proteins in the brain. Yet researchers are continuing to explore new and more sophisticated methods of imaging these proteins that may yield more valuable details about the development of AD.13

Recently, scientists have imaged tau fibrils at the atomic level,14 using cryo-electron microscopy (the inventors of which won the 2017 Nobel Prize in chemistry) to create high-resolution images of C-shaped tau filaments. Using solid-state nuclear magnetic resonance, another NIH-funded team has discovered unique “structural fingerprints” of beta amyloid associated with AD.15 Because amyloid PET imaging exposes patients to considerable ionizing radiation, a more precise alternative with less radiation would be of great value.

Dr. Masliah notes that although tau PET is one of the most remarkable developments of recent years, scientists are still looking for ways to improve this form of imaging as well.

“We have learned a lot more about tau in the brain and how it’s involved in AD,” says Dr. Masliah. “Tau alone is very powerful because it’s more strongly tied to cognitive impairment than amyloid deposition. That being said, we’re still in the stages of developing better tau ligands. While tau PET is certainly useful, it has some limitations. It’s clear, for example, that it only sees tau of AD but not of other tauopathies. These ligands also cross-react, and bind to things that are not tau. This is an area that’s still under development, but research toward developing new tau ligands is a priority.”

NIA is also funding a series of projects to discover ligands that will help measure synapse loss in living people with AD, which is associated with cognitive impairment caused by the disease. PET imaging has been used to measure SV2A, a protein that reflects the density of synapses.16 Before this
research was conducted, measurement of synaptic density was possible only during autopsy.

“This is really very exciting technology,” says Dr. Masliah, whose own work more than 20 years ago established a relationship between AD symptoms in living people and the density of synaptic terminals in their brains as measured during autopsy. “Having the ability to image these synapses in the brain in living people and quantify this could provide a very strong correlate of cognitive impairment. If these ligands can be validated as a biomarker, they will, in the AT(N) scheme, be a welcome new measure of neurodegeneration.”

Other candidates for future biomarkers of neurodegeneration include neurogranin[17] and neurofilaments.18 Neurogranin is a protein expressed in the cortex and hippocampus that plays an important role in synaptic plasticity. Measures of neurogranin in CSF have been shown to reflect neurodegeneration associated with clinical symptoms in AD—an indicator that some experts believe is superior to CSF measures of total tau. Neurofilament proteins indicate injury to neuronal axons, regardless of the cause, so they signal neurodegeneration that is not necessarily caused by AD. Because the levels of these proteins rise in response to neuroaxonal damage in both CSF and blood, they represent a promising candidate for blood-based biomarkers of neurodegeneration.

“We are heavily invested in the development of blood-based biomarkers,” says Dr. Masliah. “The problem is that they require very sophisticated technology for detection, and still need further research for validation, so they’re not yet ready for prime time. However, we’re supporting a wide range of studies aimed at large-scale development of these biomarkers.”

In an NIH-sponsored study, Randall J. Bateman, MD, professor of neurology at Washington University School of Medicine in St. Louis, Missouri, has been exploring whether measures of amyloid beta in the blood can identify people with altered levels of amyloid beta in their brain or CSF. The study is carefully examining both the relationship and timing of changes in amyloid-beta blood levels relative to measures of amyloid PET and CSF amyloid beta, in an effort to understand, for the first time, whether changes in the blood occur before, at the same time as, or after changes in CSF and in the brain.

Although all biomarker candidates require extensive testing in diverse populations before they can be used in clinical trials, the hope is that a range of new biomarkers will help to significantly refine the inclusion and exclusion criteria for new clinical trials.

Examining Risk Factors for AD

Genetic information is not formally included in the AT(N) scheme as gene variants do not measure pathologic change—instead, they indicate the risk for developing pathologic change. An individual may have the ApoE4 allele, for example, without the presence of AD-related pathologic changes. Yet recent discoveries of novel AD-risk genes[19] are expected to help improve early prediction and early detection of AD, which should in turn pave the way for intervening earlier.

“We have seen huge advances in the discovery of new polymorphisms that likely contribute to sporadic AD,” says Dr. Masliah. “And researchers are using this new information to do some really exciting work toward developing polygenetic risk scores for sporadic AD and correlating various biomarkers with those risk scores in late-onset disease.”

Dr. Masliah adds that there are also some intriguing new directions in the study of sporadic early-onset forms of AD.

“We already know a good deal about familial early-onset AD, caused by autosomal dominant mutations in APP, PSEN1, or PSEN2,” says Dr. Masliah. “We know that in people with these mutations, there’s nearly a 100% chance of developing AD. But there is also a sporadic form of early-onset disease that’s similar to late-onset AD—instead of starting at age 60 or 70, clinical symptoms emerge around age 40 or 50. We really don’t know anything yet about the genetics of early-onset sporadic AD, but we’re now funding studies in this area. This research is critical because for people who are not yet Medicare-eligible, a diagnosis of sporadic early-onset disease can be both unpredictable and devastating.”

In an effort to identify other potential risks for AD, NIA has funded more than 80 new AD-related epidemiological studies since NAPA was signed into law. Research to date suggests that in some individuals, AD is likely caused by a mix of genetic, environmental, and other factors. Current studies are examining how sleep, diet, and factors such as air pollution and heavy metals may play a role in AD’s development. Exposure to lead, cadmium, and mercury, for example, has been shown to cause neurological and neuropsychological symptoms in people of all ages, and recent studies suggest that long-term exposure can contribute to age-related cognitive decline.[20] In one NIH-sponsored study, investigators found that increased levels of cadmium in urine and blood samples were associated with an increased risk of AD-related mortality approximately five to 13 years after exposure.[21]

In another area of study, researchers are focusing on what are essentially the opposite of risk factors—that is, factors that may confer resilience or resistance in individuals at risk for AD.[22] The Resilience—Alzheimer’s Disease Consortium, launched by NIH in 2017, has brought together six multidisciplinary teams to investigate mechanisms that lead to cognitively resilient phenotypes, with the goal of discovering new interventions that may be protective.

“Why is it that there are so many individuals who have AD pathology, and may even have risk genes, who don’t develop the clinical symptoms? Do these people have a neurological reserve? Or is it possible that there are some genes that confer protection? Research to date suggests, for example, that APOE2 does appear to be protective for some populations,” says Dr. Masliah. “We’re still in the early stages of funding studies exploring resilience to AD with the aim of developing pharmacological and nonpharmacological prevention strategies.”

Clinical Trial Research

Before the various elements of the 2018 research framework can be adapted and applied to clinical practice, they must be validated by longitudinal cohorts and randomized trials. NIA is funding a full spectrum of clinical trials and working toward refining trial populations—meticulously stratifying the cohorts based on phenotype—in an attempt to develop interventions for all patients, at all points along the disease continuum. Recently, NIA established an innovative clinical trials network, the Alzheimer’s Clinical Trial Consortium (ACTC), comprising 35 sites across the U.S.
Reframing Alzheimer’s Disease

“The NIH has had a clinical trials consortium in Alzheimer’s for a long time—the Alzheimer’s Disease Cooperative Study (ADCS), which was established in 1991 and is still active,” says Laurie Ryan, PhD, chief of the Dementias of Aging Branch in the Division of Neuroscience at NIA. “What led to the ACTC was the realization that we really need to beef up our infrastructure, to ensure that the clinical sites are fully supported with dedicated personnel who are not being pulled away for other research studies. We also knew that we needed to focus on improving recruitment of individuals with diverse backgrounds—for example, African American, Hispanic, or Asian. We know it’s critical to have a much better understanding of how this disease may look and develop in different people to ensure that we’ll have treatments for all those with the disease.”

Dr. Ryan adds that the new ACTC infrastructure will streamline the implementation of trials and speed up the launch of new ones, partly by means of a centralized institutional review board. The new consortium also is maintaining centralized tissue banking for specimens, as well as centralized imaging, bioinformatics, bioinformatics, data management, and analysis support.

“Information generated by the ACTC will be shared with the entire research community,” says Dr. Ryan, “including all of the methods and procedures, as well as study data and biological samples. Even people running trials outside of the ACTC can use the biobank, and can also tap into the electronic data-capture system. Everything is designed to move the entire field forward in terms of clinical trials for Alzheimer’s and related dementias.”

Current clinical trial research extends well beyond the testing of anti-amyloid therapies. Each year, the AD drug pipeline includes a larger number of agents with unique mechanisms of action, as researchers continue to investigate interventions that target new pathways and cellular processes believed to play a role in the disease.21 However, there is still hope that some of the anti-amyloid agents that have been the focus of failed AD clinical trials, including solanezumab, will prove to be effective interventions.

“What we’ve learned about solanezumab and some of the other anti-amyloid immunotherapies,” says Dr. Ryan, “is that if you wait until someone already has either mild cognitive impairment or early AD, it is actually too late at that point to intervene. Even if it were possible to remove amyloid, there already has been too much brain damage, so it’s not beneficial to the person receiving treatment.”

Dr. Ryan says that investigators are now exploring whether intervening with anti-amyloid agents at an earlier, presymptomatic stage in people at risk of developing AD dementia could prevent cognitive decline. The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) trial, for example, is testing whether solanezumab can prevent cognitive decline in older adults who are cognitively normal but at risk for developing AD dementia because of significant amyloid accumulation found on amyloid PET scans. A4’s results are expected to be available in 2022. Another monoclonal antibody that binds to amyloid beta, crenezumab, is being tested as a potential intervention for early-onset autosomal-dominant Alzheimer’s disease (ADAD) in a large study of families in Colombia. Participants include kindred with ADAD who are asymptomatic carriers of a PS11 mutation.

“Anti-amyloid therapies make good sense for people with this genetic mutation, because we know for sure that [they] have high levels of amyloid,” says Dr. Ryan. “This is a unique and very large study, with over 6,000 individuals in this particular kindred. One advantage of working with this population is that

---

Table 1  Selected Investigational Disease-Modifying Treatments for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Agent (Manufacturer/Sponsor)</th>
<th>Trial Number</th>
<th>Description/Mechanism of Action</th>
<th>Indications/Comments</th>
<th>Status/Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gantenerumab (Hoffman-La Roche)</td>
<td>NCT03444870 and NCT03443973</td>
<td>Monoclonal antibody directed against beta amyloid</td>
<td>GRADUATE1 and GRADUATE2 are testing gantenerumab, an amyloid-targeting treatment candidate, in patients with prodromal, or early, Alzheimer’s disease (AD). Each trial plans to enroll 760 people, aged 50–90 years old.</td>
<td>Recruiting; Phase 3</td>
</tr>
<tr>
<td>BAN2401 (Eisai/Biogen Inc.)</td>
<td>NCT01767311</td>
<td>Anti-amyloid monoclonal antibody</td>
<td>Clarity AD is a global, placebo-controlled, double-blind, parallel-group, randomized study in 1,566 patients with mild cognitive impairment (MCI) caused by AD or mild AD dementia (early AD) with confirmed amyloid pathology in the brain.</td>
<td>Active, not recruiting; Phase 2; A Phase 3 clinical study is being initiated to support a filing for BAN2401.</td>
</tr>
<tr>
<td>Insulin Detemir (intranasal) (Wake Forest University Health Sciences)</td>
<td>NCT01959646</td>
<td>Increases insulin signaling in the brain; enhances cell signaling and growth</td>
<td>Study of Nasal Insulin to Fight Forgetfulness (SNIFF) is examining the effects of intranasally administered long-acting insulin detemir on cognition in patients with AD or amnestic mild cognitive impairment (aMCI).</td>
<td>Completed; Phase 2</td>
</tr>
</tbody>
</table>

NB: The 2019 update of the Alzheimer’s disease drug-development pipeline paper by Jeffrey Cummings, MD, director emeritus of Cleveland Clinic Lou Ruvo Center for Brain Health, and colleagues, is expected to be published this summer.
## Reframing Alzheimer’s Disease

### Table 1 Selected Investigational Disease-Modifying Treatments for Alzheimer’s Disease (continued)

<table>
<thead>
<tr>
<th>Agent (Manufacturer/Sponsor)</th>
<th>Description/Mechanism of Action</th>
<th>Indications/Comments</th>
<th>Status/Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam (University of Minnesota - Clinical and Translational Science Institute) NCT02002819</td>
<td>Anticonvulsant; reduces neuronal hyperactivity (also a cognitive enhancer)</td>
<td>Participants undergo overnight brain-wave study to assess for silent epileptic (seizure-like) activity. Epileptic activity on screening exam is not required to enter trial. Participants are randomized to receive levetiracetam for 4 weeks, then no drug for 4 weeks, and then placebo for 4 weeks—or to receive treatments in reverse order. Cognitive abilities of participants will be retested every 4 weeks and compared with baseline.</td>
<td>Recruiting; Phase 2</td>
</tr>
<tr>
<td>RO7105705 (RG6100, MTAU9937A) (Genentech, Inc.) NCT03289143</td>
<td>Humanized anti-tau monoclonal antibody with high specificity for pathological tau; designed to interfere with spread of extracellular pathologic tau</td>
<td>Study evaluating efficacy and safety in participants with prodromal-to-mild AD. Optional 96-week, open-label extension period will be available to participants who complete double-blind treatment period and who, in investigator’s judgment, might benefit from open-label RO7105705 treatment.</td>
<td>Recruiting; Phase 2</td>
</tr>
<tr>
<td>Nicotinamide (Vitamin B3) (University of California, Irvine) NCT03061474</td>
<td>Anti-tau; neuroprotective</td>
<td>Study timeline includes screening phase of up to 60 days and treatment phase expected to last for approximately 48 weeks that will include 4 study visits. Using cerebrospinal fluid (CSF) biomarker outcomes at 12 months, primary outcome for trial is change in p-tau231.</td>
<td>Recruiting; Phase 2</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex) (New York State Psychiatric Institute/National Institutes of Health/National Institute on Aging) NCT03282916</td>
<td>Neuroprotective, anti-inflammatory antiviral agent</td>
<td>Study evaluating efficacy of treating patients with mild AD with anti-viral generic valacyclovir hydrochloride (500-mg caplet). Valacyclovir at 2 g–4 g per day, repurposed to treat AD, will be compared with matching placebo in 130 patients with mild AD (65 valacyclovir, 65 placebo) who test positive for herpes simplex virus-1 (HSV1) or HSV2.</td>
<td>Recruiting; Phase 2</td>
</tr>
<tr>
<td>Candesartan (Emory University) NCT02646982</td>
<td>Angiotensin receptor blocker</td>
<td>Candesartan’s Effects on Alzheimer’s Disease And Related Biomarkers (CEDAR) is investigating effect of this blood pressure medication on cognitive function in patients with MCI.</td>
<td>Recruiting; Phase 2</td>
</tr>
<tr>
<td>AADvac-1 (Axon Neuroscience SE) NCT02579252</td>
<td>Causes production of antibodies that target conformational epitopes in microtubule-binding region of tau. These antibodies are expected to prevent tau protein from aggregating, facilitate removal of tau-protein aggregates, and prevent spreading of the pathology.</td>
<td>Study evaluating safety and efficacy of AADvac1 in treatment of patients with mild AD. 60% of participants receive AADvac1 and 40% of participants receive placebo.</td>
<td>Active, not recruiting; Phase 2 study in AD (Phase 1 in another therapeutic area)</td>
</tr>
</tbody>
</table>
we have a good idea of when symptoms will emerge, because younger generations are expected to have symptoms at about the same time that their parents did. This will give us a much better idea of when to intervene in order to delay symptoms.”

Beyond Anti-Amyloid Approaches

Dr. Ryan stresses that because AD is a complex disease, effective treatment will most likely require a combination of therapies, the components of which will vary depending on an individual’s stage of disease and particular risk factors.

“It’s important to note,” says Dr. Ryan, “that while it may be too late to use amyloid as an intervention in individuals who are already symptomatic, it might not be too late for other medications to be effective. We know that amyloid deposition is among the first events that occur during the development of AD, so anti-amyloid interventions likely need to be started very early. However, there may be other therapeutics that are effective at a later stage of disease—we may even find that some have a regenerative effect. Our goal is to have effective treatments for people at all points along the AD spectrum.”

Dr. Ryan adds that some of those treatments may involve targeting other pathologies, in addition to amyloid and tau. Researchers at Rush University Medical Center in Chicago, for example, who have examined large numbers of donated brains, have discovered that mixed pathologies often exist in the brains of people who received a specific diagnosis of Alzheimer’s dementia.24 Many people with a pathologic diagnosis of AD at autopsy have vascular and a wide range of other co-existing pathologies, each of which, the Rush researchers theorize, represents a “hit” to the brain that likely increases the risk of developing AD. Interventions targeting these pathologies could potentially halt the progression of the disease.

Among the drugs in the AD pipeline with new mechanisms of action are a handful of so-called “repurposed” drugs, for which significant research data and well-characterized safety profiles already exist. One agent, levetiracetam, has been used to treat epilepsy, but in smaller doses has been shown to reduce brain hyperactivity that may be linked to dementia. With more than $8 million in funding from NIA, and in partnership with Johns Hopkins University, AgeneBio is testing their once-a-day, low-dose formulation of levetiracetam in a phase 3 trial (HOPE4MCI)25 to determine whether it can prevent or delay the onset of dementia in people with mild cognitive impairment.

“The theory is that subclinical hyper-excitability, or seizures in the hippocampus, may lead to the development of Alzheimer’s pathology,” says Dr. Ryan, “so investigators are using this drug to see if reducing this excitability can help slow the trajectory of mild cognitive impairment. A lot of basic science already has been done on this hypothesis, which has helped the intervention to advance to phase 3 studies.”

Another repurposed agent in the AD pipeline is valacyclovir, a drug that has been FDA approved to treat herpes and shingles. Scientists have discovered that both oral and genital herpes viruses (HSV-1 and HSV-2) trigger amyloid aggregation, and their DNA has been discovered in beta-amyloid plaques. In mice, anti-HSV drugs have reduced the accumulation of both beta amyloid and p-tau. Davangere P. Devanand, MBBS, MD, and other investigators at Columbia University are currently testing valacyclovir’s efficacy in individuals with mild AD in a randomized, phase 2 proof-of-concept trial.

A novel mechanism of action also is being explored in a phase 2a study examining LM11A-31, which targets microglial activation, a key pathological feature of AD. Frank M. Longo, MD, PhD, at Stanford University is leading the investigation of this first-in-class small-molecule agent.

“This agent is a modulator of P75, a neurotrophin receptor, so it’s a nerve growth factor,” says Dr. Ryan. “The thought is that the drug may prevent the activation of neurodegenerative processes, and protect nerve cells and their connections. This is an exciting and novel approach to therapy that’s still in the early stages of research. It has gone through phase 1, where investigators were just looking at safety, and now both safety and dose are being examined in phase 2.”

Non-Pharmacological Studies

Research thus far strongly suggests that a variety of non-pharmacological interventions, including a range of lifestyle modifications, may have beneficial effects on brain functioning, which may help to delay or prevent AD and other dementias. Findings from the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) study suggest that maintaining normal blood pressure may offer some protection against mild cognitive impairment and perhaps, in turn, AD.26

“It’s important to note that this trial was stopped early because the intensive control of blood pressure proved to be so beneficial for heart health that it would not have been ethical to continue,” says Dr. Ryan. “We don’t yet have evidence that intensive lowering of blood pressure will reduce dementia, but the study did clearly show that it has a measurable impact on mild cognitive impairment (MCI). And this is important, because MCI is a risk factor for Alzheimer’s and other dementias. This is the first large, randomized clinical trial to show that if we intervene by lowering blood pressure, we can reduce the risk of developing cognitive impairment.”

The AA is funding SPRINT MIND 2.0, with the original participants from the hypertension study, a 2-year follow-up study aimed at a more definitive understanding of whether blood pressure can help reduce the risk of dementia. Meanwhile, NIH has funded related research examining how dietary interventions may help to reduce the risk of dementia. A combination of the “Dietary Approaches to Stop Hypertension” (DASH) diet and Mediterranean diet, called the MIND Diet (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay) trial, is ongoing, and it is hoped that it may be associated with improving or maintaining cognitive health and/or lowering the risk of cognitive impairment.

Among other important studies examining lifestyle modifications is the NIH-sponsored Exercise in Adults with Mild Memory Problems (EXERT), which is evaluating the effects of physical exercise on cognition, functional status, brain

Laurie Ryan, PhD
atrophy, and blood flow in adults with mild memory impairment. Conducted at YMCAs in the U.S., the study has randomized one half of participants to engage in a mild exercise program involving stretching and the other half to engage in a moderate-to-high-intensity aerobic training program. In 2019, AA also launched the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) study, a two-year clinical trial to determine whether a range of lifestyle modifications may help protect cognitive function in older adults who are at increased risk for cognitive decline.

Research Depends on Participants

NIA has been intensifying its efforts to proactively recruit and retain diverse volunteers for studies of AD and related dementias. In October 2018, NIH launched A National Strategy for Recruitment and Participation in Alzheimer’s and Related Dementias Clinical Research to increase the enrollment of diverse populations in clinical research through community, national, and international forms of outreach. This new strategy is in response to a pressing need to have large, diverse populations of volunteers available as research opportunities emerge. “One thing that’s absolutely critical to all the research we conduct is the volunteers,” says Dr. Ryan. “In order to make a difference for the growing numbers of adults with dementia and those who are at risk for the disease, it’s essential to ensure we have the volunteers we need for the success of AD research. Our newest studies will require many more people from across the disease spectrum, including healthy and preclinical individuals, and adequate representation from various racial, ethnic, and socioeconomic groups who may be affected by dementia in different ways. We greatly value our volunteers, and we know that we are not going to find treatments for AD unless people continue to participate in these research studies.”

REFERENCES


Vol. 44 No. 5 • May 2019 • P&T® 289