Neurotheranostics: The Next Frontier for Health Span

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With an aging U.S. population, advancements in the treatment of Alzheimer disease (AD) and other neurodegenerative diseases are key to the maximization of health span. The recent approval of 2 antiamyloid antibodies, which decrease brain amyloid load, places us on the cusp of breakthrough therapies that target the mechanism of the disease rather than just treating the symptoms. Although the trials that led to these approvals studied patients with mild early symptoms, multiple ongoing trials have enrolled cognitively normal patients screened for AD biomarkers including risk factors for amyloid positivity, family history, and genetic markers. Thus, amyloid PET can help identify an at-risk population that can be enrolled for antiamyloid therapy to prevent AD symptoms from ever developing. In this review, we examine the paradigm of neurotheranostics and how PET biomarkers of amyloid, tau, inflammation, and neurodegeneration could characterize the pathologic stage of AD and therefore allow for personalized therapy.

Key Words: PET; antibodies; dementia; health span; neurotheranostics; theranostics

J Nucl Med Technol 2023; 51:266–270
DOI: 10.2967/jnmt.123.265502

Over the 2 decades before the coronavirus disease 2019 pandemic, remarkable progress had been made in increasing life span, with the World Health Organization reporting a global increase in the average age of mortality of approximately 6.6 y from 2000 to 2019 (*1*). Although an impressive feat with regard to technologic and scientific advancements in preventive and treatment strategies, the global population does not display a matched increase in the maximum length of time the average individual remains healthy. As such, the health-care community must widen its traditional focus on life span, the length of time an individual is alive, to include health span, how long an individual maintains full function and quality of life (*2*).

Received Jan. 23, 2023; revision accepted Apr. 14, 2023.
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Published online Aug. 16, 2023.

In light of these life span advancements and necessary recognition of patient health longevity, the following question arises: wherein lies the future of health span? Since the 1980s, as life expectancy has increased, according to data from the Longitudinal Study of Aging and the National Health Interview Survey, U.S. population rates of disability and other ailments affecting daily physical function have steadily declined (*3*). Unfortunately, the same clear-cut progress in patient health has not been observed in the domain of cognitive functioning (*4,5*). Given that dementia directly correlates with increased age, prolongation of brain health stands out as the key to lengthening health span to keep up with life span.

As the leading cause of dementia, the most important threat to brain health and future health span is Alzheimer disease (AD), a neurodegenerative disease characterized by the stepwise aggregation of β-amyloid protein fibrils into extracellular plaques, accumulation of intracellular tau protein in neurofibrillary tangles, and progressive neuronal death. This neuronal death, or neurodegeneration, ultimately results in atrophy of the brain, memory loss, and cognitive dysfunction that severely reduces quality of life (*6,7*).

WHY SHOULD WE CARE?

Anywhere from 50%–75% of dementia cases in the United States are caused by AD, with disease prevalence doubling every 5 y after the age of 65 y (*8*). As cited by the Alzheimer Association, using 2011 data from the U.S. Census Bureau and the Chicago Health and Aging Project, a population study highlighted the stark increase in AD diagnosis with age. For individuals between the ages of 65 and 74 y, the study found an average annual incidence of 0.4%, with this incidence rate increasing to 3.2% between the ages of 75 and 84 y, and an even greater rate of 7.6% for individuals 85 y and older (*9*). Using statistics from the Framingham Heart Study, an additional study comparing the incidence of AD by sex demonstrated that women possess a lifetime risk twice that of men (20% for women as compared with 10% for men) (*10*).

Because of the combination of the increasing incidence of AD with age and the aging U.S. population, one study

found that the annual incidence of AD is expected to more than double by 2050 (*11*). A more recent study estimated that the number of elderly individuals with a clinical AD diagnosis will increase by 18% from 6.07 million in 2020 to 7.16 million in 2025 and by 128% to 13.85 million in 2060 (*12*).

Between 2000 and 2019, whereas the rates of other illness-related causes of death have remained stagnant, there has been a striking increase in AD as a cause of death in the U.S. population, increasing by approximately 145.2% within this time frame (*13*). If these trends continue, the gap between death rates related to AD and those related to other ailments will grow even further, having an even greater impact on death and population health span. Beyond its position as an obvious threat to population health and mortality, AD has created a major financial strain on the U.S. health-care system, with treatment costs currently estimated to increase from $305 billion in 2020 to more than $1 trillion by 2050, and these costs do not include the billions of hours of unpaid help from caregivers (*14*).

CURRENT DIAGNOSTIC METHODS FOR AD

Before the development of the appropriate neurologic imaging techniques, clinicians depended solely on clinical assessments for AD diagnosis, with the definitive method to confirm neuropathology being postmortem autopsy. Clinical testing classified patients into one of the following categories: preclinical AD, mild cognitive impairment due to AD, and dementia (generally further categorized into mild, moderate, or severe) (*15*). However, after development and wider use of brain imaging techniques such as CT, MRI, and PET in the early 2000s, this clinical spectrum can now be used in conjunction with a patient's AD biomarker status to proceed with appropriate diagnosis and treatment (*16*). PET using amyloid tracers (amyloid PET) revolutionized the field by allowing for assessment of amyloid burden in clinical trials and in practice (Fig. 1). Since amyloid accumulation in the brain precedes development of cognitive decline, amyloid PET can identify at-risk subjects before clinical symptoms arise (*17,18*).

Diagnostic imaging techniques have revolutionized patient care in several domains, allowing for decreased mortality across a range of diseases. For example, according to the 2011 National Lung Screening Trial, lung cancer mortality for high-risk individuals decreased by 20% after 3 y of annual low-dose CT lung screening (*19*). The wide array of cancer screening techniques available has allowed for earlier detection of pathology and thus greater potential for cure. For example, in the case of colorectal cancers, death rates are reduced by detection via endoscopic screening, subsequent resection of precancerous lesions, and identification of tumors while still resectable for cure.

Unfortunately, because of a lack of adequate treatment options after diagnosis, a decrease in disease-related mortality similar to that for cancer and cardiovascular disease has not been achieved with screening for AD. According to recommendations published by the U.S. Preventive Services Task Force, whereas screening instruments help detect dementia earlier, current evidence does not support benefit to patient or caretaker quality of life or to patient-care outcomes from early screening of cognitive impairment (*20*). For their study, the U.S. Preventive Services Task Force selected primary care patients above the age of 65 y lacking symptoms of cognitive impairment. These patients were then randomly selected and received either no screening or screening for AD dementia. The study found no statistically significant variation of Health Utilities Index scores between groups, indicating negligible differences in health-related quality of life (*21*).

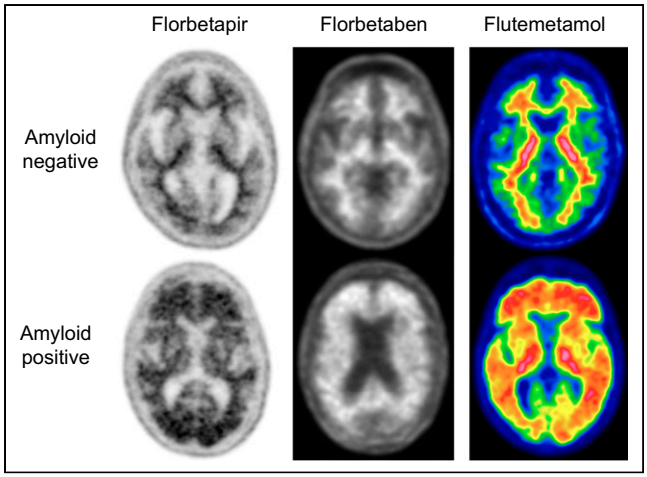

FIGURE 1. Examples of negative and positive amyloid PET scans using 3 FDA-approved ^{18}F tracers. Each tracer has its own specific guidelines for image interpretation, and cases are displayed here according to those recommendations. They all share the same basic principles for image interpretation. Negative scans show white matter pattern of uptake. Positive scans show uptake in both gray and white matter and thus loss of white matter pattern. (Courtesy of Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network.)

A/T/N FRAMEWORK

Important to the determination of proper therapy for dementia and AD is accurate diagnosis and staging; however, the complexities of AD pathology and related dementias pose limitations on the accuracy of the diagnostic clinical framework (*22*). Given the challenges of clinical assessment and concurrent developments in imaging, a new classification system was established based on the critical biomarkers of AD. The A/T/N framework classified the biomarkers of AD into 3 core categories: "A" for amyloid, "T" for tau, and "N" for neurodegeneration (*23*). An individual is assigned the binary status of positive or negative for each biomarker. Although serum and cerebrospinal fluid assays are actively under development to allow complete classification, PET can already do so with U.S. Food and Drug Administration (FDA)–approved agents for amyloid, tau, and neurodegeneration with ^{18}F-FDG. Amyloid PET first gained FDA approval in 2012, tau PET

was more recently approved in 2020, and ^{18}F-FDG PET was initially approved for epilepsy in 1989 and has been used for many years in the assessment of dementias. The A/T/N biomarkers typically become positive sequentially, with first amyloid, then tau, and finally neurodegeneration. Patients become amyloid-positive many years before symptomatic cognitive decline. Although the presence of brain amyloid is necessary for the diagnosis of AD, it is not sufficient since diagnosis of AD requires the presence of symptoms.

THERANOSTICS

The first use of the term *theranostics* is often attributed to John Funkhouser in a 1998 press release for Cardiovascular Diagnostics, in which theranostics describes a method of integrated screening, diagnosis, and treatment of disease, existing as a useful tool to render medicine and therapy personalized and individualized. Nuclear medicine physicians play a critical role in this theranostic strategy using amyloid PET to diagnose amyloid positivity and thus confirm the target for amyloid-targeted therapies. In integrated diagnostics and assessment of an individual's risk for AD, genomics, pathology, and imaging work hand in hand to optimize patient care with personalized medicine (*24*). A screening population can be enriched first by checking for genetic markers or a family history that increases risk for AD and then imaged with amyloid PET to identify the presence of amyloid even before the development of symptoms. Theoretically, imaging can further pathologically stage a patient to provide individually tailored patient care, for example, by knowing whether to target amyloid or tau. In a manner analogous to the role in oncology, PET is also being used in trials to monitor response to therapy. Although nuclear medicine is often primarily thought of as functional imaging as with ^{18}F-FDG, amyloid and tau PET have expanded the scope of nuclear medicine into molecular pathology by identifying and quantifying proteinopathies in the brain (*25*).

AMYLOID AND ANTIAMYLOID ANTIBODIES

Multiple steps are required to go from amyloid precursor protein to amyloid plaque, and the form of amyloid at each step can be a specific target for an antibody (Fig. 2). Amyloid accumulation begins with the cleavage of the transmembrane amyloid precursor protein by a secretase enzyme that releases the soluble monomer of β-amyloid, generally thought to be nontoxic. Solanezumab is an antibody that binds this soluble monomer in the bloodstream with the hope of decreasing further amyloid aggregation in the brain. The second phase of aggregation involves the oligomerization of β-amyloid monomers to form a still-soluble protofibril. There were 2 antibodies in trials targeting this stage of amyloid accumulation, gantenerumab and lecanemab (*26*). Lecanemab became the second FDA-approved amyloid-targeted treatment (*27*). Next, as more β-proteins stick to one another, the protofibril grows further to form a fibril.

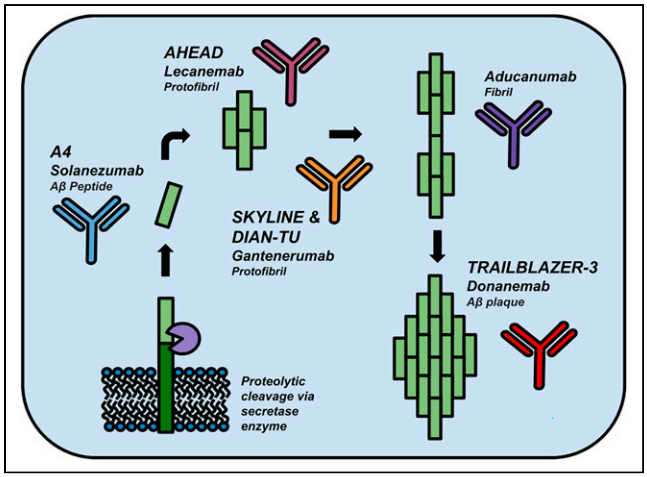

FIGURE 2. Schematic diagram of cumulative phases of amyloid aggregation in AD with respective antibodies currently in clinical trials that bind them. Names of clinical trials are listed next to respective antibodies being tested in amyloid-positive, cognitively normal subjects.

The first FDA-approved (somewhat controversially) amyloid-targeted treatment was aducanumab, an antibody that targets this fibril stage. Clinical trials of this drug have demonstrated dose-dependent removal of amyloid as assessed by amyloid PET at baseline compared with imaging results 1 y after treatment, with some patients even converting from an amyloid PET–positive to a negative status (*28*). Despite its approval via the accelerated pathway due to its ability to lower amyloid in the brain, this antibody was not a commercial success because of lack of reimbursement. The final stage of aggregation occurs when the amyloid fibers clump together to form full-fledged neuritic plaques; it is the widespread accumulation of these clumps that is characteristic of AD neuropathology. The antibody donanemab binds to these amyloid neuritic plaques and is in late-stage trials, which have shown that the drug can decrease amyloid burden in the brain through serial amyloid PET (*26*).

Many antiamyloid antibody therapeutic trials focus on the population with early, mild AD, as done for the trials that resulted in the FDA approval of aducanumab and then lecanemab. Although aducanumab therapy did decrease amyloid in the brain, it did not definitively show clinical benefit. Lecanemab showed both a decrease of amyloid in the brain and a modest clinical benefit by slowing but not stopping cognitive decline (*29*). To do more than slow AD, trials have moved so early in the disease state that subjects are cognitively normal in an attempt to prevent symptoms from ever developing, the epitome of increasing health span. With amyloid testing such as amyloid PET, patients can be identified who are amyloid-positive before development of symptoms. The first preventive trial is the Anti-Amyloid Treatment in Asymptomatic Alzheimer Study, otherwise known as the A4 Study. This study is currently assessing the efficacy of solanezumab in subjects age 65–85 y old with normal cognition and memory but screened as positive

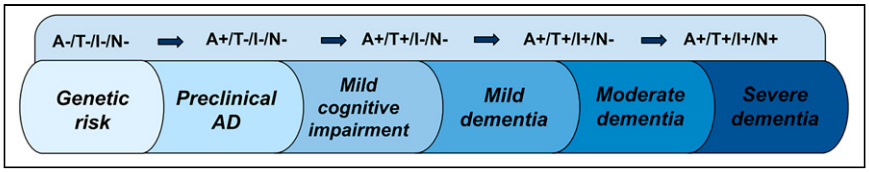

FIGURE 3. Schematic combining AD clinical diagnostic continuum with correlated biomarker progression using A/T/I/N framework.

on amyloid PET. Of the 4,486 participants, 1,323 were PET amyloid–positive and enrolled in the study. The selected individuals were then randomized to receive either the investigational drug solanezumab or a placebo and were tested every 6 mo for 3 y (*30*).

Highlighting the importance of the results of the A4 Study, a cross-sectional study analyzed correlations between elevated amyloid levels and risk factors of A4 Study participants. The study demonstrated the feasibility of using amyloid PET to screen cognitively normal at-risk patients. Researchers confirmed that increased amyloid on PET was indeed associated with patient family history and the APOE4 allele, an allele that when homozygous, confers a greater risk of AD. Additionally, increased amyloid scores were associated with lower cognitive assessments and a subtle increased decline in cognitive function. Ultimately, these findings support that PET amyloid can stratify high-risk groups for selection of subjects for prevention trials of AD (*31*).

Several preventive phase 3 AD trials using these various antiamyloid antibodies have been under way. The results of the A4 Study with solanezumab are expected to be released in 2023 (*32*). One of the 2 trials with gantenerumab, the DIAN-Trials Unit study was read out as negative in 2022; the SKYLINE trial was halted early (*33,34*). The AHEAD trial with lecanemab should be completed in 2027 (*35*). Lastly, TRAILBLAZER-ALZ 3 using donanemab is expected to be read out in 2027 (*36*).

TAU PROTEIN

The second biomarker in the A/T/N framework is the pathologic accumulation of tau protein, a protein that normally supports the internal structure of the neuron. Tau makes up neurofibrillary tangles, another pathologic hallmark of AD. Currently, flortaucipir is the only PET agent FDA-approved for imaging of tau neurofibrillary tangles in AD. Pathologic tau accumulation typically occurs after amyloid positivity and correlates with development of AD symptoms and thus clinical assessment (*37,38*). Since amyloid PET is often diffusely positive by the time symptoms of AD present, tau PET is theoretically better for monitoring disease since tau deposition usually ascends from the basal regions of the brain superiorly as symptoms worsen. Optimal clinical use taking advantage of the complementary information provided by amyloid and tau PET and avoiding redundancy is in development.

Given that amyloid positivity is typically necessary before pathologic tau accumulation, the success of preventive trials targeting amyloid could serve as the key to preventing tau accumulation and thus the development of AD symptoms. Donanemab, the antibody binding amyloid plaque, is currently in phase 3 trials for both prevention and early AD. The preceding phase 2 trial of donanemab in early AD selected a population that was PET-positive for both amyloid and tau. After 1 y of drug administration, serial amyloid PET displayed a conversion from positive to negative in most patients. Additionally, amyloid PET was used not only to monitor therapy but also to direct therapy, as the antibody was either reduced in dose or stopped if patients converted to an amyloid-negative status (*39*).

NEURODEGENERATION AND INFLAMMATION

The third biomarker of the A/T/N cascade is neurodegeneration, or progressive neuronal death. Neuronal loss manifests as atrophy, which can be measured volumetrically by MRI and as decreased perfusion and metabolism via ^{18}F-FDG PET. This neuronal loss marks the onset of more severe, irreversible dementia and symptom progression. Research suggests that pathologic inflammation plays a crucial role in neurodegeneration. PET can be used to measure a recognized marker of glial inflammation, the translocator protein (TSPO); however, clinical research and potential future clinical utility of TSPO PET still need to overcome variability in binding affinity due to a prevalent single-nucleotide polymorphism in the TSPO gene (*40*). For TSPO PET measurements, high numbers indicate increased inflammation. Importantly, a TSPO PET study found an association between increased inflammation and conversion from mild cognitive impairment to AD (*41*). This connection suggests the critical addition of "I" for inflammation to the current A/T/N biomarker sequence to create an updated A/T/I/N framework (Fig. 3).

CONCLUSION

Ultimately, these ongoing preventive AD trials could revolutionize therapeutic strategies for Alzheimer patient care, making a massive difference in the maximization of health span and quality of life for patients and their families. Furthermore, in conjunction with the currently accepted clinical diagnostic continuum of AD, judicious use of PET imaging could play a critical role in earlier and more precise neurotheranostics. With brain health increasingly becoming the determinant of health span, these developments in AD patient care will be integral to traversing this frontier for longer and healthier lives.

DISCLOSURE

Phillip Kuo is a consultant or speaker for Amgen, Bayer, Blue Earth Diagnostics, Chimerix, Eisai, Fusion Pharma, GE Healthcare, Invicro, Novartis, Radionetics, and UroToday. He is a recipient of research grants from Blue Earth Diagnostics

and GE Healthcare. He was previously an employee of Invicro. John Seibyl acknowledges the support of the Michael J. Fox Foundation for PD research and is a consultant to Invicro, Biogen, AbbVie, GE Healthcare, Life Molecular Imaging, Xingimaging, and Likeminds. He has equity in Invicro. No other potential conflict of interest relevant to this article was reported.

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