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Recent Breakthroughs in the Diagnosis and Treatment of Neurodegenerative Disorders

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ABSTRACT

This paper covers recent breakthroughs in diagnosis and treatment of neurodegenerative disorders, specifically diagnostic biomarkers and disease modifying treatments for Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS). Biomarkers in the brain, spinal fluid and blood are helping identify the pathologic misfolded proteins that specifically characterize these neurodegenerative disorders. The signature proteins include beta-amyloid and hyperphosphorylated tau (P-tau) in AD, alpha-synuclein in PD, and recently discovered in ALS, TDP-43. As new biomarkers are validated, there is increasing optimism that innovative disease modifying treatments will prevent, reverse or delay the progression of these neurodegenerative diseases. The growing trend of FDA approval of medications through the Accelerated Approval program based on biomarker indicators is expediting drug development for AD, PD, and ALS. Using this pathway, the FDA has granted conditional approval for an AD treatment that lowers brain amyloid and another AD treatment that is associated in studies with slowing of both cognitive and functional loss. The FDA also granted conditional approval for an ALS treatment demonstrating reduction in a neurodegeneration biomarker. The FDA granted Breakthrough Device designation for a blood test as a diagnostic biomarker for AD and the recent breakthrough in the ability to diagnose PD with an accurate biomarker is a major milestone. Continued collaboration among the drug discovery and clinical research communities is needed to accelerate our understanding of the underlying biology and develop disease modifying treatments for these neurodegenerative disorders.

Introduction

Neurodegenerative disorders including Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS) occur when nerve cells in the brain or other parts of the nervous system lose function and die (Thorpe, PhD et al., 2021) (*Neurodegenerative Diseases*, n.d.). The most common neurodegenerative disorders, AD and PD, affect approximately 6.2 million individuals in the US (*Neurodegenerative Diseases*, n.d.). These neurodegenerative diseases were responsible for 272,644 deaths in 2016, and the annual cost of these diseases was $655 billion in 2020 (Thorpe, PhD et al., 2021). There are no available cures for these diseases and most routinely used medications function only as symptomatic treatments, meaning the medications help with symptoms but do not change the overall course of the disease (McFarthing et al., 2022).

New potentially disease modifying treatments that delay or slow progression by addressing the underlying cause of the disease have recently been approved and clinical trials continue to evaluate new therapies (Cummings et al., 2022) (McFarthing et al., 2022). Central to these clinical trials are biomarkers, which help to identify the misfolded proteins characteristic of these neurodegenerative diseases (Alzheimer's Stages, n.d.). This paper will review the recent successes in both diagnostic biomarkers and disease modifying treatments for AD, PD, and ALS. These advances are important as new biomarkers and methods of detection help facilitate the development of new disease modifying medications, and these new therapies are needed to prevent, delay, or slow the decline of these neurodegenerative

diseases (Cummings et al., 2022). Collaboration in the research community combined with clinical trials are key to bolstering the creation, testing, and FDA approval of new treatments (Drug Development Pipeline, n.d.).

Biomarkers

Generally, biomarkers are medical signs or laboratory results that can be accurately measured (Strimbu & Tavel, 2010). Biomarkers should accurately measure the presence of disease as well as stage, rate of progression and therapeutic response (Konickova et al., 2022). For AD, PD and ALS research, biomarkers in the brain, spinal fluid, and blood are helping to identify the misfolded proteins and other cellular dysfunction markers common with most neurodegenerative disorders. Furthermore, biomarkers are helping to speed up the rate at which new medications can reach patients by acting as surrogate endpoints in clinical trials, meaning patients do not have to demonstrate a measurable clearcut clinical response if the biomarkers are showing significant improvement *(FDA Approves Qualsody, 2023)* (*FDA Approves Aducanumab*, 2021) (*Alzheimer's Stages*, n.d.). As new biomarkers are identified and validated, there is increasing optimism that new disease modifying therapies will prevent, reverse, or delay the progression of neurodegenerative disorders (Sweeney et al., 2017).

Misfolded Proteins

Many of these biomarkers rely on our ability to accurately detect human proteins. There have been 20,000 genes identified that code for human proteins (Aebersold et al., 2018). Proteins naturally fold into formations linked to their activity. However, some proteins can become incorrectly folded and combine with similar misfolded proteins, causing cellular toxicity. In many neurodegenerative diseases, the pathologic hallmark is a misfolded protein which aggregates, forming deposits either in or around healthy cells (Sweeney et al., 2017). Scientists have identified many of these toxic and misfolded proteins, mainly beta-amyloid and hyperphosphorylated tau (P-tau) in AD, alpha-synuclein in PD, and TAR DNA-binding protein 43 (TDP-43) in ALS (Sweeney et al., 2017).

FDA Approvals & Collaboration Within Research Community

Traditionally, most FDA approvals of neurodegenerative disease medications have relied on clinical outcomes, but a growing FDA trend is the conditional approval of medications through special approval pathways based on biomarker results. The FDA's Accelerated Approval program can be used for serious or life-threatening illnesses based on the drug's effect on a surrogate endpoint (*Accelerated Approval*, 2023). This endpoint does not have to be a statistically significant clinical improvement or slowing of disease but can be an endpoint such as a biomarker that is reasonably likely to predict a clinical benefit to patients (*FDA Approves Aducanumab*, 2021). In fact, advances in neurodegenerative biomarkers have been recently highlighted by two FDA approvals using the accelerated drug approval pathway where the medications showed improvement in biomarkers without statistically significant clinical improvement *(FDA Approves Qalsody,* 2023*)* (*FDA Approves Aducanumab*, 2021). Once the medication is conditionally approved via the accelerated pathway, further clinical testing is required to verify that the drug provides the expected clinical benefit (*FDA Approves Aducanumab*, 2021) (*Accelerated Approval*, 2023). Similarly, the FDA gives Breakthrough Device designation to devices (*Breakthrough Devices Program*, 2023).

In addition to the recent use of FDA accelerated pathway approvals in the identification of new biomarkers and potential disease modifying treatments is the trend of cooperative research among biotechnical and pharmaceutical companies with academia, industry, private foundations and government agencies (Sweeney et al., 2017). This collaboration among the drug discovery community can help to accelerate the identification of biomarkers and disease modifying therapies (Sweeney et al., 2017).

Alzheimer's Disease (AD)

Overview

Alzheimer's Disease (AD) is the most common form of dementia. AD is a debilitating and progressive neurological disease of the brain with no current cure (Sindi & Kivipelto, 2015). Clinically, it is characterized by gradual cognitive deterioration with symptoms such as memory loss, decline in judgment and thinking, changes in personality and behavior, and loss of language skills (*Diagnosing Alzheimer's*, 2022). Approximately 50 million people worldwide suffer from AD (Sindi & Kivipelto, 2015). According to the US Census Bureau, the number of Americans aged 65 and older will increase from 58 million today to 88 million by 2050 with cases of AD to 12 million cases (*2023 Alzheimer's Disease Facts and Figures*, 2023, page 20). It is also one of the medical community's most expensive diseases. In 2023, AD cost an estimated $345 billion dollars, and by 2050 AD is estimated to cost $1 trillion (*2023 Alzheimer's Disease Facts and Figures*, 2023, page 84).

Scientists have begun to unravel the origin of AD and believe it is caused by an insidious buildup of two misfolded proteins aggregating and depositing in the brain. The first protein to misfold and aggregate in the brain is beta-amyloid and is considered the first hallmark of AD (*2023 Alzheimer's Disease Facts and Figures*, 2023, page 6). Recently, strong genetic and clinical evidence has emerged that the amyloid protein accumulation begins up to two decades prior to symptom onset (Sperling et al., 2014). As amyloid plaques develop, they lead to the dysfunction of another brain protein - tau - a key intraneuronal protein that stabilizes neuron microtubules. The tau proteins become hyperphosphorylated leading to intracellular microtubules breaking down. This P-tau protein then misfolds into neurofibrillary tangles and become the second major hallmark protein of AD (*2023 Alzheimer's Disease Facts and Figures*, 2023, page 6).

Current Diagnosis and Treatment

The definite diagnosis of AD can only be made with tissue confirmation and the best clinical diagnosis that can be made is probable Alzheimer's Disease, made by a physician's review of symptoms and physical exam. Brain imaging such as MRI or CT scan is very helpful to rule out other causes of memory loss (*Diagnosing Alzheimer's*, 2022).

To assist in the diagnosis of AD, PET scans using amyloid tracers and cerebrospinal fluid (CSF) collection via lumbar puncture are both accurate and approved ways to detect the misfolded proteins (*FDA Permits New Test to Improve Diagnosis of AD*, 2022). However, there are barriers to the widespread acceptance of PET scans and CSF collection to detect brain amyloid. PET scan roadblocks include high cost, exposure to radiation, and limited availability of both the scanner and PET tracer (Hameed et al., 2020). CSF collection problems can arise during or after the lumbar puncture procedure (inserting a spinal needle into the spinal canal) with potential side effects including nerve injury from the needle, headache, or bleeding into the spinal canal (Blazel et al., 2020). These significant barriers are preventing the widespread acceptance of PET scans and CSF collection to detect brain amyloid for AD diagnosis.

Current treatment for Alzheimer's Disease includes the use of Acetylcholinesterase Inhibitors which prevent the breakdown of acetylcholine, a neurotransmitter involved in memory and thinking (*How Is AD Treated?* n.d.). Another commonly used medication, a N-methyl-D-aspartate (NMDA) receptor antagonist, regulates brain glutamate and may help AD patients retain function for a longer period of time (*How Is AD Treated?* n.d.). These symptomatic medications are not considered disease modifying as they do not slow or stop the progression of AD (*How Is AD Treated?* n.d.).

Recent Advancements in Diagnostic Biomarkers and Disease Modifying Treatments

New blood tests as diagnostic biomarkers for AD are emerging that can identify people who have an increased likelihood of having brain amyloid, a risk factor for developing AD, prior to having AD symptoms *(New Blood Test for AD,* 2021*)*. The tests should have few barriers to adoption as collecting a blood sample via venipuncture is a common clinical procedure with an estimated 1.4 billion procedures performed in the US each year (Leipheimer et al., 2020). A new AD blood-based biomarker, PrecivityAD, has recently received approval in the United States and involves a simple venous blood collection (*AD Blood Test PrecivityAD*, 2020). This test measures plasma beta-amyloid and combined with detecting a genetic marker (ApoE) and age of the patient, gives a probability score of having brain amyloid (*AD Blood Test PrecivityAD*, 2020) (*Plasma Aβ Test Wins Approval*, 2020). Data from one recent trial showed 81% accuracy in predicting the level of amyloid on a PET scan (*New Blood Test*, 2021). Given the potential roadblocks and possible complications with PET scans and CSF collection to diagnose AD, the FDA considered blood detection of amyloid to be a significant scientific breakthrough and granted the PrecivityAD test Breakthrough Device designation (*AD Blood Test PrecivityAD*, 2020).

Scientists have developed new plasma tests requiring only a commonly used and simple antibody-based procedure that detects hyperphosphorylated tau (P-tau) protein - the second hallmark protein implicated in AD. P-tau comes in multiple isoforms and the specific P-tau 217 version appears to be the most sensitive when it comes to predicting brain amyloid plaques and neurofibrillary tangles. Scientists are now stating plasma P-tau 217 and plasma beta-amyloid 42:40 ratio could one day soon replace amyloid PET scans for diagnosis in cognitively normal adults which will significantly reduce the barrier to diagnosis (*Plasma P-Tau217*, 2022). Another very important finding is plasma P-tau 217's ability to predict cognitive decline (*Blood Tests Go Head to Head*, 2022). These remarkable P-tau 217 biomarker tests are currently being developed by multiple scientific groups and validation is nearing completion (*Plasma Aβ Test Wins Approval*, 2020).

There have also been important successes in AD treatments that alter the underlying pathology of AD itself. Recently, the FDA has conditionally approved two monoclonal antibody medications, lecanemab and aducanumab (*FDA Approves Aducanumab*, 2021) (*FDA Approves Lecanemab*, 2023). These are disease modifying treatments that bind to brain amyloid allowing the brain's immune system to remove the amyloid deposits (Bard et al., 2000). Aducanumab works by tagging the beta-amyloid plaques found surrounding brain cells while lecanemab works by preferentially binding amyloid protein protofibrils and toxic oligomers which are the precursors to amyloid plaque formation. Once the antibodies bind amyloid, the brain's immune cells are alerted and begin removing the foreign substance.

These two medicines slow loss of cognition and also slow the loss of daily living activities, key for AD patients to maintain daily functioning. There was controversy surrounding the approval of aducanumab by the FDA but the effectiveness of lecanemab is not disputed. Lecanemab removes the sticky protein deposits that cause AD to advance, and results of a published clinical trial demonstrated slowing of cognitive decline by 27% and functional decline by 37% (van Dyck, MD et al., 2023) (MacMillan, 2023).

In May 2023, clinical trial data from yet another monoclonal antibody, donanemab, was released revealing the strongest data yet. Donanemab showed a 35% slowing of memory loss and an astounding 40% slowing in loss of function (*Lilly's Donanemab*, 2023). Some experts argue that slowing of functional loss might be more important than slowing of memory loss as caregivers can more easily navigate around memory impairments, but functional loss is why patients with AD end up in full-time care facilities (Cipriani et al., 2020).

There are potential problems with the use of monoclonal antibodies for the treatment of AD. These roadblocks include cost, limited access to patients with only the earliest of AD symptoms, and a potential side effect, Amyloid Related Imaging Abnormality (ARIA) which reflects areas of brain swelling and/or bleeding.

One potential problem with the use of monoclonal antibodies is cost. It is estimated the cost for treatment with an AD monoclonal antibody could be anywhere from $25,000 to over $50,000 per year (Brockmann et al., 2023). In addition, another significant roadblock is limited access to monoclonal antibodies as they are currently only

approved for certain AD subjects with the earliest AD symptoms. The earliest signs of AD most often include short-term memory loss, termed mild cognitive impairment (MCI) and doesn't affect function. This stage can last 3-5 years and slowly worsens. When the disease progresses beyond simple memory impairment to include loss of ability to perform daily tasks, the diagnosis becomes mild AD.

The monoclonal antibodies lecanemab and aducanumab are only approved for patients with MCI and mild AD. As AD progresses even further, patients develop symptoms such as impulsivity, behavioral changes and loss of physical abilities requiring full-time assistance. The diagnosis then becomes moderate AD**.** The medications have been tested in moderate AD subjects but show no benefit to patients, and scientists hypothesize it was too late to stop the progression of AD symptoms (Rygiel, 2016). The next level is severe AD, where patients lose their ability to speak or carry on a conversation and are often confined to bed as they lose the ability to control movement (*Alzheimer's Stages*, n.d.). Monoclonal antibodies are not approved for use in either moderate AD or severe AD patients.

Another potential side effect, amyloid related imaging abnormality (ARIA), occurs in up to 30% of patients using disease modifying monoclonal antibodies. ARIA is seen on MRI brain imaging and presents in 2 forms: ARIA-Edema (ARIA-E) and ARIA-Hemorrhage (ARIA-H). ARIA-E is characterized by fluid collection that causes swelling around the brain cells and can be symptomatic (headache, dizziness, confusion) or asymptomatic. Most often, ARIA-E is asymptomatic. ARIA-H presents as bleeding in the brain, typically "microbleeds" at just a few millimeters in size. Rarely, there has been symptomatic bleeding in and on top of the brain in patients using monoclonal antibodies (van Dyck, MD et al., 2023).

ARIA is believed to have multiple causes and occurs more often in those with a certain gene variant. One mechanism could be due to blocking the brain's clearing mechanisms when attempting to quickly remove large amounts of amyloid. The other leading theory is a vascular leaking theory arising from monoclonal antibodies binding amyloid that is directly attached to blood vessel walls. When amyloid is removed from the blood vessel walls by the immune cells, the vascular walls become weakened and "leaky" (Salloway, MD et al., 2022). ARIA-E incidence in the Lecanemab trial was 12.6% in the treatment group and 1.7% in the placebo group. ARIA-H occurred in 17.3% of treated subjects and 9% of the placebo group (van Dyck, MD et al., 2023).

There is also ongoing research developing tau monoclonal antibodies. Aggregated tau proteins make up the other pathologic deposits found in the brains of AD patients, and most closely correlate with cognitive decline (*First Hit on Aggregated Tau*, 2023). As tau deposits increase, memory loss and other symptoms also increase making removal of tau an important therapeutic target (*BIIB080 Hits Its Target*, 2023). In April 2023, clinical trial results were published for a small, early phase trial using the experimental medication BIIB080. This medication is an anti-sense oligonucleotide that functions by stopping translation of RNA into proteins. BIIB080 stops the formation of tau protein and in this small trial, it significantly lowered tau deposits in the brain. Research is ongoing and it remains to be seen if the reduction of the tau protein biomarker equates to a slowing of disease progression or slowing of neuro-degeneration. However, Alzheimer's scientists have called the findings "phenomenal" and "groundbreaking" in the ongoing search for disease modifying AD treatments (*First Hit on Aggregated Tau*, 2023).

Parkinson's Disease (PD)

Overview

Parkinson's Disease (PD) is a progressive neurological disorder characterized by tremors, muscle stiffness, unsteady or uncontrollable movements and impaired balance and coordination, with symptoms that begin gradually and worsen over time (Lamptey et al., 2022) (*Parkinson's Disease*, 2022) (*PD: Causes, Symptoms, and Treatments*, 2022). PD affects nearly one million people in the United States and costs an estimated $52 billion per year (*Parkinson's Disease*, 2022) (*Parkinson's Foundation*, n.d.). The cause of PD is unknown, but most scientists agree that genetics plus

environmental factors play a role in PD onset and progression (*Parkinson's Disease*, 2022) (*PD: Causes, Symptoms, and Treatments*, 2022).

Like AD, PD is a protein misfolding disorder. In these diseases, proteins misfold and aggregate leading to neurodegeneration. In AD, the protein culprit is beta-amyloid which aggregates outside of the brain's neurons. In PD, it is the protein alpha-synuclein which aggregates inside the dopaminergic neurons leading to neuron death and resulting motor symptoms (Murakami et al., 2023) (Gordian-Velez et al., 2021). The clumps of alpha-synuclein protein found inside of the neurons in PD are termed Lewy bodies (*PD: Causes, Symptoms, and Treatments,* 2022).

Current Diagnosis and Treatment

The current diagnosis of PD relies on a clinical diagnosis as there are currently no approved blood or laboratory tests to diagnose the condition. Doctors evaluate a person's symptoms and perform a physical examination looking for motor signs of the disease (*PD: Causes, Symptoms, and Treatments*, 2022). The gold standard for treatment of PD is levodopa, which only helps the symptoms of the disease (Murakami et al., 2023, 33-34). A helpful aid in making a diagnosis is the patient's response after taking a medication such as levodopa; if the patient's symptoms improve, then it is more likely to be Parkinson's Disease (*PD: Causes, Symptoms, and Treatments*, 2022).

Other medications to address PD symptoms include dopamine agonists along with enzyme inhibitors to increase dopamine, amantadine to reduce involuntary movements, and anticholinergic drugs to reduce tremors (*PD: Causes, Symptoms, and Treatments,* 2022). None of the currently available medications are disease modifying treatments and Parkinson's patients will ultimately progress (*PD: Causes, Symptoms, and Treatments*, 2022).

Recent Advancements in Diagnostic Biomarkers and Disease Modifying Treatments

The Michael J. Fox Foundation recently reported on a significant scientific breakthrough: the ability to accurately detect via cerebrospinal fluid (CSF) the misfolded and dysfunctional alpha-synuclein protein that causes Parkinson's Disease (*Parkinson's Disease Biomarker Found*, 2023). In a published report, the misfolded alpha synuclein protein was detected in CSF of high-risk patients with early, non-motor signs of PD (Siderowf, MD et al., 2023). This is significant as it is the first time in the history of PD that abnormal alpha synuclein could be reliably detected in living people. Prior to this development, the detection of abnormal, misfolded aggregated alpha-synuclein could only occur during a brain autopsy.

The test to detect abnormal, misfolded alpha-synuclein uses a process known as a seed amplification assay (SAA). These assays detect extremely low concentrations of abnormal proteins by using a "seed" protein (such as alpha-synuclein) and amplify the number of these proteins to enable detection. The seeded samples undergo cycles, where new non-aggregated protein building blocks (reactant) are added until sufficient quantity is available for detection (Vaneyck et al., 2023). Since blood is more easily accessible than spinal fluid, scientists have set a future goal of using seed amplification assays on blood samples (Vaneyck et al., 2023).

With recent breakthroughs in disease modifying treatments for AD, PD patients are hopeful they are next in line. Two current and ongoing clinical trials for PD are testing potentially disease modifying therapies. One investigational medication under study, buntanetap, is a translational inhibitor of aggregating proteins such as alpha-synuclein. The medication stops the formation and buildup of additional neurotoxic proteins by binding their mRNA *(Annovis Science, n.d.)*. In a phase 2 trial in PD patients, buntanetap demonstrated statistical improvement in motor function and coding speed on various tests (*Annovis Science*, n.d.). Due to these potentially important findings, the medication is now in a large, multinational clinical trial in PD patients (*Buntanetap in Early PD Patients*, n.d.).

The other potentially PD disease modifying treatment currently being tested in a large Phase 3 clinical trial, BIIB122, is targeting the most frequent genetic mutation found in PD patients, an abnormality in the leucine-rich repeat kinase 2 (LRRK2) gene (*Phase 3 Lighthouse Study in PD*, 2022). Scientists believe that a dysfunctional

LRRK2 gene leads to a buildup of toxic proteins and formation of Lewy bodies (Madureira et al., 2020). When the LRRK2 gene is functioning properly, it plays a role in neuron autophagy, a lysosomal process involved in breaking down and recycling cellular waste and old proteins. By inhibiting the abnormal LRRK2 protein, scientists hope to fix the damaged lysosomal pathway. (Madureira et al., 2020).

Amyotrophic Lateral Sclerosis (ALS)

Overview

ALS, also known as "Lou Gehrig's disease," is the most common motor neuron disease with 20,000 Americans living with ALS and 5,000 new cases in the United States every year (*Amyotrophic Lateral Sclerosis*, 2016) (*ALS - About the Disease*, 2023) (*FDA Approves Relyviro*, 2022). ALS is progressive and gets worse over time by attacking and killing nerve cells that control most voluntary muscles, while sparing voluntary control of eye and bladder muscles. This leads to paralysis and death from respiratory failure typically within three to five years of symptom onset (*FDA Approves Relyviro*, 2022). The national cost of ALS is estimated at $1.02 billion (Thorpe, PhD et al., 2021).

There are two types of motor neurons: upper motor neurons in the upper brain and lower motor neurons in the brainstem and spinal cord. In ALS, both upper and lower motor neurons are affected and atrophy over time, leading to muscle weakness, loss of muscle mass, inability to control movement, and eventual respiratory failure (Lamptey et al., 2022) (*Amyotrophic Lateral Sclerosis*, 2016). In about 90% of cases, the disease is sporadic, with only a small percentage of cases with a known genetic cause (*Amyotrophic Lateral Sclerosis*, 2016) and it is believed that a person's environmental exposure may be a contributing factor in the development of ALS. Mutations in four main genes, C9orf72, SOD1, TARDBP, and FUS, account for 80% of genetic ALS cases (Lamptey et al., 2022) (*Amyotrophic Lateral Sclerosis*, 2016).

Current Diagnosis and Treatment

The pathological hallmark in the majority of ALS cases is the accumulation of spinal cord intraneuronal protein aggregates, with the TAR DNA binding protein (TDP-43) as the most abundant protein observed in ALS patients (Lamptey et al., 2022). Since this important discovery, follow up findings have solidified TDP-43's role in sporadic ALS cases and provided evidence that abnormal TDP-43 aggregation could lead to neurodegeneration seen in ALS (Mejzini et al., 2019). Recent evidence also supports the role of aggregating misfolded proteins similar to underlying mechanisms in AD and PD (Mejzini et al., 2019).

The diagnosis is made via clinical examination as no ALS biomarker is currently available (Cho & Shukla, 2020). Onset of ALS usually begins in late middle life presenting as progressive, voluntary muscle atrophy and weakness. Early symptoms of ALS may be subtle and can also include muscle twitching, cramping and stiffness (*Amyotrophic Lateral Sclerosis*, 2016) (*ALS - About the Disease*, 2023). As the disease progresses, ALS patients lose muscle strength and become wheelchair dependent (*Amyotrophic Lateral Sclerosis*, 2016) (*ALS - About the Disease*, 2023). Current symptomatic treatments for ALS patients include riluzole, a glutamate-receptor antagonist, and edaravone, a free radical scavenger (Lamptey et al., 2022). None of the medications halt or reverse ALS progression (*Berry et al.,* 2023*).*

Recent Advancements in Diagnostic Biomarkers and Disease Modifying Treatments

There have been two potentially disease modifying treatments recently approved for ALS patients. In September 2022, the FDA approved a medication, Relyvrio, with a mechanism of action that is poorly understood but in clinical testing the medication prolonged life in ALS patients by almost 7 months compared to placebo and those on the active

medicine declined more slowly (*Alzforum Relyvrio*, 2022) (*FDA Approves Relyvrio*, 2022). It is believed the medicine works by blocking stress signals between two cellular compartments, mitochondria and the endoplasmic reticulum (*Relyvrio for ALS*, 2023).

Another novel therapeutic for ALS, Qalsody (tofersen), received conditional FDA approval in April 2023 by demonstrating a reduction in plasma neurofilament light (NfL) in ALS patients who are SOD1 carriers (*FDA Approves Qalsody*, 2023). Neurofilament light is a blood-based neurodegeneration biomarker that shows protein released from damaged neurons (*Biogen Qalsody*, 2023). Tofersen works by blocking translation of the messenger RNA that leads to production of excessive superoxide dismutase, which is felt to be toxic to motor neurons. The conditional FDA approval was the first ALS treatment approved based on a biomarker finding and the first approved treatment to target a genetic cause of ALS *(Biogen Qalsody*, 2023). A confirmatory clinical trial demonstrating clinical improvement is underway (*FDA Approves Qalsody*, 2023).

Conclusion

Neurodegenerative disorders including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS), occur when nerve cells in the brain or other parts of the body lose function and die. Alzheimer's Disease (AD) is the most common form of dementia, characterized by gradual cognitive and functional deterioration. Parkinson's Disease (PD) is a progressive neurological movement disorder with symptoms that begin gradually and worsen over time. And finally, ALS, also known as "Lou Gehrig's disease," is the most common motor neuron disease, characterized by the loss of nerve cells that control voluntary muscles which leads to paralysis and death within three to five years of symptom onset. Most medications for these neurodegenerative diseases are symptomatic treatments, as opposed to disease modifying treatments that delay or slow the progression of disease by targeting the underlying cause.

Central to researchers searching for disease modifying treatments are biomarkers, both new and old, that detect the underlying causes of these neurodegenerative diseases and also accelerate development of the most promising disease modifying treatments. Most neurodegenerative disorders share a common pathway involving misfolded proteins leading to aggregation and loss of function. For AD, PD, and ALS researchers, new biomarkers in the brain, spinal fluid, and blood are helping to identify these misfolded proteins and other cellular dysfunction markers. These advances are important as new biomarkers and methods of detection help facilitate the development of disease modifying therapies, which are needed to prevent, delay, or slow the decline of these neurodegenerative diseases.

Reliable and accurate biomarkers for misfolded proteins in AD has accelerated the search for disease modifying treatments, as demonstrated by recent FDA Accelerated Approvals of a treatment that lowers brain amyloid and also a treatment that slows both cognitive decline and functional loss. The use of a simple blood test to identify people with an increased likelihood of brain amyloid before symptoms of memory loss begin is a huge step in AD detection. Another groundbreaking advancement in AD research is the use of a novel experimental treatment resulting in the decrease of tau deposits in the brain, which is currently undergoing further testing to determine if these results equate to a slowing of disease progression or neurodegeneration.

The recent breakthrough in the ability to diagnose PD with an accurate biomarker is also a major milestone and will hopefully accelerate the search for disease modifying PD therapies. And the conditional approval of the first ALS treatment approved based solely on a biomarker is an important advancement.

Indeed, the growing trend of FDA approval of medications through special approval pathways based on biomarker indicators that are likely to correlate with meaningful clinical outcomes should accelerate drug development for AD, PD, and ALS. Further investigation and clinical trials are needed to increase understanding of the underlying disease mechanisms and develop promising disease modifying medications for the treatment of these and other neurodegenerative diseases. Moreover, continued collaboration between biotechnical and pharmaceutical companies with

academia, industry, private foundations, and government agencies will help to accelerate the discovery of new biomarkers and disease modifying treatments.

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