Neurodegenerative Diseases

A Report of Degenerative Diseases of the Central Nervous System

More Than **260** Medicines in Development for 29 Neurodegenerative Diseases

Neurodegenerative diseases affect millions of people in the United States, and it is estimated one in four Americans will develop one.[5] Neurodegenerative diseases occur when nervous system cells (neurons) in the brain, spinal cord and/or peripheral nervous system begin to deteriorate or become functionally impaired. As the neurons deteriorate, those affected first experience relatively mild symptoms, such as coordination issues or problems remembering names. But as a larger number of neurons are affected, symptoms will progressively worsen. In some cases, patients will lose the ability to walk independently, think clearly or function with the independence they once were accustomed to. Ultimately, many of these diseases are fatal or lead to shorter life expectancy.

Although existing treatments can help relieve some of the physical and/or mental symptoms associated with these conditions, neurodegenerative diseases are currently incurable and debilitating, resulting in the progressive deterioration and/or death of nerves. Alzheimer's disease, multiple sclerosis and Parkinson's disease are the most common neurodegenerative diseases.

JUST THE FACTS

6.2 Million
Americans are living
with Alzheimer's disease.[1]

Nearly
1 Million
Americans are living with
Parkinson's disease.[2]

5,000
new cases of ALS are diagnosed
each year in the U.S.[3]

More than
40,000
Americans are living with
Huntington's disease.[4]

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Finding new treatments and cures for neurodegenerative diseases has been a focus of biopharmaceutical companies for decades despite an exceptionally challenging research landscape, but new treatments are increasingly needed more than ever. Because neurodegenerative diseases strike primarily in mid- to late-life and the risk of being affected increases dramatically with age, the incidence is expected to soar as the population ages.[6,7]

By 2030, the U.S. Census Bureau estimates that as many as one in five Americans will be over the age of 65.[8] With more Americans living longer, the number of people affected by neurodegenerative diseases in the coming decades will only increase. If new, effective treatments are not found, 30 years from now, more than 12 million Americans will suffer from one form of them.[7] Additionally, neurodegenerative diseases cost the U.S. economy more than $655 billion a year in medical expenses and economic losses.[9]

While research and development (R&D) for neurodegenerative diseases has been challenging with more setbacks than success, biopharmaceutical innovation has resulted in significant new medical milestones and scientific advancements. America's biopharmaceutical research companies are continuing to work to uncover new targets for earlier detection, treatments and ultimately, cures for neurodegenerative diseases.

Difficulties in Researching and Developing Medicines for Neurodegenerative Diseases

From drug discovery through U.S. Food & Drug Administration (FDA) approval, developing a new medicine takes, on average, 10 to 15 years and costs $2.6 billion. This number incorporates the cost of failures — of the thousands and, sometimes, millions of compounds that may be screened and assessed early in the R&D process, only a few will ultimately receive approval. For all disease areas, less than 12% of the candidate medicines that make it into Phase I clinical trials are ultimately approved by the FDA.[10]

In the area of neurodegenerative diseases, R&D is even more difficult. While there has been increased knowledge about the underlying biology of disease in general, less is known directly about neurodegenerative diseases. Most medicines approved for neurodegenerative diseases only treat the symptoms, which provides some relief to patients, but does not inhibit the central nervous system from continuing to deteriorate, leading to negative long-term outcomes. Disease-modifying therapies (DMTs)

which can create an enduring change in the trajectory of clinical and cognitive decline are needed to address the underlying causes of these diseases, such as nerve cell death. But progress in this area has proven challenging. From 1998 to May 2021, there were 198 unsuccessful medicines in clinical trials for Alzheimer's. During the same time, only four medicines were approved to treat symptoms of the disease.

There are a wide range of challenges associated with the R&D of DMTs to treat these diseases that researchers are working to overcome. For example, development of new drugs targeting the central nervous system has significantly higher failure rates than non-central nervous system drugs in both pre-clinical and clinical trials. Failure rates have been even higher in neurodegenerative diseases specifically, where it inherently requires longer development time to demonstrate stopping progression versus improvement of symptoms. As a result of these challenges, it has taken longer for biopharmaceutical companies to make progress in advancing new treatments in this space.

Scientific complexities in neurodegenerative diseases include many factors, such as getting medicines across the blood-brain barrier, finding appropriate animal models that can inform human efficacy, a lack of validated molecular targets for drug development and a lack of well-defined biomarkers that can help measure consistency of treatment effect in clinical trials.[11]

Additionally, many neurodegenerative diseases are heterogenous conditions, meaning there are multiple root causes that make it difficult to diagnose patients, identify the appropriate treatment and to predict how individual patients will respond to treatment. In Alzheimer's disease, there is currently no single test available for diagnosis. Diagnosis is based on an individual's history, physical examination, and cognitive testing that may require amyloid positron emission tomography (PET) imaging or magnetic resonance imaging (MRI). These challenges with diagnosis, especially at earlier stages of disease progression, can pose significant challenges for recruiting eligible patients for clinical trials.

Successes in Neurodegenerative R&D

Some success has been found in treating neurodegenerative diseases caused by specific gene mutations and in diseases where a better understanding of the disease process has been achieved. Examples include:

- Multiple sclerosis is a heterogenous disease with several root causes. While the actual cause of multiple sclerosis is unknown, it is primarily considered a neurodegenerative disease in which the immune system is activated to destroy the protective sheath that surrounds nerves and can eventually lead to vision problems, impaired speech and even inability to walk. In recent years there have been tremendous advancements in treatment with the development of several DMTs that can prevent the irreversible damage caused by the disease and slow progression to disability. Despite this progress, there is still an unmet need, as the DMTs do not fully eliminate disease activity, and more treatment options are needed for those who do not respond to current FDA-approved therapies.

- Spinal muscular atrophy (SMA) is a condition involving the loss of nerve cells called motor neurons in the spinal cord, and symptoms and outcomes vary depending on which SMA gene is involved. Biopharmaceutical research companies have led the development of new treatments for SMA, which is the most common genetic cause of infant mortality. In 2016, the first of three novel therapies were approved to treat SMA. One modifies the SMN2 gene in order to increase the production of normal and functional SMN2 protein. A second treatment is the first FDA-approved gene replacement therapy for any neuromuscular disease and delivers missing genes to patients with SMN1 gene mutation. This therapy is a one-time intravenous infusion that aims to halt the disease by producing sufficient levels of the SMN protein. A third approved treatment is an oral medication designed to increase levels of the SMN protein by enhancing production from the SMN2 "backup" gene. However, more treatment options are still needed targeting SMA associated with different mutations.
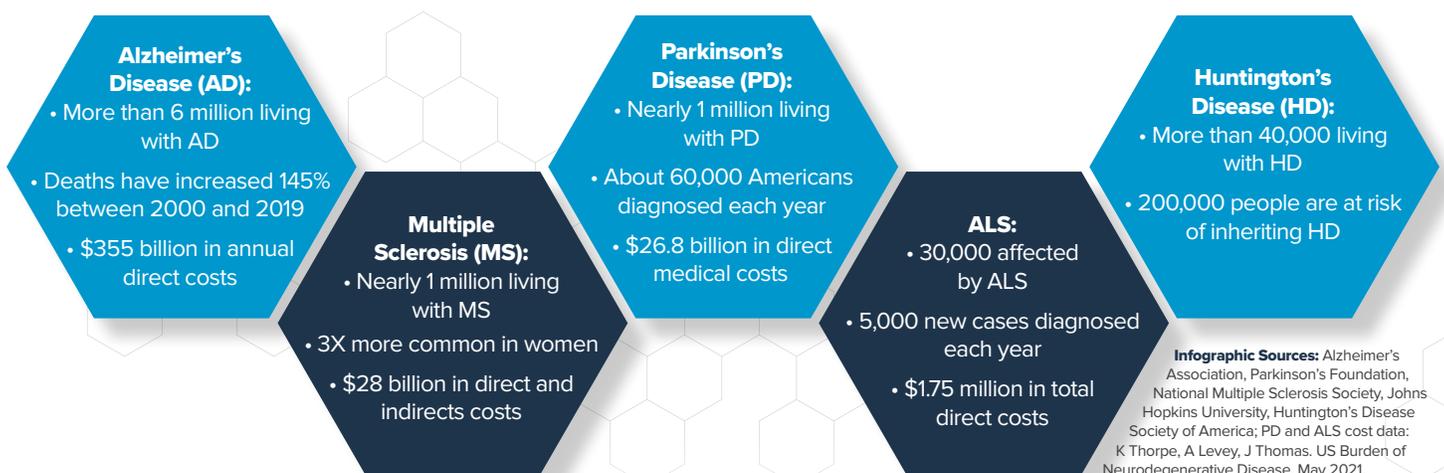
The Neurodegenerative Disease Pipeline

Today, biopharmaceutical research companies are developing 261 medicines for several neurodegenerative diseases, all of which are in clinical trials or awaiting review by the FDA.[12] There is hope on the horizon as scientists are uncovering more about how the central nervous system works at the molecular and genetic levels, driving the development of innovative treatments for neurodegenerative diseases. The 261 medicines in development include:

- **85** medicines in development for **Alzheimer's disease**, the most common form of dementia. Alzheimer's affects more than 6 million Americans and, along with other dementias, will cost the American economy an estimated $355 billion in 2021.[1]

- **64** medicines for **Parkinson's disease**, which affects nearly one million Americans. This is a disorder that mainly targets the dopamine-producing neurons in the brain, causing tremors, balance issues and cognitive changes. Incidence of the disease is expected to rise to 1.2 million by 2030.[2]

- **38** medicines for **amyotrophic lateral sclerosis (ALS)**, a fatal, progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Most people are diagnosed with ALS between the ages of 40 and 70. About 5,000 people are diagnosed with ALS each year in the U.S.[3]

- **33** medicines for **multiple sclerosis**, a chronic neurological disease that affects nearly one million Americans, a number that is substantially higher than previously reported based on a new 2017 study. For multiple sclerosis patients, the immune system attacks the protective sheath around nerve fibers, causing walking difficulties, muscle weakness and spasticity and fatigue. Women are three times more likely to develop multiple sclerosis than men.[13]

- **25** medicines for neurodegenerative **genetic diseases**, including Rett syndrome, a rare disease affecting brain development in girls, and SMA, a rare disease affecting the motor nerve cells in the spinal cord. Both disorders are caused by a gene defect and affect about one in 10,000 children.[14,15]

- **14** medicines for **Huntington's disease**, a genetic brain disease caused by an error in the "Huntington" gene. Huntington's causes deterioration in a person's physical, mental and emotional abilities, usually during their prime working years, and currently has no cure. There are more than 40,000 symptomatic Americans and another 200,000 at-risk of inheriting the disease.[4]

Other neurodegenerative medicines in development target Alexander disease, Batten disease, Friedrich's ataxia, and progressive supranuclear palsy and multiple system atrophy, among others.

Impact of Selected Neurodegenerative Diseases in the United States

Alzheimer's Disease (AD):
- More than 6 million living with AD
- Deaths have increased 145% between 2000 and 2019
- $355 billion in annual direct costs

Multiple Sclerosis (MS):
- Nearly 1 million living with MS
- 3X more common in women
- $28 billion in direct and indirects costs

Parkinson's Disease (PD):
- Nearly 1 million living with PD
- About 60,000 Americans diagnosed each year
- $26.8 billion in direct medical costs

ALS:
- 30,000 affected by ALS
- 5,000 new cases diagnosed each year
- $1.75 million in total direct costs

Huntington's Disease (HD):
- More than 40,000 living with HD
- 200,000 people are at risk of inheriting HD

Infographic Sources: Alzheimer's Association, Parkinson's Foundation, National Multiple Sclerosis Society, Johns Hopkins University, Huntington's Disease Society of America; PD and ALS cost data: K Thorpe, A Levey, J Thomas. US Burden of Neurodegenerative Disease, May 2021.

Neurodegenerative Diseases and Children

The neurodegenerative diseases of infancy and childhood are a particularly devastating subset of these diseases in which previously healthy children begin to exhibit progressive loss of neurologic function due to a deteriorating central nervous system. Unlike other neurologic diseases of childhood, neurodegenerative diseases escalate quickly, are often misdiagnosed and typically lead to an early death.[16] The wide-ranging symptoms exhibited by patients pose a significant challenge to health care providers in terms of diagnosis and disease management. It is estimated that pediatric neurodegenerative diseases account for more than a quarter of all admissions to pediatric neurology services.[17]

While most pediatric neurodegenerative diseases are caused by gene mutations, they can also be caused by chronic viral infections and even unknown causes. Improved understanding about these conditions will lead to more therapies, better methods for decreasing morbidity and improving survival in these pediatric patients.[16]

The development pipeline includes several therapies for neurodegenerative diseases[12] of childhood, including Batten disease or neuronal ceroid lipofuscinoses, a family of rare diseases caused by genetic mutations that interfere with a cell's ability to function normally, leading to progressive neurological impairment because of the damaged cells; infantile neuroaxonal dystrophy, rare inherited disorder that affects the part of a nerve cell that carries messages from the brain to other parts of the body and causes progressive loss of vision, muscular control, and mental skills; and spinal muscular atrophy, a genetic disease that involves the loss of nerve cells called motor neurons in the spinal cord, and symptoms and outcomes vary depending on which SMA gene is involved. As discussed earlier, three new treatments have been approved by the FDA for SMA in recent years.

The mapping of the human genome has led to the identification and understanding of the cause of some pediatric neurodegenerative diseases, highlighting the power of genetic sequencing to speed up diagnoses. Recently, two new neurodegenerative diseases in children were identified as being tied to specific genes using genome sequencing. One is a new form of ALS that begins attacking patients in childhood, although ALS normally develops between the ages of 40 and 70.[18] Another is a never-before-seen brain disorder in which children experience development delay and severe epilepsy.[19]
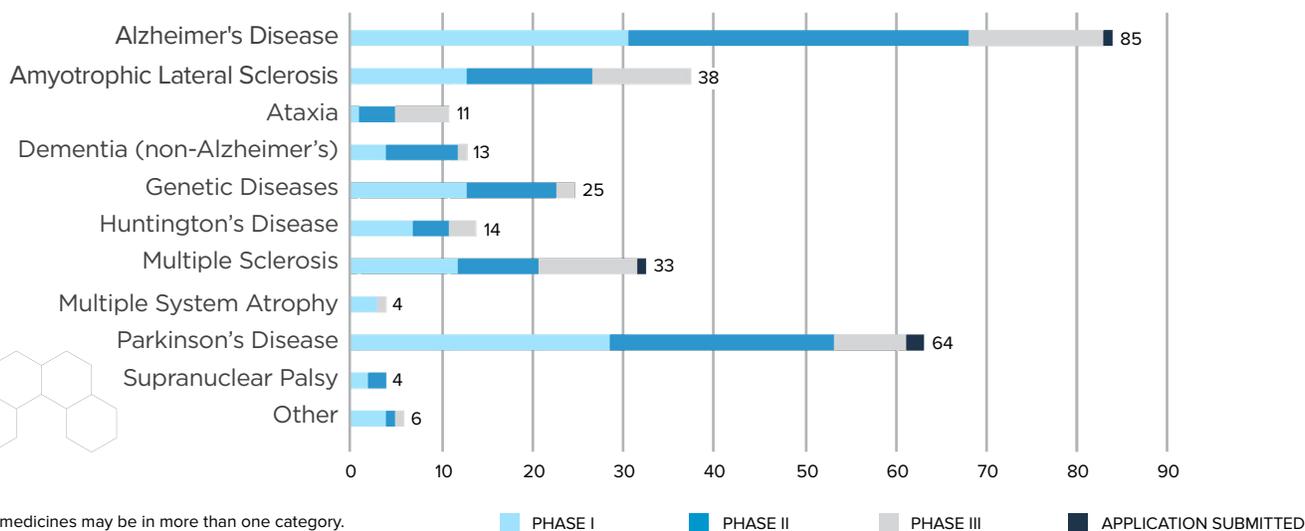
Medicines in Development for Neurodegenerative Diseases

Many of the 261 medicines in development represent a growing understanding of the underlying mechanisms of neurodegeneration. This enhanced understanding creates scientific progress over time and allows researchers to explore new pathways and scientific approaches to treat these complex diseases. Examples of innovative treatments in development include:

- Several medicines in development for **Alzheimer's disease** are disease-modifying treatments that may stop or slow disease progression by targeting one or more of the changes in the brain associated with the disease. These targets include beta-amyloid plaques that appear between nerve cells, tau protein tangles that damage and kill brain cells and a receptor that decreases a neurotransmitter necessary for the brain to think and function normally. Other areas of research target neuroinflammation, immune response and metabolic changes. One monoclonal antibody medicine in development is a Tau protein inhibitor designed to block and reduce the spread of Tau from neuron to neuron and potentially from forming damaging Tau tangles.

- An antisense treatment in development for **amyotrophic lateral sclerosis (ALS)** is thought to reduce the production of mutated superoxide dismutase (SOD1) protein and potentially the fatal progression of SOD1-ALS. This mutated protein has been associated with the degeneration of motor neurons in ALS. SOD1-ALS is a rare form of the disease that accounts for 20% of inherited or familial ALS and 2% of all ALS cases.[20]

- A monoclonal antibody in development for **Huntington's disease** binds to and blocks the activity of Semaphorin 4D (SEMA4D), a protein that plays a key role in the neuroinflammatory processes that can cause inflammation in the brains of individuals with the disease. By blocking the activity of SEMA4D, it may slow or prevent the neurodegeneration in Huntington's disease, a fatal disorder that causes the breakdown of nerve cells in the brain.

- A disease-modifying treatment in development for relapsing **multiple sclerosis** is an inhibitor of Bruton's tyrosine kinase (BTK) and targets the source of multiple sclerosis damage in the brain (lesions). The BTK inhibitor not only inhibits the peripheral immune system, but also crosses the blood-brain barrier to suppress immune cells that have migrated into the brain, while also modulating microglia cells that are responsible for removing damaged neurons that have been implicated in multiple sclerosis progression. The medicine shows promise for reducing neuroinflammation and neurodegeneration, both implicated in disease progression.

- A disease-modifying gene therapy is being tested as a single-dose treatment for patients with GBA1-mutated **Parkinson's disease**. The GBA gene contains instructions for making glucocerebrosidase (GCase), which is needed for the removal and recycling of the glycolipids. Glycolipids are a cellular component that accumulates with age, causing lysosomal dysfunction and aggregation of alpha synuclein in the cells, which is thought to lead to inflammation and neurodegeneration. The gene therapy delivers a non-mutated GBA1 gene to the brain. Another DMT being tested against Parkinson's disease is a monoclonal antibody that targets alpha-synuclein and is designed to block cell-to-cell transmission of aggregated alpha-synuclein found in Parkinson's.

Medicines in Development for Neurodegenerative Diseases

Disease	Value
Alzheimer's Disease	85
Amyotrophic Lateral Sclerosis	38
Ataxia	11
Dementia (non-Alzheimer's)	13
Genetic Diseases	25
Huntington's Disease	14
Multiple Sclerosis	33
Multiple System Atrophy	4
Parkinson's Disease	64
Supranuclear Palsy	4
Other	6

* Some medicines may be in more than one category.

PHASE I PHASE II PHASE III APPLICATION SUBMITTED

Increasing the Application of Digital Health Tools in Digital R&D

Digital health technologies are creating new opportunities to modernize health care and empower patients to make more informed decisions about their health. In fact, digital tools have already begun to transform the biopharmaceutical R&D process and health care delivery system in myriad ways—including by increasing access to clinical trials, enabling efficient information exchange, accelerating biopharmaceutical R&D and delivery of new treatments, enhancing clinical decision making and furthering patient engagement.

As a result of advancements in science and technology, the biopharmaceutical industry is leveraging the potential of digital R&D to improve drug development and speed access to medicines. Digital R&D is rapidly evolving with the potential to reduce barriers to innovation for novel medical products and therapeutics. Artificial intelligence/machine learning (AI/ML) and wearables and sensors represent the most commonly leveraged technologies for digital R&D. For example, AI/ML tools afford sponsors the ability to analyze large data sets, including safety-related adverse event information, to identify safety signals and better protect the public health.

Real World Examples of AI/ML in Action in Neurodegenerative Diseases

AI/ML tools have been used to research neurodegenerative diseases and have shown promise in early diagnosis, the likely course of disease and the development of new therapies.[21]

- Researchers recently identified three new subtypes of **multiple sclerosis** using AI. These new subtypes may help identify which patients are likely to have disease progression and may assist in the identification and development of more targeted treatments for the disease.[22]

- **Huntington's disease** presents great variability in the onset of symptoms and disease progression in patients. For some patients, symptoms begin in their 20s, while others don't experience symptoms until their 60s. This leaves a lot of uncertainty for each patient as to their disease progression and future. A research collaboration is developing AI models to learn patterns in Huntington's disease patient brain images that can inform individualized information about disease progression. This information may also distinguish it from other neurodegenerative diseases, help with treatment design and assist in understanding the disease better.[23]

- A team of researchers developed an AI tool that can diagnose **Alzheimer's disease** with more than 95% accuracy. This has potential to be a game changer for diagnosing Alzheimer's. Currently, doctors must conduct a series of tests to assess memory impairment and thinking skills, judge functional abilities and identify behavior changes. Diagnosing Alzheimer's earlier and more accurately can lead to earlier treatment and reduced health care costs.[24] Researchers are also looking at digital biomarkers linked to Alzheimer's disease, such as a patient's own retina. The roughness of the retina layers can determine the stage of the disease.[24]

- A recent research collaboration used a new AI model to group typical **Parkinson disease** symptom patterns. Additionally, using long-term data of patient's clinical status, the model can predict the progression of these symptoms in timing and severity.[25]

Looking to the Future

Alzheimer's disease, multiple sclerosis, ALS and other neurodegenerative diseases affect millions of Americans and even more people around the world, driving a demand for innovative solutions to complex illnesses. In order to fully understand how America's biopharmaceutical research companies are tackling these complex diseases, we spoke to company research experts in the field of neurological health.

What do you see as the biggest scientific challenges that need to be addressed for neurodegenerative diseases?

In recent years there has been great progress in several areas of neurodegeneration drug development, which has increased the optimism in tackling these devastating diseases. Our understanding of the underlying causes is expanding and has triggered a lot of activity in many indications. Familial FTD and ALS being two examples. There is also a broadening of drug modalities from the traditional small molecule approach to biologics as well as oligonucleotide and gene therapy approaches. The next step is to see if we can use our genetic insights and broaden our understanding to sporadic disease. With respect to the new modalities there are also still challenges with getting enough of the therapy into the brain. - *Markus Haeberlein, Ph.D., Senior Vice President, Research, Alkermes, Inc.*

How is your company working to unlock the biology of neurodegenerative diseases and overcome research hurdles?

Biomarkers have always been an important part of our research and development efforts to improve patient treatment and care. They aid in the diagnosis of various diseases we help to treat with our medicines and are valuable in evaluating responses to those treatments.

As our understanding progresses, biomarkers will play an important role in how we think clinically about the progression of disease and new treatment approaches that continue to move toward earlier intervention and even prevention. Biomarker science allows us to imagine a world where an earlier, accurate diagnosis leads to a personalized treatment that slows, stops or even prevents disease progress.

Roche and Genentech are leading the development of the NeuroToolKit — a platform designed to generate high-quality comparable clinical biomarker data across academic and industry cohorts to accelerate the identification of biomarkers for diagnostic development and advance the scientific understanding of neurological disorders like Alzheimer's disease. - *Gregory Rippon, M.D., Ph.D., Vice President and Chief Medical Partner of Neurology and Ophthalmology, Genentech*

What are you most excited about for the future of neurodegenerative disease treatment and what developments do you think hold most promise?

Everything we do at Eisai is rooted in our human health care (hhc) mission: giving our first thoughts to patients and their families and to increasing the benefits health care provides. As we look toward the future, we will continue to discover and develop breakthrough new medicines. But we will also harness the latest digital and AI technologies, data science, societal trends, and psychological insights to help people identify their precise risk factors and make meaningful lifestyle changes. We will both treat disease and work to prevent it. All with the goal of helping people live their lives to the fullest. - *Ivan Cheung, Chairman, Eisai Inc. President Neurology Business Group & Global Alzheimer's Disease Officer, Eisai Co., Ltd.*

What motivates you to work in such a challenging disease space?

It's easy to think of the reason to keep working on Alzheimer's. It's the people that are suffering with limited progress in treatment. Because it's so hard, and because there's been finite progress, that's the reason we keep working on it. We've been focused on diagnostics to see the pathology of the disease in the brain and therapeutics that can reverse that pathology in the brain. For the most part, we haven't been distracted from that vision of how we can treat Alzheimer's disease. And that's what's starting to pay off now. - *Daniel M. Skovronsky, M.D., Ph.D., Senior Vice President and Chief Scientific and Medical Officer, Eli Lilly and Company*

How is your company engaging in partnerships and collaborations to advance new treatments forward for neurodegenerative diseases?

At Lundbeck, partnerships and collaborations have always been an integral component of our R&D activities. We believe it is important to leverage the research activities that take place within our own walls with innovation across the neuroscience ecosystem. We collaborate with the best minds in brain science – partnering with organizations across the public and private sectors – to advance research and novel therapies. For example, we are partnering with Cambridge-based Rgenta Therapeutics, a biotechnology company, to discover small molecules targeting RNA regulation and splicing of disease-causing genes. - *Dr. Doug Williamson, SVP U.S. R&D, Global Deputy Chief Medical Officer, Lundbeck*

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