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Amyotrophic Lateral Sclerosis: V. Research and Latest Developments

Dr. Alain L. Fymat*

Professor, International Institute of Medicine & Science, California, USA.

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***Corresponding Author:** Dr. Alain L. Professor, International Institute of Medicine & Science, California, USA.

Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects motor neurons in the brain and spinal cord, leading to muscle weakness, atrophy, eventual paralysis, and ultimately respiratory failure and death. In this article. I will discuss the various models used in research on the disease (mice, zebra fish, human cells) and present the prominent ALS research centers both in the U.S. and internationally and will review the latest research and development achievements at these institutions. I will also provide recommendations for future developments. Lastly, in a sidebar, I will chart a path forward including strategic priorities for ALS.

Abbreviations

ABF: American Brain Foundation; AD: Alzheimer's disease; ALA: Alpha-linolenic acid; ALS: Amyotrophic lateral sclerosis; ALSA: ALS Association; ALS-TDI: ALS Therapy Development Institute; ARC: ALS Research Collaborative; ASO: Antisense oligonucleotide; BNI ALSC: Barrow Neurological Institute ALS Center; CSF: Cerebrospinal fluid; CUG ALSC Columbia University Eleanor and Lou Gehrig ALS Center; DALS CRC: Duke ALS Clinic & Research Center; EAP: Expanded Access Program; ESC: Embryonic SC: iPSC: induced pluripotent SC; FDA: Food & Drug Administration; FTD: Frontotemporal dementia; FTLD: Frontotemporal lobar degeneration; JHALS CRC: The Johns Hopkins ALS Center for Cell Therapy and Regeneration Research: JHALS CRC: Johns Hopkins ALS Clinic & Research Center; MC ALSC: Mayo Clinic ALS Center MDA: Muscular Dystrophy Association; MGH: Massachusetts General Hospital; MND: Motor neuron diseases; MOVR: MOVR: neuroMuscular ObserVational Research; NANDSC: National Advisory Neurological Disorders and Stroke Council; NIH: National Institutes of Health; NINDS: (U.S) National Institute of Neurological Disorders and Stroke; PD: Parkinson's disease; SC: Stem cells; SOD: Sodium dismutase;

SITN: (U.K.) Sheffield Institute for Translational Neuroscience; SMA: Spinal Muscular Atrophy; TCD MNDRG: Trinity College Dublin, Motor Neuron Disease Research Group; USC: University of Southern California; UT ALSRP: University of Toronto ALS Research Program; UU ALSRC: Umeå University ALS Research Center.

Keywords

Amyotrophic lateral sclerosis; brain-computer interface; C9orf72 zebrafish; precision amyotrophic lateral sclerosis; profilin 1 mice; SOD1 mice; SOD1-G93A mice; stem cells; TDP43 mice.

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Amyotrophic lateral sclerosis (ALS) often occurs with no clearly associated risk factors and no family history of ALS. Given the typical survival time after symptom onset, time is of the essence. Researchers in the field ought to strive to understand the molecular basis of the clinical heterogeneity in ALS and improve methods for following the trajectory of the disease course, from pre-symptomatic to late symptomatic phases. In tandem with these fundamental biology efforts, clinical therapies should be initiated as early as feasible, including when the earliest symptoms appear. In addition, repositories to collaborate on research tools, protocols, and biospecimens, and other resources will be immensely valuable. The entire ALS community must develop collaborative, openly accessible research infrastructures, bringing together all the valuable data, so it is accessible for exploration by scientists around the world. The field could greatly benefit from the acquisition of multidimensional data collected longitudinally and harmonized to permit data sharing.

Current research projects funded by the American Brain Foundation (ABF), the National Institute of Neurological Disorders and Stroke (NINDS), the ALS Association, the Muscular Dystrophy Association (MDA), and several other advocacy organizations seek to understand the mechanisms that selectively trigger motor neurons to degenerate in ALS and to identify ways to halt the processes leading to cell death. Scientists are also working to develop better biomarkers and tools to diagnose and assess disease progression and the efficacy of treatments.

This article will succinctly cover the development and use of disease models and their role including animal models (rodents) and human cellular models. It will also present the several preeminent research organizations dealing with ALS both in the U.S. and internationally. Lastly, notable latest research developments in the field will be briefly summarized.

Animal disease models and their role

Before a new drug can be tested in humans, researchers must demonstrate that it has the potential to be efficacious and safe. An essential part of this process is to first test the drug in disease models – cells or animals that recreate some aspects of a human disease. A disease model can vary from a single cell to an animal like a mouse or a rat. In addition to testing drugs, these models can also be used to aid research about the biology of a disease. Thus, at the ALS Therapy Development Institute (ALS-TDI), purportedly the world's most comprehensive preclinical drug discovery laboratory focused solely on ALS, all kinds of drug testing are undertaken. A drug may move from early testing in cells provided by smaller animal models like fish and on to mouse models of the disease. Clinical research, cell biology, and pharmacology teams work together closely to make sure that treatments that show potential can move from stage to stage – and model to model – as efficiently and effectively as possible.

Many animal models are created by genetically modifying them to demonstrate symptoms of a disease. However, introducing a human gene mutation into an

animal does not necessarily mean that it will show symptoms of the disease – a necessity for testing if a drug is slowing or stopping those symptoms. Animal models currently in use for drug testing include:

SOD1 mice

In the mid-1990s, researchers discovered that mice genetically modified with a mutated human superoxide dismutase SOD1 gene would go on to develop motor neuron degeneration, muscle weakness, and paralysis like in human ALS. A mutation in this gene is responsible for one of the more common forms of familial ALS. Mutations in the SOD1 gene are thought to cause the protein to misfold and clump up (aggregate) within motor neurons and astrocytes. This allowed researchers to observe whether potential drugs for the disease could slow or stop the progression of these symptoms in an animal model.

Of the several mice models experimented with, the (SOD1-G93A) transgenic model displays the fastest and most aggressive disease progression. This is a major reason it has remained the most common animal model of ALS for over 25 years. The faster a model's symptoms progress, the faster researchers can see whether a treatment is slowing or stopping them, reducing the timeframe for drug testing experiments.

The SOD1 model is used to study presymptomatic pathology of the disease applying multimodal magnetic resonance imaging (MRI). Data indicate that it showed no evidence of copper-zinc superoxide dismutase (CuZnSOD) expression in any tissues and the types of cells involved in ALS development and progression.

However, while SOD1-G93A mouse remains the most used animal model in use for drug testing across the ALS space, there are now many additional tools to model the disease. These include other genetically modified animals like zebrafish as well as mice with other ALS-related mutations.

SOD1-G93A mice

The SOD1-G93A (or G93A-SOD1) transgene was designed with a mutant human SOD1 gene driven by its endogenous human SOD1 promoter. It may be useful in studying neuromuscular disorders such as ALS. Hemizygotes exhibit a phenotype similar to ALS in humans, becoming paralyzed in one or more limbs with paralysis due to loss of motor neurons from the spinal cord and an abbreviated life span.

Profilin 1 mice

Among several cellular functions, profilins are thought to play a central role in the regulation of de novo actin assembly by preventing spontaneous actin polymerization through the binding of actin monomers, and the adding of monomeric actin to the barbed actin-filament ends. Profilins are ubiquitous proteins found in mammals, animal cells, plants, and viruses. In mouse, two profilins are expressed from two distinct genes that are 62% identical. Biochemically, both isoforms are related closely, the major differences between the two isoforms being their distinct expression patterns and their isoform-specific interactions with certain ligands.

Profilin I is expressed at high levels in all tissues and throughout development, whereas profilin II is expressed in neuronal cells. Profilin I is an essential protein that has dosage-dependent effects on cell division and survival during embryogenesis.

However, despite a wealth of biochemical data on profilin function, the in vivo role is still under debate. Whereas profilin I has been suggested as a tumor suppressor, no human diseases linked to profilin have been described and no mouse models are available yet.

TDP43 mice

The transgene expression of the TDP43 mice is confined primarily to the central nervous system (CNS), accumulating in the nuclei of neurons as well as glial cells of the spinal cord and brain with very low to no expression in other tested tissues and a corresponding

downregulation of the endogenous TDP43 mouse. It develops adult-onset motor dysfunction accompanied by a loss of hindlimb-grip strength and the appearance of muscle fasciculations.

C9orf72 zebrafish

Zebrafish are small fish that are widely used in pharmaceutical research to model many diseases. They have been modified with several versions of the C9orf72 mutation. Because of their small size and relatively rapid lifecycle, they represent a "happy medium" between cellular models of the disease and larger animals like mice. They can be used as an intermediary step between these cells and larger animals, allowing drugs to be tested in a model closer to the complex biology of a human, but in a relatively shorter timeframe. This can help to further weed out treatments that would likely fail before dedicating the several months that experiments in a mouse model usually take.

Additionally, these fish provide a chance to study the biology of the C9orf72 mutation — the most common form of familial ALS — in an animal model.

Diseased human cellular models

After a genetic mutation was discovered in a small group of ALS patients, scientists transferred that gene to animals and began to search for drugs that might treat those animals. A neuroscientist at the Waisman Center at UW-Madison (Su-Chun Zhang) has cast doubt on the value of this approach. Instead, he advocates studying diseased human cells in laboratory dishes. Those cells, called motor neurons, direct muscles to contract and are the site of failure in ALS. Zhang grew motor neurons from human embryonic stem cells ESCs) and later updated that approach by transforming skin cells into induced pluripotent stem cells (iPSCs) that were transformed, in turn, into motor neurons. Induced pluripotent stem cells (iPSCs) can be used as "disease models" as they carry many of the same traits as their donor. This approach offers a key advantage over the genetic approach in that it can take a cell from any patient and grow up motor neurons that have ALS, thus offering a new way to look at the basic disease pathology.

Zhang and colleagues have pointed a finger at proteins that build a transport structure inside the motor neurons. Called neurofilament (NF), this structure moves chemicals and cellular subunits to the far reaches of the nerve cell. It combines structural and functional roles. The cargo needing movement includes neurotransmitters, which signal the muscles, and mitochondria, which process energy. If the proteins cannot form correctly and be transported easily, they form tangles that cause a cascade of problems. (Very similar "tangles" appear in Alzheimer's and Parkinson's diseases.) A patient lacking this connection becomes paralyzed; tellingly, the first sign of ALS is often paralysis in the feet and legs.

Scientists have known for some time that in ALS, "tangles" along the nerve's projections that are formed of misshapen protein block the passage along the nerve fibers, eventually causing the nerve fiber to malfunction and die. The core of the new discovery is the source of these tangles - a shortage of one of the three proteins in the neurofilament. It is in the protein subunits that compose the neurofilaments. In other words, the disease ALS is caused by misregulation of one step in the production of the neurofilament.

Research at established centers

There are several major research centers dedicated to ALS worldwide. These centers focus on studying the disease, developing treatments, and conducting clinical trials. Here is a brief description of some of the leading ALS research centers:

In the United States

National Institute for Neurological Disorders and Stroke

Since its establishment in 1950, the National Institute for Neurological Disorders and Stroke (NINDS) has played a pivotal role in unraveling the complexities of the brain and nervous system. The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people. Through groundbreaking research, training the next generation of scientists, working closely with people with lived experience, and improving diagnosis, treatments, and prevention strategies, NINDS continues to lead the way in neuroscience discoveries.

Over the decades, NINDS has made significant advancements in understanding and treating a wide range of neurological disorders including ALS, from breakthroughs in understanding how brain cells communicate with one another to the development of cutting-edge therapies.

In 2024, NINDS conducted a comprehensive and multifaceted process through a Working Group of the National Advisory Neurological Disorders & Stroke Council (NANDSC) to establish strategic priorities for the ALS research community. The culmination of that work has been the development of draft priorities for accelerating research on the biology behind ALS, translating fundamental research into potential ALS therapies, optimizing ALS clinical research, improving the quality of life of persons living with ALS and caregivers, and identifying opportunities for collaborations and partnerships.

Guided by new strategic priorities and through these collective efforts, there is a path forward to advance our understanding of what triggers ALS, what drives its rapid progression, and how we can leverage that knowledge to develop more effective treatments and better the lives of people living with ALS and their families.

ALS Therapy Development Institute (ALS TDI) and ALS Research Collaborative (ALS RC)

ALS TDI is one of the world's largest nonprofit biotech organizations focused solely on ALS research. It conducts preclinical drug development and clinical trials.

In the quest to discover effective treatments for ALS, researchers have long faced a significant challenge: the lack of a widely accessible, shared source of data from people living with the disease. The ALS Research Collaborative (ARC) aims to fill this gap and accelerate global research in ALS by providing scientists with unprecedented access to the data and tools they need to discover new treatments and accelerate progress toward cures for ALS. This ambitious global initiative was developed to better understand the underlying biology of the disease and significantly accelerate the discovery of ALS treatments.

For the above stated purpose, ARC collects natural history data from people with ALS and layers this with additional data that measures their underlying biological processes through omics. This extensive collection of data – that patient participants continue to add to – is made freely accessible to researchers worldwide. Through the ARC Data Commons (ADC), researchers can log in from anywhere in the world and easily search, analyze, and download the wealth of de-identified data. By providing a large, ever-expanding dataset, and powerful tools to filter and visualize the data, scientists are provided with key insights – that previously might have required months or years of research – in a matter of minutes.

This pioneering program utilizes traditional methods for tracking disease progression, like functional assessment

surveys, while also applying cutting-edge accelerometry, digital voice recordings, machine learning technologies, and molecular and cell biology approaches to reveal the processes driving ALS disease progression. All this promises to unlock a clearer understanding of the underlying biology of ALS, with the goal of developing new treatments to slow, stop, or reverse ALS.

Johns Hopkins ALS Clinic & Research Center

The Johns Hopkins ALS Clinic & Research Center (JHALS CRC), located at Johns Hopkins University in Baltimore, Maryland, is one of the most prestigious ALS research and treatment centers in the world. It is also one of the longest-running ALS research programs conducting studies on neurodegenerative disease mechanisms.

The clinic provides exceptional patient care, conducting groundbreaking research, and leading clinical trials to find effective therapies for ALS. Key features are its comprehensive multidisciplinary ALS care. It provides cutting-edge ALS research and clinical trials including novel drug therapies aimed at slowing disease progression, stem cell therapy trials to repair damaged motor neurons, gene therapy studies targeting genetic forms of ALS, immunotherapy, and anti-inflammatory approaches to slow neurodegeneration.

The Center works closely with leading organizations and plays a key role in international ALS research collaborations aimed at developing new treatments.

Johns Hopkins University ALS Center for Cell Therapy and Regeneration Research

The Johns Hopkins ALS Center for Cell Therapy & Regeneration Research (JHALS CCTRR) at Johns Hopkins is committed to identifying the causes of ALS and discovering new and effective treatment options. The Center's research focuses on the use of stem cells to research the disease, drug screening, and cell transplantation, as well as the development of pharmaceuticals for treating ALS. However, the goal is to promote parallel research into ultimately preventing ALS altogether, as well as investigate the regrowth or repair of nervous tissues, cells or cell products affected by the disease.

Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

The Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital (MGH) in Boston, MA, is another one of the world's leading ALS research and treatment centers. It is a major hub for ALS clinical trials and innovative therapies. The Healey ALS Platform Trial is a groundbreaking approach to ALS clinical trials. Instead of testing one drug at a time, the platform trial allows multiple drugs to be tested simultaneously, speeding up the research process. This model reduces time, costs, and the number of placebo participants compared to traditional trials. The trial is conducted at 54 sites across the U.S., making participation accessible to more patients.

The Healey Center conducts cutting-edge research in: Gene therapy, stem cell therapy, biomarker discovery, neuroinflammation studies, understanding the role of inflammation in ALS progression, and drug repurposing. It is also one of the largest ALS clinical trial sites in the world.

Mayo Clinic ALS Center

The Mayo Clinic ALS Center (MC ALSC) is another leading institution in the research and treatment of ALS. It operates across three main campuses in the U.S.: Rochester, Minnesota; Jacksonville, Florida; and Scottsdale, Arizona. It conducts cutting-edge genetic and biomarker research to improve ALS diagnosis and treatment, focusing on familial (genetic) ALS (fALS) cases, identifying disease subtypes to create targeted

therapies, engaging in drug development and testing for potential ALS treatments, and offering stem cell therapy and gene therapy trials for eligible patients. It studies how genes like C9orf72, SOD1, FUS, and TDP-43 contribute to ALS.

Duke ALS Clinic & Research

The Duke ALS Clinic & Research Center (DALS CRC), based at Duke University Medical Center in Durham, North Carolina, is a leading institution dedicated to treating ALS patients and conducting cutting-edge research to find new therapies.

It is recognized as a Certified ALS Center of Excellence by the ALS Association, offering state-of-the-art care and innovative clinical trials. It is home to several innovative research projects on ALS biomarkers and treatment.

DALS CRC is a leader in new drug therapies targeting ALS progression, stem cell and gene therapy approaches, neuroinflammation studies to understand the immune system's role in ALS, and neuroprotective strategies to slow disease onset.

Barrow Neurological Institute ALS Center

The Barrow Neurological Institute ALS Center (BNI ALSC), located in Phoenix, Arizona, is a leading research and treatment facility dedicated to ALS. The Center is known for its advanced research in ALS genetics and therapeutics and groundbreaking research into the causes and potential treatments for ALS.

It conducts cutting-edge ALS clinical trials, testing new drug therapies to slow disease progression, stem cell therapy and gene therapy treatments, neuroinflammation studies to understand the role of the immune system in ALS, and neuroprotective strategies to slow motor neuron degeneration.

Columbia University Eleanor and Lou Gehrig ALS Center

The Columbia University Eleanor and Lou Gehrig ALS Center (CUG ALSC), located at Columbia University Irving Medical Center in New York City, is one of the leading ALS research and treatment centers in the world. The center conducts groundbreaking research and advancing clinical trials to find new therapies for ALS. It focuses on ALS genetics, drug discovery, and clinical trials.

The Center conducts advanced clinical trials to explore new ALS treatments, including novel drug therapies targeting motor neuron degeneration, gene therapy trials for genetic forms of ALS, stem cell research to repair damaged neurons, and neuroinflammation and immune system studies to understand ALS progression. Its generic and biomarker research focuses on familial (genetic) ALS cases and the role of mutations such as C9orf72, SOD1, FUS and TDP-43. It develops biomarkers to improve early ALS diagnosis and track disease progression.

International

(U.K.) Sheffield Institute for Translational Neuroscience (SITN)

The Sheffield Institute for Translational Neuroscience (SITN) is a leading research center dedicated to combating neurodegenerative diseases, including ALS. It integrates basic scientists and clinicians to understand disease mechanisms and develop new treatments.

One of its significant research focuses is on genetic therapies for motor neuron diseases (MND). The Institute has identified groundbreaking genetic therapies using disease models and producing promising results. For instance, SITN researchers have been involved in developing M102, a potential ALS treatment. In addition to genetic therapies, SITN has partnered with

Metabolon to utilize its metabolomics platform to profile plasma and cerebrospinal fluid (CSF) from patients with MNDs. motor neuron disease with aim to uncover novel pathogenic mechanisms of ALS, potentially expanding therapeutic options.

Trinity College Dublin, Motor Neuron Disease Research Group (TCD MNDRG)

Trinity College Dublin (TCD) hosts a prominent Motor Neuron Disease (MND) Research Group dedicated to advancing the understanding and treatment of ALS. Key research initiatives include:

- **Precision ALS:** This program aims to harness artificial intelligence (AI) to analyze extensive clinical data. The goal is to facilitate personalized treatment approaches for ALS patients by integrating clinicians, computer scientists, and data analysts.
- **Population-based genetic research:** The MND research group contributes to a global effort to sequence the genomes of 15,000 ALS patients and 7,500 control subjects. This large-scale genetic analysis seeks to identify mutations responsible for ALS, paving the way for targeted interventions.
- **Clinical and cognitive phenotyping:** The MND research group has conducted pioneering studies on the cognitive and behavioral aspects of ALS, enhancing the understanding of disease progression and patient care needs.
- **Collaborations and clinical services:** The group collaborates with various international consortia, including the European Network for the Cure of ALS (ENCALS) and Treatment Research Initiative to Cure ALS (TRICALS), to advance clinical research and trials. The national ALS clinical service, co-located between Beaumont Hospital and TCD, provides comprehensive multidisciplinary care to patients across Ireland, integrating clinical services with cutting-edge research.

University of Toronto ALS Research Program (UT ALSRP) – Canada

The University of Toronto (U of T) is at the forefront of ALS research, collaborating with affiliated institutions to advance understanding and treatment of this neurodegenerative disease. It incorporates the Sunnybrook Health Sciences Center ALS Clinic and the Focused Ultrasound Research (SHSC ALSCFUR), which pilots a clinical study to enhance the delivery of therapeutic agents to the brain with aim to improve treatment efficacy for ALS patients by temporarily opening the blood-brain barrier and facilitating targeted therapy delivery.

Umea University ALS Research Center (UU ALSRC) – Sweden

The ALS Research Center at Umeå is a leading institution dedicated to understanding and treating ALS. Key research areas include:

- **Biobank:** The development of Sweden's largest biobank for ALS research, supporting extensive studies into the disease's mechanisms.
- Genetic research: Focused on the role of protein aggregates, particularly the SOD1 protein, in ALS progression.
- **Innovative gene therapy:** It targets SOD1 protein, significantly slowing the disease progression in a patient with an aggressive form of ALS.

Latest research developments

From the (U.S.) National Health Institutes (NIH)

ALS is a rare but devastating neurological disease wherein misfolded proteins build up within motor neurons—the nerve cells in the brain and spinal cord that control voluntary muscle movement. The inability to clear this toxic protein buildup leads to muscle weakness, paralysis, and eventually death. Some cases of ALS are caused by known, inherited genetic

mutations. But most are from sporadic, unknown causes. Rather than target each genetic cause of ALS, NIH (National Institutes of Health) researchers and their affiliates have been seeking treatments that could be used across different types. A research team from the University of Southern California (USC), Los Angeles, has been searching for cellular processes that could be manipulated to treat ALS regardless of the genetic drivers of a person's disease. They found that compounds that blocked a protein called PIKFYVE kinase - a small molecule called Apilimod, extended the lives of ALS motor neurons. They subsequently tested Apilimod in motor neurons with many different drivers of ALS using several genetic methods to shut down PIKFYVE. All methods of PIKFYVE inhibition extended the lives of the various ALS neuron types tested. Further work teased out the cellular mechanisms responsible for this protective effect. The researchers found that inhibiting PIKFYVE helped neurons clear misfolded, toxic proteins. This happened because a waste-removal process called exocytosis became activated when PIKFYVE was shut down. The toxic version of a protein called TDP-43 has been linked to ALS and other neurodegenerative diseases (NDDs). This protein was effectively cleared from the cells through exocytosis after PIKFYVE was inhibited.

Next, the USC team screened a library of almost 2,000 approved drugs and other compounds for their ability to extend the life of ALS motor neurons. They found that some of the most promising compounds altered cellular signaling driven by hormones called androgens (such as testosterone) in the body.

The long-term manipulation of such hormones may have unwanted side effects. So, the researchers searched for other targets that altered gene activity levels in similar ways in motor neurons. Their top candidate was called SFY2. The team found that suppressing SYF2 levels using genetic techniques increased survival in most types of ALS motor neurons tested, including those that accumulate toxic TDP-43.

From the (U.S.) National Institute for Neurological Disorders & Stroke (NINDS)

Advances are being made along the following streams.

• **Cellular defects:** Ongoing studies seek to understand the mechanisms that selectively trigger motor neurons to degenerate in ALS, which may lead to effective approaches to stop this process. Research using cellular culture systems and animal models suggests that motor neuron death is caused by a variety of cellular defects, including those involved in protein recycling and gene regulation, as well as structural impairments of motor neurons. Increasing evidence also suggests that glial support cells and inflammation cells of the nervous system may play an important role in ALS.

• **Stem cells:** These cells are being used to grow human spinal cord sections on tissue chips to help better understand the function of neurons involved in ALS.

• **Genetics:** Scientists are investigating ALS symptoms changes over time in people with C9orf72 mutations. Other studies are working to identify additional genes that may cause or put a person at risk for either familial or sporadic ALS. Together with other collaborators, they are analyzing genetic data from thousands of individuals with ALS to discover new genes involved in the disease. By using novel gene sequencing tools, they are now able to rapidly identify new genes in the human genome involved in ALS and other neurodegenerative diseases.

• **Epigenetics:** Additionally, researchers are looking at the potential role of epigenetics in ALS development. Epigenetic changes can switch genes on and off during a person's lifetime, which can greatly impact both health and disease. Although this research is exploratory, scientists hope that understanding epigenetics can offer new information about how ALS develops.

• **Biomarkers:** Research is conducted on the development of biomarkers which can be molecules derived from a bodily fluid (blood or cerebrospinal fluid), an image of the brain or spinal cord, or a

measure of the ability of a nerve or muscle to process electrical signals. ALS biomarkers can help identify the rate of progression and the effectiveness of current and future therapies.

From the Mayo Clinic

The Mayo Clinic (MC) reported two significant announcements:

• **Potential key role of an immune molecule in ALS progression:** Mayo Clinic researchers and collaborators have identified a protein expressed by immune cells that may play a key role in the development of ALS. The protein, known as α5 integrin is expressed by microglial cells (immune cells specific to the nervous system) and macrophages (general immune system "cleanup" cells present in the peripheral nervous system), which have pro-inflammatory properties. It is present in abundance in the motor system in people with ALS, including in those with a genetic cause of the disease. An immunomodulatory treatment that blocks the protein was able to restore motor function in preclinical models.

• **A new experimental drug:** This is an innovative study that will provide hundreds of ALS patients access to the experimental drug Ibudilast over six months. The (U.S.) FDA had granted Expanded Access Program (EAP) status to the study. This program offers a pathway for patients with a serious or life-threatening disease or condition to gain access to an investigational medical product (drug, biologic or medical device) for treatment outside of a clinical trial when no effective therapy options are available.

From the American Brain Foundation

The American Brain Foundation (ABF) has awarded Next Generation Research Grants to researchers studying frontotemporal dementia (FTD), which has many similarities to ALS, specifically frontotemporal lobar degeneration (FTLD), which is responsible for 10-20% of all dementia cases. One study will explore why FTLD symptoms vary for different people, and why the age of onset also varies. Another study is analyzing blood and spinal fluid samples to learn more about a gene mutation associated with FTLD to better understand the disease's progression and identify biomarkers. Because the diseases are linked, discoveries about FTD can also lead to advancements for ALS.

Other developments

Recent advances in ALS research include the FDA approval of Tofersen (Qalsody) for SOD1-ALS, a gene, and the identification of biomarkers for predicting treatment response, along with ongoing research into gene therapies for sporadic ALS and other neuromuscular diseases. Here's a more detailed look at the latest advancements:

• **Tofersen (Qalsody) approval:** In 2023, the FDA approved Tofersen (Qalsody), an antisense oligonucleotide (ASO) therapy, for treating ALS associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

• **Biomarkers for treatment response:** Researchers have identified a biomarker that predicts clinical response to Tofersen using a blood test, paving the way for more efficient drug screening and treatment selection.

• **Gene therapy for sporadic ALS (sALS):** Researchers are working to identify genes associated with sALS, which accounts for most ALS cases, to develop gene therapies for that form of the disease.

• **Potential for other neuromuscular diseases:** The research into ALS may also lead to gene therapies for other neuromuscular diseases like FTD and spinal muscular atrophy (SMA), which share similar disease mechanisms.

• **Stem cell research:** Stem cell therapies are being investigated for their potential to modulate the immune system and reduce inflammation, which may be

beneficial in managing ALS progression.

• **Brain-computer interface technology:** New brain-computer interface technology can translate brain signals into speech with high accuracy, offering potential for communication and assistive technologies for people with ALS.

• **MOVR data hub:** The Muscular Dystrophy Association (MDA) launched the MOVR (neuroMuscular ObserVational Research) Data Hub to capture and aggregate clinical data from its Care Center Network (CCN), accelerating the development of new treatments and improving health outcomes for patients with neuromuscular diseases.

• **New drug candidates:** Researchers are investigating new drug candidates, such as ASHA-624, which is currently in the preclinical stage with plans to enter clinical trials in early 2025.

• **Potential for halting or reversing ALS progression:** Research is ongoing to understand the mechanisms that cause motor neuron degeneration in ALS and to find effective ways to halt or reverse the disease's progression.

• **Focus on protein interactions:** Recent studies have focused on targeting interactions between proteins involved in ALS to prevent nerve cell death.

• **Omega-3 fatty acids:** Some studies suggest that consuming omega-3 fatty acids, particularly alpha-linolenic acid (ALA), may help slow the progression of ALS.

Future developments

Being a syndrome with low incidence and short survival, most recommendations are GCPPs based on the consensus of experts in the field of ALS. Further randomized and double-blind clinical trials are urgently needed to improve the management of ALS.

Research recommendations

1. Further studies of biomarkers (imaging, blood and cerebrospinal fluid proteomics and metabolomics, neurophysiological markers) to aid earlier specific ALS diagnosis and to monitor possible effects in clinical trials.
2. Further studies of the impact of specialist MND clinics on clinical outcomes, quality of life, and carer burden.
3. Further studies to optimize the symptomatic treatment of muscle cramps, drooling, and bronchial secretions in patients with ALS.
4. Better criteria for defining the use of percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG), non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV).
5. Further studies to evaluate the effects of PEG/PRG, cough-assisting devices and ventilation support on quality of life and survival.
6. Further studies to evaluate language dysfunction and its treatment in ALS.
7. Systematic studies to assess cognitive impairment and the frequency of frontal lobe dysfunction in ALS and to standardize clinical, neuropsychological and neuroradiological methods in this field. Future ALS diagnostic criteria should include parameters regarding cognitive dysfunction and dementia.
8. Studies of the medico-economic impact of more expensive procedures (NIV, IMV, cough-assisting devices, advanced communication equipment).
9. Further studies to harmonize the patient databases of ALS centers.
10. Further studies on the psychosocial and spiritual determinants of quality of life in patients and their family caregivers are needed, as well as studies on the prevalence of, and determinants for, wishes for a hastened death.

Conclusions and take-aways

- Current research projects seek to understand the mechanisms that selectively trigger motor

neurons to degenerate in ALS and to identify ways to halt the processes leading to cell death. Scientists are also working to develop better biomarkers and tools to diagnose and assess disease progression and the efficacy of treatments.

- Before a new drug can be tested in humans, researchers must demonstrate that it has the potential to be efficacious and safe. An essential part of this process is to first test the drug in disease models - cells or animals that recreate some aspects of a human disease. A disease model can vary from a single cell to an animal like a mouse or a rat. In addition to testing drugs, these models can also be used to aid research about the biology of a disease.

- Many animal models are created by genetically modifying them to demonstrate symptoms of a disease. However, introducing a human gene mutation into an animal does not necessarily mean that it will show symptoms of the disease - a necessity for testing if a drug is slowing or stopping those symptoms.

- Animal models currently in use for drug testing include SOD1 mice, SOD1-G93A mice, Profilin 1 mice, TDP43 mice, and C9orf72 zebrafish.

- Using human embryonic stem cells or skin-induced pluripotent stem cells transformed, in turn, into motor neurons can be used as disease models.

- ALS may be caused by mis-regulation of one step in the production of the neurofilaments - the shortage of one of the three proteins that compose the neurofilaments.

- The several preeminent ALS research centers in the U.S. and worldwide have been presented.

- The latest developments in ALS research have been summarized.

- Recommendations have been provided for future research.

Sidebar 1 - A path forward: Strategic priorities for ALS

In 2022, the (U.S.) National Institute for Neurodegenerative Diseases and Stroke (NINDS) conducted a comprehensive and multifaceted process through a Working Group of the (U.S.) National Advisory Neurological Disorders & Stroke Council (NANDCS) to establish priorities for the ALS research community. Comprised of scientists, clinicians, people living with ALS, people with genetic risk for ALS, and caregivers, the Working Group explored the landscape of ALS and engaged the ALS community. The culmination of their work has been the development of draft priorities for accelerating research on the biology behind ALS, translating fundamental research into potential ALS therapies, optimizing ALS clinical research, improving the quality of life of persons living with ALS and their caregivers, and identifying opportunities for collaborations and partnerships.

It identified the most promising priorities for research that may lead to the discovery of effective interventions for the diagnosis, management, treatment, prevention, or cure of ALS. The engagement, experiences, and insights shared by the ALS community greatly enhanced and strengthened the Working Group's efforts and recommendations.

The NINDS report highlighted the following:

- The urgency for progress in ALS research. The

disease often occurs with no clearly associated risk factors and no family history of ALS. Given the typical survival time after symptom onset, the clock is ticking, and quickly.

- The field must understand the molecular basis of clinical heterogeneity in ALS and improve methods for following the trajectory of the disease course, from pre-symptomatic to late symptomatic phases. In tandem with these fundamental biology efforts,

- Clinical therapies should be initiated as early as feasible, including when the earliest symptoms appear. In addition,

- Repositories to collaborate on research tools, protocols, and biospecimens, and other resources will be immensely valuable.

- The entire ALS community must develop collaborative, openly accessible research infrastructures, bringing together all the valuable data, so it is accessible for exploration by scientists around the world. The field could greatly benefit from the acquisition of multidimensional data, collected longitudinally and harmonized to permit data sharing. Also:

- Attending to quality of life in ALS is of paramount importance, as is improving access to information about ALS and options for participating in clinical research and therapeutic trials.

These new strategic priorities will be addressed in several ways with the goal to facilitate many ongoing and future efforts to enable the identification of biomarkers to diagnose ALS as early as possible, to gauge disease progression, discover new targets for highly effective therapies, and utilize expanded access for investigational drugs or biological products for individuals who are not otherwise eligible for clinical trials in ALS.

Guided by these new strategic priorities and through these collective efforts, there is a path forward to advance our understanding of what triggers ALS, what drives its rapid progression, and how we can leverage that knowledge to develop more effective treatments and better the lives of people living with ALS and their families.

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