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REVIEW ARTICLE

Development of novel treatments for amyotrophic lateral sclerosis

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Abstract
Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that causes paralysis whose etiology and pathogenesis have not been fully elucidated. Presently it is incurable and rapidly progressive with a survival of 2–5 years from onset, and no treatments could cure it. Therefore, it is urgent to identify which therapeutic target(s) are more promising to develop treatments that could effectively treat ALS. So far, more than 90 novel treatments for ALS patients have been registered on ClinicalTrials.gov, of which 23 are in clinical trials, 12 have been terminated and the rest suspended. This review will systematically summarize the possible targets of these novel treatments under development or failing based on published literature and information released by sponsors, so as to provide basis and support for subsequent drug research and development.

Keywords Rare Disease · Clinical trials · Therapeutic target(s)

Introduction

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease, which the global incidence of 2–3/100,000 population over the age of 15 year (Tiryaki and Horak 2014; Kukharsky et al. 2021; Ustyantseva et al. 2020; Al-Chalabi and Hardiman 2013). Extensive loss of lower motor neurons in the anterior horn of spinal cord and brainstem is the main neuropathological feature of ALS (Grad et al. 2017). However, the specific pathogenesis is still unclear. ALS typically occurs in adults and presents as a relentlessly advanced loss of motor function and ultimately death, due to respiratory failure (Grad et al. 2017). Presently it is incurable and rapidly progressive with a mean survival of 2-5y from onset (Tiryaki and Horak 2014; Kukharsky et al. 2021; Ustyantseva et al. 2020; Grad et al. 2017). Thus, for most patients, ALS is a disease with short survival and poor prognosis.

Currently, there is no effective therapy available for ALS patients, only seven well-recognized disease-modify drugs. Three dosage of riluzole,, including tablet (Rilutek), suspension (Tiglutik) and oral film (Exservan), as well as edaravone (Radicava) and Nuedexta, have been approved for the treatment of ALS and its associated symptoms (Jaiswal 2019; Miller et al. 2012; Rothstein 2017). Riluzole, a glutamate antagonist, prolongs the patient survival of ALS patients by about 3 months. Edaravone, is a free radical/reactive oxygen species (ROS) scavenger, and improves the patient symptoms slightly. Nuedexta only improved swallowing function in patients in some degree. Relyvrio (oral fixed dose formulation of sodium phenylbutyrate and ursodoxicoltaurine, AMX0035), was approved for marketing in Canadian and the United States which playing a role by improving the health of endoplasmic reticulum and delaying the death of nerve cells. After a three-year follow-up of 137 patients with ALS, patients on active drug which compared with historical placebo groups from other trials, and this post-hoc analysis showed that the median survival time

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in the relyvrio group was 6.5 months longer than in these placebo groups (25.0 months vs. 18.5 months). Currently, a phase III clinical trial (Phoenix), is well underway, and this will establish whether relyvrio has a disease modifying effect (Paganoni et al. 2021). Subsequently, Qalsody (tofersen) has been approved by U.S. Food and Drug Administration (FDA), which can reduce SOD1 protein synthesis by promoting degradation of SOD1 messenger RNA. According to its phase III results, there was 38% and 26% difference in CSF total SOD1 proteins between the tofersen and placebo groups in patients with faster and slower progression, respectively. Plasma Nfl, a potential marker of neurodegeneration, differed 67% and 48% between the tofersen group and the placebo group in patients with faster and slower progression (Vacchiano et al. 2021). The efficacy of tofersen also needs phase III clinical trial (ATLAS) to further prove, and the drug is only suitable for ALS patients with SOD1 mutations (only 2% of 68,000 patients worldwide).

It may be due to the fact that the pathological mechanism underlying neurodegeneration in ALS are multifactorial and may function through interconnected molecular and genetic pathways. To be specific, neurodegeneration in ALS may be caused by a complex interaction of glutamate excitoxicity, generation of free radicals, cytoplasmic protein aggregates, superoxide dismutase1 (SOD1) enzymes, combined with mitochondrial dysfunction, and disruption of axonal transport processes through accumulation of neurofilament intracellular aggregates (Feldman et al. 2022). However, it is not clear which pathway is the key to the disease, and the drugs that on the clinical trial may target non-critical pathways and therefore have not shown efficacy. Therefore, there is still an urgent need to determine the key pathogenic mechanism and develop new therapeutic methods for the treatment of ALS. According to ClinicalTrials.gov and literature retrieval website (including PUBMED, Embase and Web of Science), we have selected 23 ongoing novel treatments (excluding old drugs for new approaches) with ALS as an indication, including innovative small molecule drugs, biological drugs, genetic therapies, cell therapies and non-drug approaches (Table 1). At present, 4 trials of these (17%) in the Phase I, 11 trials of these (48%) in the Phase II and 8 trials of these (35%) in the Phase III (Fig. 1A). Most of clinical trials for ALS are still in the Phase I and II, with some progressing to Phases III, possibly for four reasons below. First of all, the pathogenesis of ALS disease is multifarious, cellular and animal models that can characterize ALS disease cannot be constructed, and the efficacy results in the current models are not sufficient to predict the efficacy in heterogeneous human patients. Secondly, due to the unclear pathogenesis of ALS, effective drug targets for ALS cannot be determined at present. Researchers can only speculate about the mechanism and try different targets, some of which are low quality, and thus have a high failure rate. Thirdly, clinical trial design still has some drawbacks. There are many reasons for the onset of ALS, including genetic, environmental or age-related dysfunction. Different factors lead to different pathogenic mechanisms. In the early stage of clinical trials, it is impossible to distinguish different patient subgroups according to genetic background or other pathogenic factors, resulting in poor efficacy outcomes of drugs. Finally, clinical trials should reasonably use biomarkers as secondary endpoints of efficacy, including neurofilament heavy chain or neurofilament light chain (Nfl) et al.,. The results of biomarkers may provide a reference when primary efficacy indicators (such as survival time, etc.) are not met the requirements in clinical trials. However, whether biomarkers can independently be used as indicators to predict the efficacy of drugs for ALS remains controversial.

To clarify the probably pathogenesis of ALS disease and find possible targets for different patient subgroups is a reliable way to break the bottleneck of ALS treatment. This review will focus on summarizing novel treatments in clinical trials or terminations for ALS based on the possible signaling pathways of drugs action (Figs. 1B and 2). Meanwhile, under the corresponding potential targets, preclinical drugs with good effects will also be introduced, so as to analyze the future development prospects of the potential targets and provide ideas for the selection of them for subsequent drug development.

Genetic therapies (antisense oligonucleotide (ASO) therapies)

There are two types of ALS patients: familial amyotrophic lateral sclerosis (fALS) and sporadic ALS (sALS). The overall pooled mutation frequencies of ALS-related genes were 47.7% in fALS and 5.2% in sALS. In European populations, the most common mutations were the chromosome 9 open reading frame 72 (*C9orf72*) repeat expansions (fALS 33.7%, sALS 5.1%), followed by SOD1 (fALS 14.8%, sALS 1.2%), TARDNA-binding protein of 43 kDa (TDP43) (fALS 4.2%, sALS 0.8%) and fused-in-sarcoma (FUS) mutations (fALS 2.8%, sALS 0.3%) (Hardiman and Berg 2020). Therefore, gene targeting therapy, which reduces the mRNA level of the above proteins, may be a feasible approach. In 1993, the first gene associated with familiar ALS (fALS), SOD1 was discovered by a team of researchers at the University of Massachusetts Medical School. SOD1 is an antioxidant enzyme, which can directly participate in the inactivation of toxic superoxide radicals by binding copper and zinc ions, so as to protect cells from the damage of superoxide radicals (Kaur et al. 2016; Hayashi et al. 2016). Mutated SOD1 gene can obtain gain and loss of function mutations, and

Table 1 The Overview of innovative drugs that are currently being tested in clinical trials

	Drug	Suspected mechanism	Year of drug development	Category	Route of administration	Phase	ClinicalTrials.gov Identifier	Status	Sponsor
1	ISIS 333611	Reduce SOD1 protein synthesis (Medical Advisory Secretariat 2021)	2009	genetic therapies	IT	I	NCT01041222	Completed	Ionis Pharmaceuticals, Inc.
2	ION363	Reduce fused in sarcoma (FUS) protein production (Korobeynikov et al. 2022)	2021	genetic therapies	IV	III	NCT04768972	Recruiting	Ionis Pharmaceuticals, Inc.
3	WVE-004	Protect C9orf72 protein (Liu et al. 2022)	2021	genetic therapies	IT	I/II	NCT04931862	Recruiting	Wave Life Sciences Ltd.
4	SLS-005 Trehalose	Increase TDP-43 clearance and reduce SOD1 polymers and monomers	2020	Biological drug	IV	II/III	NCT05136885/ NCT04297683	Recruiting /Enrolling by invitation	Merit E. Cudkowicz, MD
5	GDC-0134	Dual leucine zipper kinase (DLK) inhibitor (Katz et al. 2022)	2016	Small-molecule drug	PO	I	NCT02655614 NCT03237741	Completed	Genentech, Inc.
6	RT001	Tender mitochondria and cell membranes resistant to lipid peroxidation (Yerton et al. 2022)	2021	Small-molecule drug	PO	II	NCT04762589	Recruiting	Retrotope, Inc.
7	Verdiperstat	Myeloperoxidase inhibitor (Jiang et al. 2022)	2020	Small-molecule drug	PO	II/III	NCT04436510	Active, not recruiting	Merit E. Cudkowicz, MD
8	Pridopidine	Sigma-1 receptor agonist (Ionescu et al. 2019)	2020	Small-molecule drug	PO	II/III	NCT04615923	Active, not recruiting	Merit E. Cudkowicz, MD
9	NP001	Regulating inflammatory cells (Zhang et al. 2022; Miller et al. 2022a)	2010	Small-molecule drug	IM	II	NCT01281631 NCT02794857	Completed	Neuraltus Pharmaceuticals, Inc.
10	3K3A-APC Protein	Genetically modified version of a human blood protein called activated protein C (APC) (Shi et al. 2019)	2021	Biological drug	IV	II	NCT05039268	Completed	Macquarie University, Australia

Table 1 (continued)

	Drug	Suspected mechanism	Year of drug development	Category	Route of administration	Phase	ClinicalTrials.gov Identifier	Status	Sponsor
11	MN-166	Phosphodiesterase 4 inhibitor (Babu et al. 2021)	2014	Small-molecule drug	PO	II/III	NCT04057898	Recruiting	MediciNova
12	AL001	increase the level of pregranulin in the brain (Rhinn et al. 2022)	2021	Biological drug	IV	II	NCT05053035	Active, not recruiting	Alector Inc.
13	BLZ945	colony stimulating factor-1 receptor (CSF-1R) inhibitor (Pognan et al. 2022)	2019	Small-molecule drug	PO	II	NCT04066244	Recruiting	Novartis Pharmaceuticals
14	NurOwn	1. Cell differentiation, 2. Delivery of nutrient factors,	2017	Cell therapy	IT	III	NCT03280056	Completed	Brainstorm-Cell Therapeutics
15	Intrathecal autologous stem cell	3. Immune regulation, 4. Homing, 5. Exosome secretion. (Gothelf et al. 2014; Petrou et al. 2021; Bonafede and Mariotti 2017)	2013		IT	II/III	NCT01933321	Completed	Hospital Universitario Dr. Jose E. Gonzalez
16	Reldesemtiv	Increases skeletal muscle contractility (Shefner et al. 2021)	2020	Small-molecule drug	PO	III	NCT05442775	Recruiting	Cytokinetics
17	ILB	Produce hepatocyte growth factor(HGF) protein (Logan et al. 2022)	2018	Biological drug	SC	II	NCT03705390	Completed	University of Birmingham
18	VM202	Produce HGF protein (Sufit et al. 2017)	2014	Biological drug	IM	I/II	NCT02039401	Completed	Helixmith Co., Ltd.
19	MD1003	Increase in oligodendrocytes (OGs) (Juntas-Morales et al. 2020)	2017	Small-molecule drug	PO	II	NCT03114215	Completed	MedDay Pharmaceuticals SA
20	GSK1223249	Neurite outgrowth inhibitor (Meininger et al. 2017)	2009	Biological drug	IV	II	NCT00875446	Completed	Glaxo-Smith-Kline

Table 1 (continued)

	Drug	Suspected mechanism	Year of drug development	Category	Route of administration	Phase	ClinicalTrials.gov Identifier	Status	Sponsor
21	High-Caloric Nutrition	Increasing body mass index and keep the levels of circulatory hormones stable (Kawahara and Kwak 2005; Funakoshi et al. 2007)	2019	/	PO	I	NCT04172792	Completed	Albert Christian Ludolph, Prof.
22	QRL-201	The expression of STATHMIN-2 (STMN2) was restored	2023	Biological drug	IT	I	NCT05633459	Recruiting	QurAlis Corporation
23	GM604	Regulates developmental neurogenesis pathways (Kindy et al. 2017)	2013	Peptide drug	IV	II	NCT01854294	Completed	Genervon Biopharmaceuticals, LLC

The table summarizes specific information about the drugs for ALS under development

Notes: IT: Intrathecal; IV: Intravenous; PO: Oral; SC: Subcutaneous; IM: Intramuscular; IP: Intraspinal; /: Unknown

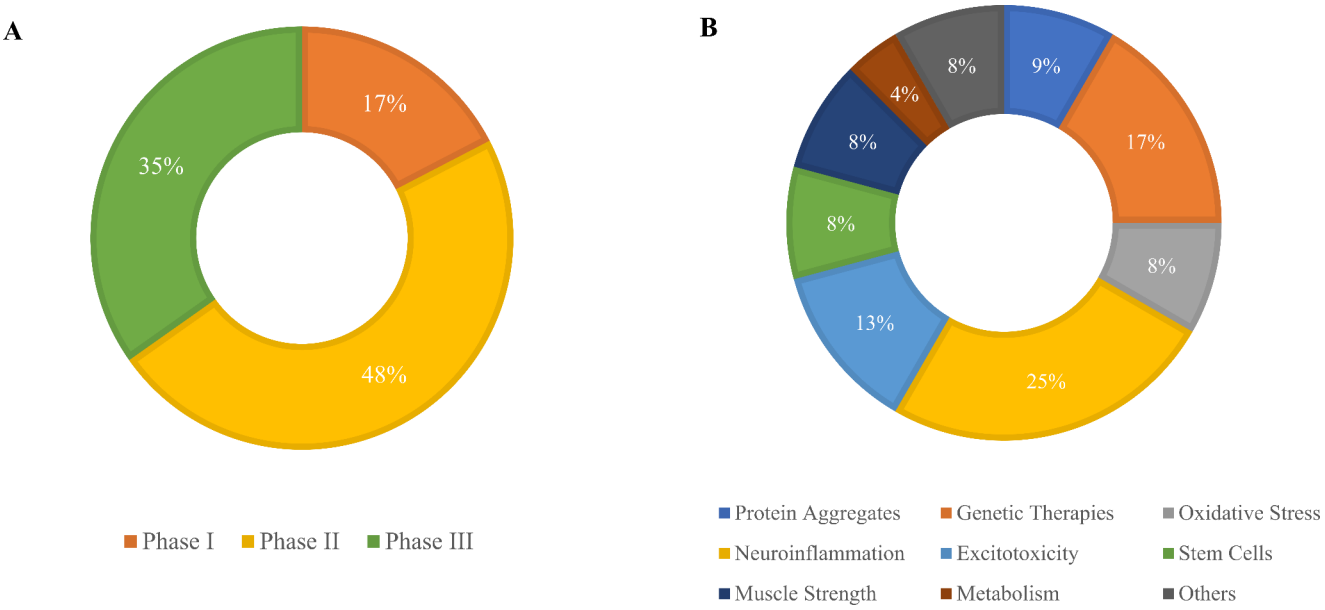

Fig. 1 Distribution of novel treatments under development in different phases (**A**) and different pathways (**B**). Different colors represent different clinical trial phases (phase I, I, III) of drugs. The area of each color graph represents the proportion of drugs at different phases to the total number of ALS treatments under development (**A**); Different colors represent different targets of treatments. The area of each color graph represents the proportion of drugs acting on different targets to the total number of ALS treatments under development (**B**)

the functional toxic gain is the main part (Kaur et al. 2016; Miller et al. 2013). Tofersen is an intrathecally administered ASO, that worked primarily by inhibiting the gain of toxicity from the mutant SOD1.

WVE-004 is a stereopure oligonucleotide designed to selectively target transcriptional variants containing the *C9orf72* gene-associated hexanucleotide repeat expansion (G4C2), thereby leaving the C9orf72 protein intact (Phase I/II, NCT04931862) (Liu et al. 2022). However, phase I

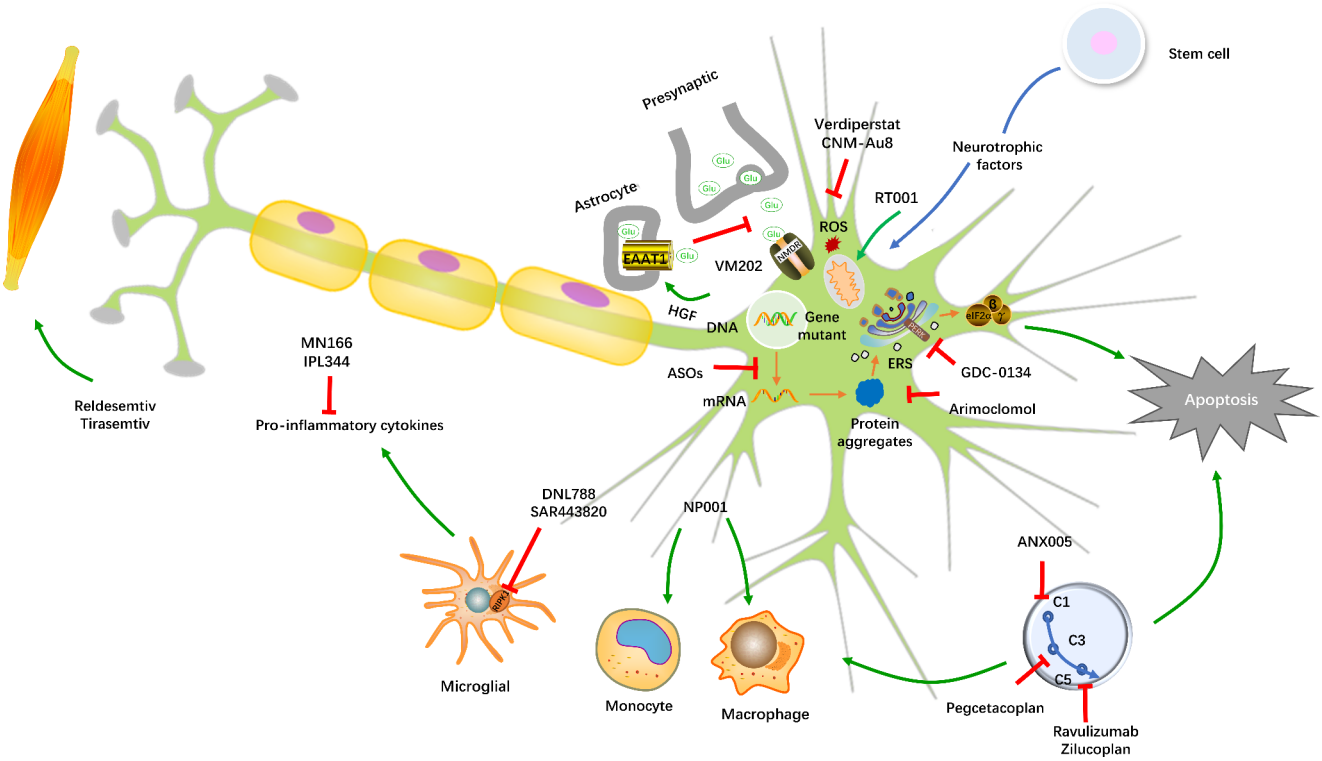

Fig. 2 Mode of action of the drugs presented in this review. Red T-shaped arrow: inhibit; blue, green, and orange arrows: active

results of BIIB078, an ASO in development for the treatment of C9orF72-associated ALS, showed no clinical benefit and the company decided to terminate the clinical trial. More insight is needed why them had poor efficacy, may be due to the late treatment, which targeted only one chain, rather than the reverse stand of C9orf72. There were indications that C9orF72-associated ALS and frontotemporal dementia (FTD) was in part also a developmental disease (e.g. very early other abnormalities can be found like lower body mass index (BMI), or magnetic resonance imaging (MRI) changes without having ALS or FTD) (Table 1) (Nolan et al. 2016; Nolan et al. 2016; Pang and Hu 2021). So further trials are needed to verify if including some early-stage patients in the trial will make a difference. FUS is an RNA-binding protein with 526 amino acids encoded by 15 exons. It belongs to the FUS/EWSR1/TAF15 (FET) family and contains a few different functional domains, including RNA recognition motifs and highly conserved C-terminal nuclear localization signals. *FUS* gene mutations were considered to be a pathogenic factor in a few cases of ALS in 2009 (Nolan et al. 2016). ION363 is an ASO targeting FUS RNA that reduces FUS protein production. Antisense-mediated reduction of mutant FUS proteins prevents motor neuron loss in a mouse model of FUS-associated ALS (Korobeynikov et al. 2022). By targeting the underlying cause of FUS-associated ALS, ION363 has the potential to reduce or prevent disease progression in patients, and a Phase III trial is currently underway (NCT04768972). In addition to ASO, which directly reduces the mRNA level of the above protein, has achieved some effect, ASO, which reduces the toxicity of the toxic protein, is also being further verified. TDP-43 is a nucleic acid binding protein that exists mainly in the nucleus but can travel between the cytoplasm and the nucleus. However, TDP-43 mistakenly self-aggregates in the cytoplasm of motor neurons in ALS patients, causing toxicity. We also found that overexpression of the yeast ortholog human Ataxin-2 (ATXN2) enhanced TDP-43 toxicity, while null mutation of ATXN2 ortholog suppressed TDP-43 toxicity (St Martin et al. 2020). Drugs that target it are being developed. Moreover, dysfunction of TDP-43 leads to missplice of the precursor mRNA of the stathmin-2 (STMN2) gene, which leads to loss of STMN2 protein (required for axon regeneration), as well as further loss of motor ability and paralysis specific to ALS. QRL-201, an ASO drug, containing the human STMN2 gene sequence and injected it into a mouse model with TDP-43 dysfunction, which can successfully correct the splicing of STMN2 precursor mRNA, restore normal STMN2 protein levels in the nervous system of mice, and promote neuronal axon regeneration, thereby treating ALS (Baughn et al. 2023). For ALS, the first ASO drug was already on the market, and QRL-201 was in phase I clinical trial (NCT05633459), which is also hopeful based on its mechanism of action.

Drugs targeting protein aggregates

Protein misfolding, aggregation, and deposition of specific proteins are biochemical and histopathological hallmarks of ALS (McAlary et al. 2019). The pathological specific protein inclusions observed in ALS patients are immunoreactive for SOD1, TDP-43, and FUS etc. (Kim et al. 2020). Therefore, TDP-43, SOD1, and FUS etc., are disease-associated proteins. By reducing the amounts of aggregated proteins and waning the degree of reactions they cause, there may also be an impact on disease. Heat shock proteins (HSPs) can prevent and clear inclusions such as SOD1 and TDP-43 etc., suggesting that the ability of ALS motor neurons to induce the heat shock response (HSR) is impair (Seminary et al. 2018). Likewise, the induction rate of HSPs was reduced in the human post-mortem samples and mouse models compared to the unaffected control group. Arimoclomol acts by amplifying the production of HSPs and has completed its pivotal clinical study (NCT03491462), but was discontinued due to its failure to meet the primary endpoint (The completed data have not yet been published). SLS-005 Trehalose is a low molecular weight disaccharide with a variety of uncertain drug action mechanisms, including modulation of autophagy, gut brain microbiome, and targeting TDP43 mislocalization and accumulation et al., which is also undergoing clinical trials (Phase II/III, NCT04297683) (Wang et al. 2018).

Accumulation and aggregation of mutated proteins accumulation and aggregation can cause endoplasmic reticulum stress (ERS), unfolded protein response (UPR) and diversiform intracellular stress responses, a mechanism that a self-defense mechanism that reduces misfolded protein load (Kukharsky et al. 2021; Cai et al. 2016). Furthermore, UPR initiates apoptotic death of affected cells in response to sustained stress (Sano and Reed 2013; Bogorad et al. 2018; Bugiani et al. 2010). GDC-0134, a dual leucine zipper kinase (DLK) inhibitor that regulates cell response to the ERS through c-Jun N-terminal kinases (JNK) and protein kinase R-like endoplasmic reticulum kinase (PERK) (Kukharsky et al. 2021). In addition, DLK inhibitors can regulate axonal degeneration and GDC-0134 is being investigated for safety and efficacy in Phase I clinical trial (NCT02655614). TCH346 (Supplementary Table 1) improves protein aggregation, energy metabolism, oxidative stress and anti-apoptotic in ALS patients by binding to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Lazarev et al. 2013; Pierce et al. 2008; Desseille et al. 2017). Unfortunately, the results of its phase II trial showed no significant differences between placebo and active treatment groups in mean rate of decline in the primary outcome ALSFRS-R at 24 weeks and secondary outcomes (survival, lung function, and manual muscle testing). TCH346 has no beneficial effect on the disease progression of ALS (NCT00230074), but based on previous data, the beneficial effect was not observed until patients were treated with riluzole for 9 months, so TCH346 may also be treatment for too short to see no therapeutic effect (Miller et al. 2007).

Drugs targeting oxidative stress

Oxidative stress refers to the damage of the intracellular antioxidant defense system due to the excessive production of oxidants, resulting in the excessive accumulation of oxygen, hydroxyl free radical, and so on, thereby causing damage to cellular macromolecules such as DNA, lipids and proteins, and ultimately lead to necrotic and apoptotic cell death (Singh et al. 2019). Thus, oxidative stress is another potential therapeutic target for ALS (Table 1). The brain is particularly vulnerable to oxidation due to the abundance of polyunsaturated fatty acids, which can give rise to several oxidized metabolites. Myeloperoxidase (MPO) promotes their production and accumulation, leading to oxidative stress (Xiong et al. 2022). Verdiperstat is an inhibitor of MPO and was declared a failure in its Phase II/III (NCT04297683) development. According to the results of its Phase II/III clinical trial, there were no statistically significant differences between the verdiperstat and placebo groups in primary outcome (Change from Baseline in ALSFRS-R Total Score at week 24) and survival, as well as key secondary outcome (including respiratory function, muscle strength, and survival). As with TCH346, it may also be because the follow-up time was too short to see the drug effect. Therefore, when designing ALS clinical trials, it is necessary to clarify the follow-up time of treatment for patients, otherwise it is impossible to judge the efficacy of drugs. And given the longstanding interest and lack of success for molecules that putatively modulate oxidative stress a more critical appraisal of this biology as a therapeutic target would be appropriate. A common cause of neuronal oxidative stress is also disordered metabolism of metal ions, mainly copper, iron, and zinc. CNM-Au8 is a clean-surfaced, multi-faceted gold nanocrystals aqueous suspension with extraordinary catalytic capacity to improve the efficiency of key metabolic reactions while reducing reactive oxygen species levels (Table 1). In addition, CNM-Au8 can also promote the transcription of Heat Shock Factor 1 (HSF1) gene (Vucic et al. 2021). In addition to the protection of neurons in ALS models by upregulation of HSF1 activity, increased NAD + and ATP have also been shown to play the same role (Vucic et al. 2021; Southon et al. 2020). However, the Phase II trial of CNM-Au8 (NCT04098406) failed, mainly because it did not meet the biomarker primary (Motor Unit Index) and secondary FVC endpoint at week 36. The good news is that it may be effective in ALS

limb type patients and some degree of protective effect was observed on lower motor neurons (week 12, p = 0.0385), requiring further verification. However, the primary endpoint of ALS clinical trials is survival or ALSFRS-R Total Score, but the primary endpoint of this trial was biomarker, which may be lack of power. Glutathione peroxidase 4 (GPX4), an anti-oxidant enzyme and central repressor of ferroptosis, occurred in post-mortem spinal cords of both sporadic and familial ALS patients. GPX4 depletion is also an early and common feature of the spinal cord and brain of SOD1 G93A, TDP-43, and C9orf72 ALS mice. Overexpression of human GPX4 in SOD1G93A mice significantly delayed disease onset, improved motor function and prolonged life, which has been shown to be associated with reduced lipid peroxidation and motor neuron preservation. Therefore, GPX4 agonist may be a promising approach for ALS treatment (Hilton et al. 2017; Wang et al. 2021; Liu and Wang 2017; Vallarola et al. 2018; Liu and Wang 2017).

Mitochondria are the main sites of intracellular oxygen consumption. Under normal circumstances, about 1–4% of the oxygen molecules in mitochondria are reduced by one electron to form superoxide, which makes mitochondria become an important source of ROS (Sinha et al. 2013). Mitochondrial-specific antioxidant mechanisms do exist, including the aforementioned SOD1, which can reduce ROS production (Hayashi et al. 2016). However, oxidative damage that accumulates over time is a major cause of mitochondrial dysfunction which triggers oxidative stress and glutamate excitotoxicity in ALS. RT001 is the first drug in the new drug class deuterated polyunsaturated fatty acids (D-PUFAs) (Yerton et al. 2022; Pallardó et al. 2021). D-PUFAs are a novel approach to prevent mitochondrial lipid peroxidative damage leading to cell death (Phase II, NCT04762589) (Pang and Hu 2021). TRO19622 is a novel mitochondria-targeted neuroprotective compound belonging to a novel family of cholesterol oximes. Proteins outside the mitochondrial membrane are targeted to prevent the opening of the permeability transition pore mediated by factors such as oxidative stress (Table 1) (Bordet et al. 2010). TRO19622 has been shown to exert neuroprotective effect in various studies of in vitro and in vivo (Bordet et al. 2010). However, patients who received TRO19622 did not show a significant increase in survival compared to those who received placebo and riluzole (The completed data have not yet been published). Another drug in preclinical development that can improve mitochondrial dysfunction, 7, 8-dihydroxyflavone prodrug, which promotes mitochondrial biogenesis by activating tyrosine kinase receptor B (TrkB), and prolongs the survival rate of worms with stable expression of SOD1 G93A, which needs to be further validated clinically (Li et al. 2021).

Drugs targeting neuroinflammation

Neuroinflammation in patients with ALS is characterized by astrocyte and microglial activation, lymphocyte infiltration, and excessive production of inflammatory cytokines (Liu and Wang 2017). At the same time, there is accumulating evidence has implicated that the normal immune cells may play a protective role on the survival of motor. Consequently, some compounds affecting neuroinflammation have been the candidates for drugs in ALS (Table 1). On the whole, the drugs that target neuroinflammation (25%, 6) are the most, followed by gene therapies (17%, 3) and protein aggregate (13%, 2). NP001 is a small molecule that modulates inflammatory cells, transforming macrophages and monocytes from an inflammatory phenotype to a basal noninflammatory phenotype (Zhang et al. 2022). NP001 was found to be safe and well tolerated, showing positive trends in slowing disease progression, especially in patients 40–65 years of age, according to the results of phase I and II trials completed in ALS patients (NCT01091142, NCT01281631 and NCT02794857) (Liu and Wang 2017). Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is a critical regulator of cell death and inflammation (Ito et al. 2016). And, numerous studies have shown that the expression of RIPK1 were increased in the spinal cords of SOD1G93A transgenic mice and human ALS pathological samples (Ito et al. 2016). RIPK1 inhibitor DNL788 and SAR443820 were going on their phase I and phase II clinical trial, respectively, but another RIPK1 inhibitor DNL747 was suspended in phase I due to safety concerns (Supplementary Table 1). Therefore, the future of RIPK inhibitors in ALS field still needs to be explored.

IPL344 is a novel drug targeting the the phosphatidylinositol-3-kinase (PI3K)/ v-akt murine thymoma viral oncogene (Akt) signaling pathway to reduce the expression of pro-inflammatory molecules and is undergoing Phase II clinical trials (NCT03652805). On February 2, 2020, the FDA and the European Medicines Agency (EMA) granted IPL344 orphan drug designation for the treatment of ALS. MN-166 is a non-selective phosphodiesterase 4 inhibitor that affects the survival and activation of resident immune cells by regulating their production of pro-inflammatory cytokines (Liu and Wang 2017). In vitro evidence suggests that MN-166 is neuroprotective by suppressing neuronal cell death induced by microglial activation (Oskarsson et al. 2021). But MN-166 was not well tolerated as it required multiple dose reductions for adverse events (Babu et al. 2021). In a similar vein, Masitinib, a tyrosine kinase inhibitor known for its potential to provide neuroprotection by effectively inhibiting the activity of microglia, macrophages, and mast cells in both the central and peripheral nervous systems. This inhibition serves to mitigate neuroinflammation. A significant

survival benefit of 25 months (p = 0.037) and 47% reduced risk of death (p = 0.025) was observed for patients receiving 4.5 mg/kg/day masitinib (n = 45) versus placebo (n = 62) in an enriched cohort with ⩾2 on each baseline ALSFRS-R individual component score (i.e. prior to any complete loss or severe impairment of functionality) (Mora et al. 2021).

Complement provides the first line of defense against microorganisms and is a crucial branch of the innate immune system. There are multiple pathways of complement activation, but all ultimately converge on the central C3 and C5 invertase, promoting inflammation and apoptosis (Carpanini et al. 2019). Human studies proved the activation of the classical complement pathway and upregulation of C3 in the spinal cord, motor cortex and CSF of ALS patients. Elevated levels of C5a and sC5b-9 were found in the serum of ALS patients suggesting that terminal complement components play the most important role (Gavriilaki et al. 2020). Ravulizuma and zilucoplan are C5 invertase inhibitors, and pegcetacoplan (Phase II, NCT04579666) is C3 invertase inhibitor, which improves the efficacy of ALS patients by inhibiting complement activation (Howard Jr et al. 2020). Also, C1q participates in the classical pathway of complement activation. After the antigen is combined with the antibody, C1q can recognize and bind to the complement binding site on the antibody. ANX005 is a C1q invertase inhibitor that inhibits amplification of immune responses (Phase II, NCT04569435). However, Astrazeneca announced the termination of the development of the C5 convertase inhibitor ravulizumab (Chen 2020) because the the mid-stage analysis of its Phase III trial (NCT04248465) did not meet the clinical endpoint (Table 1). Subsequently, zilucoplan was also discontinued, which is not optimistic for the treatment of ALS with complement inhibitors (Table 1). Thus, given multiple molecular failures in relatively large, well-executed phase II or III trials, complement may not be a viable target for ALS.

Stem cells

Stem cells are emerging a prospective treatment means for neuronal replacement and regeneration in multifarious neurodegenerative diseases, including ALS (Bonafede and Mariotti 2017). Neuronata-R, mesenchymal stem cells (MSCs), collected from patient bone marrow, has been marketed in South Korea with ALS as an indication. And according to ClinicalTrials.gov, at least 37 stem cells clinical trials have been registered for ALS. However, the Phase III trial of NurOwn® (bone marrow-derived autologous MSCs) did not meet its primary endpoint (ALSFRS-R post-treatment slope improved by 1.25/ month at 28 weeks, Table 1). But surprisingly, patients with milder disease experienced better treatment outcomes, with 34.6% of patients in the NurOwn® administration group experiencing slower disease progression compared to 15.6% in the placebo group (p = 0.29) (Berry et al. 2019). This suggested that it may be the heterogeneity of the disease and short follow-up time that led to NurOwn®'s effect not being seen. Overall, there may be some hope for stem cell treatment of ALS after all. While autologous MSCs have the advantage of retaining genetic information from the donor, patient-derived MSCs derived from fALS patients may carry over the pathological effects of mutated genes. But advances in CRISPR/Cas-9, a genome-editing tool, can repair the gene mutations of the patient-derived MSCs (Wang et al. 2017). Therefore, more researches are needed to confirm the efficacy of optimized stem cell products in the treatment of ALS patients.

Usually, stem cells are administered intrathecally (Fig. 3A), which solved the problem of difficult in swallowing for ALS patients. However, intrathecal administration of drugs requires a hospital visit, which also increases the inconvenience of patients. At present, riluzole has three dosage forms and has been listed successively: tablet, suspension and oral film. Therefore, in addition to the mechanism of action, the development of innovative drugs for ALS can also start from the pharmaceutical dosage form.

Drugs targeting excitotoxicity

Excitatory toxicity of neuronal circuits can eventually lead to motor neuron death, and excitatory alterations have been found to be a common feature in almost all cases of ALS, so excitatory toxicity is considered to be one of the possible factors leading to the disease (Kukharsky et al. 2021; Kawahara anf Kwak 2005). Consequently, the compounds that affect neuronal excitability and/or neuronal synaptic transmission are potential candidates for drugs capable of preventing motor neuron death in ALS (Kukharsky et al. 2021; Kawahara and Kwak 2005).

Hepatocyte growth factor (HGF), a novel neurotrophic factor, acts on astrocytes in SOD1-G93A transgenic mice to maintain recombinant excitatory amino acid transporter 2 (EAAT2) levels in addition to direct neurotrophic activity (Funakoshi et al. 2007). EAAT2 is a glial-specific glutamate transporter that may be responsible for reducing glutamatergic neurotoxicity in motor neurons (Funakoshi et al. 2007). VM202 (Sufit et al. 2017) reduce excitotoxicity in ALS patients by producing HGF in humans, and currently in Phase II clinical trials (NCT03705390). ILB is another drug that promotes HGF protein production, and has completed the phase II clinical trial. The result showed that ILB improved clinical conditions and decreased neuronal damage in ALS patients (NCT03705390) (Logan et al. 2022; Lazzarino et al. 2021).

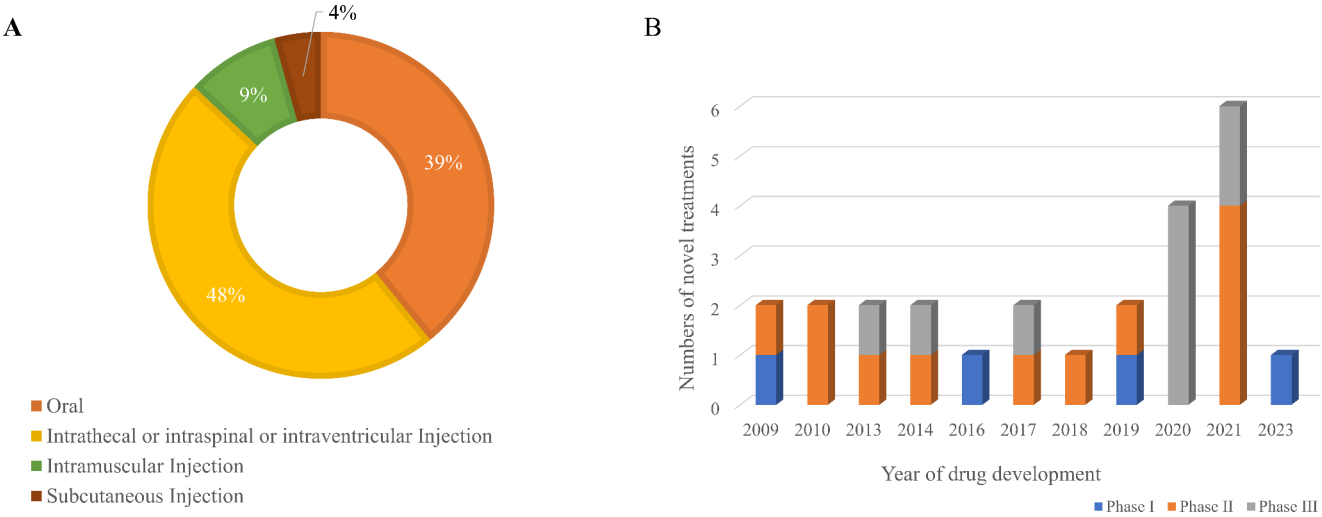

Fig. 3 The number of novel treatments under development for ALS in different routes of administration (**A**) and at different phases in the past 14 years (**B**). Different colors represent different treatments delivery routes. The area of each color plot represents the proportion of drugs in different routes of delivery ((excluding drugs with unknown routes of delivery)) (**B**); The horizontal axis is the year, the vertical axis is the number of treatments, and different colors represent different clinical trial phases (phase I, II and III). The height of each bar chart represents the number of ALS treatments developed each year, and the height of each color in each bar chart represents the number of ALS treatments at different phases in that year (**A**)

In addition to the medications mentioned above, another way to treat ALS is to use non-invasive brain stimulation (NIBS), which regulates brain activity through different forms of energy, such as electrical currents, magnetic pulses, or focused ultrasound through the scalp and skull. Corticospinal excitability can be inhibited or enhanced using NIBS techniques, namely repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), as well as invasive brain and spinal cord stimulation (Ranieri et al. 2021). At present, this technique is still in the preliminary trial stage and needs further verification with a large sample size.

Sigma non-opioid intracellular receptor 1 (Sigma-1 receptor) is a protein expressed in motor neurons, mainly in close contact with cholinergic postsynaptic sites or in the endoplasmic reticulum (ER) on the mitochondria-associated ER membrane (MAM) (Herrando-Grabulosa et al. 2021).

The sigma-1 receptor regulates calcium homeostasis, excitatory toxicity, ER stress and other basic mechanisms of survival in neurons. Therefore, it can be used as a target for the treatment of ALS (Herrando-Grabulosa et al. 2021). Pridopidine, a Sigma-1 receptor agonist originally developed for Huntington's disease, had a negative Phase II/III trial in ALS (NCT04297683). Pridopidine did not meet the primary endpoint of change from baseline to week 24 in the ALSFRS-R, rapidly declining participants on pridopidine with definite or probable ALS who were early in the disease (less than 18 months from symptom onset) had substantially less decline in the ALSFRS-R total score (-7.51 points) compared to placebo (-12.71 points, unadjusted p-value = 0.04) in post-hoc analyses. What's more, pridopidine reduced NfL levels in rapidly declining patients with disease duration less than 18 months (average reduction of 40%) at 24 weeks compared to placebo in post-hoc analyses. This suggested that the effect may not be observed due to the heterogeneity of the disease, and the short follow-up time may also be one of the factors. Later, patients can be enrolled in the early stages and treated for enough time to confirm its efficacy.

Drugs targeting muscle strength

ALS leads to muscle functional capacity decline, and then generate great impact in quality of life. Some research teams have focused on improving muscle mass and function in ALS patients, and hope to develop treatments for the corresponding symptom (Ferreira et al. 2016). Therefore, this is also a possible research target.

Reldesemtiv and Tirasemtiv are fast skeletal muscle troponin activators (FSTA), and sensitize the sarcomere to calcium and increase muscle force. The Phase II clinical trial of Reldesemtiv (NCT03160898) has completed. Although the primary efficacy (change in percent predicted slow vital capacity (SVC) at 12 weeks) analysis did not demonstrate statistical significance, there were trends in favor of Reldesemtiv for all three endpoints (change in percent predicted SVC at 12 weeks, ALSFRS-R and muscle strength mega-score) (Shefner et al. 2021; Keifer Jr et al. 2014; Vijayalakshmi et al. 2015). However, results from Phase III trials of tirasemtiv showed that it failed to meet the primary endpoint (slow vital capacity at 24 weeks) and secondary endpoints

(improvement in muscle function and strength at 48 weeks), which is not a good signal for the development of such targeted drugs. Whereas the primary endpoint of ALS clinical trials was usually survival or the ALSFRS-R total score, the primary endpoint in this trial was slow vital capacity at 24 weeks which was a more relevant measure of the drug's mechanism of action but may not fully characterize the drug's efficacy. Later, the selection of end points can be optimized to confirm its efficacy.

Drugs targeting metabolism

Epidemiological evidence suggests that ALS patients suffer from catabolism and begin to lose weight > 10 years before the onset of motor symptoms. In addition, the increased risk of ALS is associated with lower body mass index and abnormal levels of circulatory hormones, so increasing body mass index with high-caloric nutrition may be a possible way to benefit patients with ALS. High-caloric nutrition conducted a randomized controlled study with a large sample size after completing its phase I safety assessment (NCT04172792). The study enrolled 221 patients who were randomly assigned (1:1) to receive high-caloric nutrition (405 kcal/ day, 100% fat) or placebo in addition to riluzole (100 mg/ day). The primary endpoint was survival, defined as time of death or study cutoff time. The findings suggest evidence that high-caloric nutrition did not prolong life in the overall ALS population. However, postmortem analysis showed significant survival benefits in the fast- progressing patients. Furthermore, in the subgroup of patients with high NfL serum levels, patients in the high-caloric nutrition group had a significantly prolonged survival, corroborating a potential effect of high-caloric nutrition on fast- progressing patients during the 18 months of intervention (Kawahara and Kwak 2005; Funakoshi et al. 2007).

Supportive and palliative care

Paying attention to the many symptoms that can occur during the course of the disease is critical to improving the quality of life for people with ALS. Therefore, symptomatic treatment is an integral aspect of ALS treatment. Such as: thickened saliva, emotional lability and pain (i.e., musculoskeletal pain and cramps, fasciculations and spasticity, skin pressure pain caused by immobility) (Kiernan et al. 2011). Salivation, or excessive production of saliva, is one of the most disturbing symptoms of ALS patients, and is commonly seen in patients with globular onset and in advanced stages of the disease (Kiernan et al. 2011). Anticholinergic drugs such as atropine, hyrisine, amitriptyline can be used to treat the disease. For emotional lability, treatments such as Amitriptyline, Benzodiazepines, Dextromethorphan hydrobromide/quinidine sulfate can be choice (Kiernan et al. 2011). Pain is reported in 15–85% of ALS patients, and medications include gabapentin, pregabalin, and tricyclic antidepressants. Muscle spasms are the main cause of pain in about a quarter of ALS patients, especially those with spinal onset, and drugs commonly used to treat muscle spasms include quinine sulfate, levetiracetam, and mexetine (Kiernan et al. 2011). In addition, ALS patients may experience fecal incontinence as the disease progresses, delayed colon transport time, and gastric empting (Mazzini et al. 2021). At the same time, some researchers found that SOD1G93A mice also had intestinal leakage, an increase in the number of abnormal intestinal Pan's cells, and changes in microbial communities (Mazzini et al. 2021). Gut flora can communicate with the central nervous system via the gut-brain axis, a two-way pathway between the central and enteric nervous systems that links the brain's higher abilities to peripheral intestinal function (Mazzini et al. 2021). Therefore, whether the gut flora can be used as a therapeutic target needs to be further verified.

Others

The peptide drug GM604 was developed as a candidate ALS therapy and is hypothesized to bolster neuron survival through the multi-target regulation of developmental pathways, but mechanisms of action are not fully understood (Table 1) (Swindell et al. 2018). Recently, a Phase II clinical trial was reported, which compared the 2-week results of 8 patients with ALS who received GM604 and 4 patients who received placebo, and GM604 had a favorable safety profile but no efficacy (NCT01854294) (Kindy et al. 2017).

Moreover, it has been demonstrated that an anticoagulation-deficient form of activated protein C (APC), 3K3A-APC, rescued two defects in C9ORF72 and sporadic ALS induced motor neuron models (iMNs): the abnormal accumulation of glutamate receptors and impaired autophagosome formation (Shi et al. 2019). Concomitantly, APC therapy reduced C9ORF72 dipeptide-repeat protein (DPR) levels, restored nuclear localization of TDP-43, and saved the survival of both C9ORF72 and sporadic ALS iMNs(Shi et al. 2019). The phase II clinical trial of 3K3A-APC Protein is undergoing for ALS treatment (NCT05039268).

Conclusion

According to the registration from clinicaltrials.gov, the number of ALS drugs under development fluctuated from 2008 to 2019, with a significant increase between 2019 and 2021 (Fig. 3B). Also, there were many drug development failures (Supplementary Table 1), which may be due to the

target itself is not effective, or it may be due to the design of clinical trials (e.g. heterogeneity of the disease, lack of power, questionable endpoint, short follow-up time, etc.), so standardized clinical trial design will help researchers better judge the advantages and disadvantages of the target. In addition, the fundamental pathophysiological mechanisms underlying ALS are not well understood, but the neuropathological hallmark of disease is the aggregation and accumulation of ubiquitylated proteinaceous inclusions in motor neurons. In 97% of ALS subtypes, TDP43 is the primary component of these inclusion bodies. In specific ALS subtypes, other types of protein aggregation, such as neurofilamentous hyaline conglomerate inclusions, sequestosome 1 positive, and the accumulation of misfolded SOD1 can be observed. However, drugs designed to remove ubiquitylated proteinaceous inclusions in motor neurons have not worked well in ALS patients. Therefore, it is necessary to identify the key pathological mechanism of the disease, so as to explicit pathways and targets that drugs can target, and achieve breakthroughs. Currently, tofersen was the first FDA-approved ASO for ALS, and possibly the second was for FUS mutations, which will stimulate research into gene-targeted therapies. Meanwhile, relyvrio's approval spurred the development of ALS treatments and encourage sponsors to try to break the bottleneck by combining different target drugs.

Abbreviations

ALS	amyotrophic lateral sclerosis
ROS	radical/reactive oxygen species
TDP-43	TARDNA-binding protein of 43 kDa
SOD1	superoxide dismutase1
FUS	fused-in-sarcoma
ERS	endoplasmic reticulum stress
UPR	unfolded protein response
fALS	familiar ALS
ASO	antisense oligonucleotide
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
Nfl	neurofilament light chain
OLE	non-blind extended study
ATXN2	Ataxin-2
FET	FUS/EWSR1/TAF15
Exportin 1	XPO1
eIF2B	Eukaryotic translation initiation factor 2B
HSPs	heat shock proteins
HSR	heat shock response
DLK	dual leucine zipper kinase
JNK	c-Jun N-terminal kinases
PERK	protein kinase R-like endoplasmic reticulum kinase
MPO	myeloperoxidase
GPX4	Glutathione peroxidase 4
TrkB	tyrosine kinase receptor B
CuII (atsm)	bis(thiosemicarbazone) copper (II) compound
AuNPs	gold nanoparticles
D-PUFAs	deuterated polyunsaturated fatty acids
RIPK1	receptor-interacting serine/threonine-protein kinase 1
FDA	the U.S. Food and Drug Administration
EMA	the European Medicines Agency
MSCs	Mesenchymal stem cells
NTFs	neurotrophic factors
HGF	Hepatocyte growth factor
NIBS	non-invasive brain stimulation
rTMS	repetitive transcranial magnetic stimulation
tDCS	transcranial direct current stimulation
EAAT2	excitatory amino acid transporter2
FSTAs	fast skeletal muscle troponin activators
SVC	slow vital capacity
VEGF	vascular endothelial growth factor
NADH	nicotinamide adenine dinucleotide hydride
HSF1	Heat Shock Factor 1
NDA	new drug applications
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
TCP	Taylor-Couette-Poiseuille
CSNs	charge-stabilized nanostructures
PI3K	phosphatidylinositol-3-kinase
Akt	v-akt murine thymoma viral oncogene homologue
Foxp3+	forkhead box P3
APC	activated protein C
iMNs	induced motor neuron models
DPR	dipeptide-repeat protein
ER	endoplasmic reticulum
Sigma-1 receptor	Sigma non-opioid intracellular receptor 1
MAM	mitochondria-associated ER membrane

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Data Availability All data generated or analyzed during this study were included in Table 1 and Supplementary Table 1.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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