

# [Trophic factors as modulators of motor neuron physiology and survival: implicatio...](https://assignbuster.com/trophic-factors-as-modulators-of-motor-neuron-physiology-and-survival-implications-for-als-therapy/)

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## Introduction

Neuronal development and survival depend on a balanced and tightly regulated support from trophic factors. Such factors are capable of regulating several important physiological processes, such as neuronal differentiation, maintenance of synapses, neuronal survival through the inhibition of apoptosis, neurogenesis and axonal outgrowth ( [Korsching, 1993](#B42) ; [Boonman and Isacson, 1999](#B7) ; [Hou et al., 2008](#B34) ). In addition, they provide an environmental niche suitable for neuronal survival ( [Mudò et al., 2009](#B61) ). Trophic support is essential for neurons in the spinal cord and is conferred from many different cellular sources including astrocytes, microglia, neurons and endothelial cells ( [Ikeda et al., 2001](#B35) ; [Béchade et al., 2002](#B4) ; [Dugas et al., 2008](#B19) ; [Su et al., 2009](#B80) ; [Hawryluk et al., 2012](#B32) ). Therefore, trophic support is considered a promising therapeutic strategy for neurodegenerative diseases ( [Kotzbauer and Holtzman, 2006](#B43) ), and it plays an important role in cellular therapy aimed at the reinnervation of lost neuromuscular synapses ( [Casella et al., 2010](#B12) ).

Amyotrophic lateral sclerosis (ALS) is caused by the selective and progressive loss of spinal, bulbar and cortical motor neurons that lead to irreversible paralysis, speech, swallowing and respiratory malfunctions and eventually death of the affected individuals in a rapid disease course. ALS is mostly sporadic with 90% of the cases occurring without a family history of the disease. However, in the recent years it has become evident that many sporadic cases carry alterations in proteins that have been found mutated in familial cases that might, at least, increase the probability for developing ALS ( [Deng et al., 2010](#B15) ). Many of these mutations involve alterations in the TAR DNA-binding protein 43 (TDP43) and Fused in sarcoma (FUS) genes that bind RNA molecules ( [Gordon, 2013](#B25) ; [Sreedharan and Brown, 2013](#B77) ), whereas most familial cases with a dominant autosomal inheritance pattern are caused by mutations in superoxide dismutase 1 (SOD1; [Rosen et al., 1993](#B71) ). Transgenic mice expressing a mutant form of the human SOD1 are the most widely used model for *in vivo* studies of ALS ( [Gurney et al., 1994](#B30) ). Trophic factors have been thought as therapeutic targets for ALS, aiming at restoring lost neuromuscular synapses and rescuing motor neurons from toxicity.

There is a series of well characterized trophic factors for the CNS, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF), growth hormone and vascular endothelial growth factor (VEGF). Many of these have been tested for neuroprotective potential in different experimental models of ALS. In fact, viral vectors encoding growth factors are among the most effective ways to delay the progression of degenerative processes and prolong survival in ALS mice ( [Wang et al., 2002](#B94) ; [Kaspar et al., 2003](#B38) ; [Azzouz et al., 2004](#B3) ; [Dodge et al., 2008](#B18) ).

### Trophic Factors During Motor Neuron Development

Motor neuron development is differentially affected by specific trophic factor shortage, and loss of particular trophic signaling alters the development of different subpopulations of motor neurons in heterogeneous ways. The absence of GDNF alters the location of developing motor neurons that innervate the limbs in the spinal cord ( [Haase et al., 2002](#B31) ; [Kramer et al., 2006](#B45) ) and selectively affects the innervation of intrafusal muscle spindles ( [Gould et al., 2008](#B26) ). Interestingly, the overexpression of this factor in muscle during development causes a hyperinnervation of neuromuscular junctions ( [Nguyen et al., 1998](#B65) ). In contrast, BDNF may not be as important for motor neurons, because although the lack of this trophic factor severely affects the normal development of sensory neurons, motor neurons are able to develop without major alterations ( [Ernfors et al., 1994a](#B20) ; [Jones et al., 1994](#B36) ). Furthermore, distinct motor neuron subpopulations show different sensitivities to the lack of neurotrophins. For example, the absence of neurotrophin-3 produces a complete loss of spinal motor neurons while facial motor neurons are spared ( [Ernfors et al., 1994b](#B21) ; [Gould et al., 2008](#B26) ), and the absence of CNTF produces no alterations for motor neuron development at the spinal or cranial levels ( [DeChiara et al., 1995](#B14) ), although the loss of its receptor CNTFRα generates severe motor neuron deficits and mice lacking this receptor die perinatally ( [DeChiara et al., 1995](#B14) ). A possible alternate ligand for this receptor is the dimer formed by cardiotrophin-like cytokine/cytokine-like factor 1, whose deletions have been shown to cause a significant reduction in the number of motor neurons ( [Forger et al., 2003](#B22) ). The absence of other factors such as cardiotrophin-1 has also been reported to produce a significant loss of motor neurons ( [Oppenheim et al., 2001](#B69) ; [Forger et al., 2003](#B22) ), and the loss of IGF-1 causes significant reduction in the number of trigeminal and facial motor neurons ( [Vicario-Abejón et al., 2004](#B93) ). Finally, while the lack of VEGF is lethal, a deletion of the hypoxia response element in the promoter region of the VEGF gene causes a decrease in the expression of this factor that leads to an adult-onset progressive loss of motor neurons in mice ( [Oosthuyse et al., 2001](#B66) ). After this fortuitous discovery, it was reported that certain VEGF haploytpes (-2578C/A, -1154G/A and -634G/C) conferred an increased susceptibility to ALS in humans, but later on in a meta-analysis conducted with more than 7000 subjects from at least eight different populations no association between these haplotypes and ALS was found ( [Lambrechts et al., 2009](#B48) ). Moreover, no mutations in the hypoxia response element of the VEGF promoter ( [Gros-Louis et al., 2003](#B28) ), or in the VEGF receptor 2 ( [Brockington et al., 2007](#B9) ) were found in ALS patients.

Neurotrophic factors are not only important during development, but they also regulate motor neuron maintenance and survival even long after neurons have become fully differentiated. As well, they might be able to trigger the activation of endogenous regenerative processes. Aside from the synthesis of trophic factors in the local spinal microenvironment, synaptic targets of motor neurons also play important roles in the trophic feedback. As a matter of fact, this is an essential event for the development of the CNS during which originating neurons receive trophic input from their target tissues that enables them to surpass an endogenous-codified programmed cell death ( [Oppenheim, 1991](#B67) ). In the case of motor neurons these effects are mostly mediated by skeletal muscle-derived factors ( [Oppenheim et al., 1988](#B68) ; [Grieshammer et al., 1998](#B27) ; [Kablar and Rudnicki, 1999](#B37) ).

### Trophic Factor Effects on Motor Neuron Survival

Among all the trophic factors tested in experimental ALS models, VEGF has been shown to be one of the most potent motor neuron protectors. VEGF remarkably retards the progression of the disease and the loss of motor neurons in familial ( [Azzouz et al., 2004](#B3) ; [Zheng et al., 2004](#B100) ; [Storkebaum et al., 2005](#B79) ; [Wang et al., 2007](#B95) ), as well as in sporadic ( [Tovar-Y-Romo et al., 2007](#B91) ; [Tovar-Y-Romo and Tapia, 2010](#B89) , [2012](#B90) ) experimental models of motor neurodegeneration.

Activation of VEGF receptor 2 triggers the phosphorylation of intracellular pathways driven by phosphatidyl-inositol-3-kinase (PI3-K), phospholipase C-γ, and mitogen-activated protein kinase (MEK) that promote the inhibition of pro-apoptotic factors like Bad ( [Yu et al., 2005](#B98) ) and caspases 9 ( [Cardone et al., 1998](#B11) ) and 3 ( [Góra-Kupilas and Joško, 2005](#B24) ; [Kilic et al., 2006](#B39) ). The activation of these intracellular signaling pathways has been extensively studied in the CNS ( [Zachary, 2005](#B99) ). VEGF-dependent activation of PI3-K/Akt is sufficient to prevent motor neuronal death in familial models of ALS *in vitro* ( [Li et al., 2003](#B50) ; [Koh et al., 2005](#B41) ; [Tolosa et al., 2008](#B86) ) and in experimental *in vitro* models of excitotoxic neuronal death ( [Matsuzaki et al., 2001](#B54) ). Furthermore, the activation of PI3-K/Akt is required for motor neuron survival and axonal regeneration after spinal cord injury ( [Namikawa et al., 2000](#B64) ). We have demonstrated that the signaling mediated by PI3-K is critically involved in the protective effect of VEGF against AMPA-induced excitotoxic spinal neurodegeneration *in vivo* ( [Tovar-Y-Romo and Tapia, 2010](#B89) ).

VEGF also mediates neuroprotection through the inhibition of stress activated protein kinases like p38 mitogen-activated protein kinase. Increased levels of phosphorylated p38 have been found in motor neurons and glia in the familial mouse model of ALS ( [Tortarolo et al., 2003](#B88) ; [Holasek et al., 2005](#B33) ; [Veglianese et al., 2006](#B92) ; [Dewil et al., 2007](#B17) ), even at the pre-symptomatic stage ( [Tortarolo et al., 2003](#B88) ), and p38 is also an important factor in a cell death pathway specific for motor neurons ( [Raoul et al., 2006](#B70) ). Interestingly, the inhibition of p38 prevents motor neuron death in an *in vitro* familial model of ALS ( [Dewil et al., 2007](#B17) ), and we and others have proven that VEGF can suppress p38 activation in both familial ( [Tolosa et al., 2009](#B87) ) and excitotoxic ( [Tovar-Y-Romo and Tapia, 2010](#B89) ) models of spinal cord neurodegeneration.

An increased expression of the VEGF-inducing factor Hypoxia induced factor 1 (HIF-1α) in the spinal cord may occur due to relative hypoxic conditions that exist in the spinal microenvironment, although motor neurons seem to be unable to fully respond to increased downstream effectors such as VEGF ( [Sato et al., 2012](#B73) ). One possible explanation for this and for the decrease of VEGF levels found in human patients ( [Devos et al., 2004](#B16) ) might be that inducing factors such as HIF-1α are prevented from translocating to the nucleus even though their concentrations are increased in the cytoplasm ( [Nagara et al., 2013](#B63) ). This failure to mount the complete response of VEGF synthesis during hypoxia is not cell type specific and it has been demonstrated to occur in monocytes from ALS patients ( [Moreau et al., 2011](#B58) ).

In contrast to the good protection potential of VEGF, other factors like BDNF failed to protect in different experimental paradigms. BDNF is synthesized by activated microglia in the first stages of the disease when the glial response mainly exerts anti-inflammatory and protective effects, but its production is lost when microglia turns toxic at later stages ( [Liao et al., 2012](#B51) ). In addition, BDNF does not protect motor neurons from excitotoxicity in experimental models *in vitro* ( [Fryer et al., 2000](#B23) ) and *in vivo* ( [Tovar-Y-Romo and Tapia, 2012](#B90) ). This could be possibly due to the sequestration of the ligand by a truncated isoform of the high affinity receptor that is known to be expressed in motor neurons, because removing this truncated receptor significantly delays the disease onset in the mouse familial model ( [Yanpallewar et al., 2012](#B97) ). In spite of this, BDNF may be a risk factor for neurons by increasing their sensitivity to excitotoxicity ( [Fryer et al., 2000](#B23) ), or through the activation of NADPH oxidase ( [Kim et al., 2002](#B40) ), an enzyme involved in motor neuron pathology by damaging the survival pathways activated by trophic factors ( [Wu et al., 2006](#B96) ). Other growth factors have also been shown to be beneficial although to a lesser extent.

The expression of GDNF by astrocytes is up-regulated after spinal cord ischemia and this might be a mechanism of protection for motor neurons against excitotoxic death ( [Tokumine et al., 2003](#B85) ). GDNF exerts its neuroprotective effects preferentially on neuronal somas rather than on nerve endings at the neuromuscular synapse when it is administered directly in the spinal cord ( [Suzuki et al., 2007](#B83) ). Conversely, when it is administered directly in the muscle, GDNF preserves the muscle-nerve synapse and promotes motor neuron function and survival in a familial model of ALS ( [Suzuki et al., 2008](#B82) ), implying that the protective effects exerted by GDNF are rather limited by the proximity to the trophic source. Nonetheless, GDNF can be retrogradely transported along motor neuronal axons ( [Leitner et al., 1999](#B49) ), which allows the opportunity to explore a delivery route that will impact both somas and nerve endings. Interestingly, human ALS patients show an up-regulation of GDNF in muscle ( [Grundström et al., 1999](#B29) ), and the overexpression of GDNF in muscle but not in astrocytes extends lifespan in ALS mice ( [Mohajeri et al., 1999](#B57) ). Combined growth factor therapy might be an alternative that is worth exploring, as suggested by a recent report in the rat transgenic ALS model showing that VEGF and GDNF administered through an implant of human mesenchymal stem cells exert a synergistic protection in preserving nerve muscular synapses ( [Krakora et al., 2013](#B44) ).

In the case of CNTF, although the blockade of its expression has been reported to result in the loss of motor neurons and the development of motor symptoms ( [Masu et al., 1993](#B53) ), these effects are relatively mild when compared to those induced by the loss of other factors like VEGF. Interestingly, ALS patients have a selective decrease of CNTF expression in the CNS regions affected by the disease ( [Anand et al., 1995](#B2) ). Conversely, serum levels of CNTF are generally elevated in ALS patients, especially among those with the lumbar-onset form of the disease ( [Laaksovirta et al., 2008](#B46) ).

### Trophic Factors as Therapy for Amyotrophic Lateral Sclerosis (ALS)

Clinical trials administering trophic factors to ALS patients have not been successful yet. Subcutaneous injections of CNTF, which was effective in the mutant mice models of motor neuron disease *pmn/pmn* ( [Sendtner et al., 1992](#B74) ) and wobbler ( [Mitsumoto et al., 1994](#B56) ), did not affect the progression of disease in humans, but caused minor adverse side effects ( [ALS CNTF Treatment Study Group, 1996](#B1) ). Similarly, disease progression was not modified in ALS patients treated with subcutaneous administration of BDNF ( [The BDNF Study Group, 1999](#B84) ). Two randomized double-blind placebo-controlled clinical trials administering recombinant human IGF showed little ( [Lai et al., 1997](#B47) ) or no effect ( [Borasio et al., 1998](#B8) ) on disease progression, even when IGF-1 was found to be protective in the transgenic rodent model of ALS ( [Kaspar et al., 2003](#B38) ; [Dodge et al., 2008](#B18) ). A combined meta-analysis of both trials showed slight retardation in the disease progression in the group treated with IGF-1, although the results are not conclusive ( [Beauverd et al., 2012](#B110) ). Interestingly, it has been recently reported that skeletal muscle fiber production of IGF-1 is impaired in ALS patients ( [Lunetta et al., 2012](#B52) ), so that the modest effects found in some of the patients enrolled in the clinical trials might have been due to a compensation of impaired IGF-1 production by the exogenous administration of the factor. Finally, even when according to one report ( [Morselli et al., 2006](#B60) ) the majority of ALS patients showed deficiencies in growth hormone secretion, in a recent clinical trial the administration of this hormone to ALS patients did not produce any benefit as compared to patients that received placebo ( [Saccà et al., 2012](#B72) ).

The time of administration after symptom onset in a trophic factor-based therapy is critical. Trophic factors have a short time frame for protection of motor neurons once the noxious process is triggered and this is probably due to the rate at which motor neurons die during the time course of the disease. Histological studies of human spinal cord showed a large variability between the degree of motor neuron loss and muscle weakness ( [Stephens et al., 2006](#B78) ), and transgenic familial amyotrophic lateral sclerosis (FALS) mice bearing human ( [Dal Canto and Gurney, 1995](#B13) ; [Bruijn et al., 1997](#B10) ) or murine ( [Morrison et al., 1998](#B59) ) mutant SOD1 do not present a significant loss of motor neurons prior to the onset of symptoms, and the neuronal loss occurs at a very fast rate over a period of 10 days. In our model of chronic spinal cord excitotoxicity we found that the onset of motor deficits, characterized by limping of the rear limbs, occurs before the loss of motor neurons, suggesting that the time at which the cellular death process starts but prior to clear neuronal degeneration constitutes a therapeutic frame within which growth factor administration could result effective ( [Tovar-Y-Romo et al., 2007](#B91) ; [Tovar-Y-Romo and Tapia, 2012](#B90) ). In fact, in the FALS murine models the administration of VEGF ( [Azzouz et al., 2004](#B3) ; [Storkebaum et al., 2005](#B79) ) or IGF-1 ( [Kaspar et al., 2003](#B38) ; [Dodge et al., 2008](#B18) ) well before the beginning of symptoms confers a significantly better protection, observed by a delay in the progression of symptoms and increased lifespan, as compared to that produced when administered at the symptoms onset. A similar result was obtained in rats subjected to spinal AMPA-induced excitotoxicity, in which a delayed administration of VEGF clearly protected but only when administered before the beginning of motor deficit symptoms ( [Tovar-Y-Romo and Tapia, 2012](#B90) ). This difference possibly means that growth factors are helpful at preventing the accumulating toxicity that arises from neurodegenerative processes that begin before motor neuron death or symptoms onset ( [Dal Canto and Gurney, 1995](#B13) ; [Bendotti et al., 2001](#B6) ). Unfortunately, obtaining a correct diagnosis of ALS is a complicated and slow process due to the many parameters needed to meet diagnosis criteria ( [Shook and Pioro, 2009](#B75) ; [Bedlack, 2010](#B5) ), so that the earliest intervention with trophic factors once a patient is diagnosed may be already too late.

Administration routes for trophic factor therapy are also important. This is of special interest when considering that in the actual human disease cellular alterations take place along the entire spinal cord, which might be a target particularly difficult to reach. Therefore, assessing different ways to deliver trophic factors is worth trying. Intracerebroventricular (ICV) administration of VEGF has been proven efficient in the rat transgenic model of FALS ( [Storkebaum et al., 2005](#B79) ) and in our acute model of spinal cord excitotoxicity ( [Tovar-Y-Romo and Tapia, 2012](#B90) ). ICV administration has the capability to cover the entire spinal cord although it most probably creates a concentration gradient ( [Storkebaum et al., 2005](#B79) ). The continuous perfusion of trophic factors in the spinal cord by intrathecal infusions or into the brain by ICV injections overcome the blockade that the blood brain barrier represents for the delivery of these molecules. In fact, intrathecal injections have been tried in ALS patients for the delivery of IGF-1, with modest results ( [Nagano et al., 2005](#B62) ). Clinical trials for VEGF are now underway to assess the safety and tolerability of VEGF ( [Siciliano et al., 2010](#B76) ).

Other important aspects to consider in growth factor therapies are the stability of the molecule, the half-life of the proteins, the need for sustained delivery and exposure, the dose, their ability to cross the blood brain barrier, and the unwanted side effects on non-targeted cells ( [Suzuki and Svendsen, 2008](#B81) ). Nonetheless, the neuroprotective potential that growth factor represent overweighs the obstacles that need to be overcome in order to achieve a successful therapy.

## Conclusions

Because trophic support is an essential component for neuronal maintenance and survival, supplying motor neurons subjected to stressful or noxious stimuli with molecular factors that help them counteract cellular death processes, growth factors represent a therapeutic tool that is undoubtedly worth exploring for ALS. However, we still need to understand a great deal of the molecular pathways that cause growth factor shortage during the course of disease and the cellular and molecular mechanisms that limit the responses elicited by these factors when they are supplied exogenously. As well, we still need to identify proper therapeutic regimens and treatment approaches to be able to translate the findings we have made in experimental models into useful therapeutic procedures.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## References

ALS CNTF Treatment Study Group. (1996). A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. ALS CNTF Treatment Study Group. *Neurology* 46, 1244–1249. doi: 10. 1212/wnl. 46. 5. 1244

Anand, P., Parrett, A., Martin, J., Zeman, S., Foley, P., Swash, M., et al. (1995). Regional changes of ciliary neurotrophic factor and nerve growth factor levels in post mortem spinal cord and cerebral cortex from patients with motor disease. *Nat. Med.* 1, 168–172. doi: 10. 1038/nm0295-168

Azzouz, M., Ralph, G. S., Storkebaum, E., Walmsley, L. E., Mitrophanous, K. A., Kingsman, S. M., et al. (2004). VEGF delivery with retrogradely transported lentivector prolongs survival in a mouse ALS model. *Nature* 429, 413–417. doi: 10. 1038/nature02544

Béchade, C., Mallecourt, C., Sedel, F., Vyas, S., and Triller, A. (2002). Motoneuron-derived neurotrophin-3 is a survival factor for PAX2-expressing spinal interneurons. *J. Neurosci.* 22, 8779–8784.

Bedlack, R. S. (2010). Amyotrophic lateral sclerosis: current practice and future treatments. *Curr. Opin. Neurol.* 23, 524–529. doi: 10. 1097/wco. 0b013e32833c7ac2

Beauverd, M., Mitchell, J. D., Wokke, J. H., and Borasio, G. D. (2012). Recombinant human insulin-like growth factor I (rhIGF-I) for the treatment of amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst. Rev.* 11: CD002064. doi: 10. 1002/14651858. CD002064. pub3

Bendotti, C., Calvaresi, N., Chiveri, L., Prelle, A., Moggio, M., Braga, M., et al. (2001). Early vacuolization and mitochondrial damage in motor neurons of FALS mice are not associated with apoptosis or with changes in cytochrome oxidase histochemical reactivity. *J. Neurol. Sci.* 191, 25–33. doi: 10. 1016/s0022-510x(01)00627-x

Boonman, Z., and Isacson, O. (1999). Apoptosis in neuronal development and transplantation: role of caspases and trophic factors. *Exp. Neurol.* 156, 1–15. doi: 10. 1006/exnr. 1999. 7056

Borasio, G. D., Robberecht, W., Leigh, P. N., Emile, J., Guiloff, R. J., Jerusalem, F., et al. (1998). A placebo-controlled trial of insulin-like growth factor-I in amyotrophic lateral sclerosis. European ALS/IGF-I Study Group. *Neurology* 51, 583–586. doi: 10. 1212/wnl. 51. 2. 583

Brockington, A., Wokke, B., Nixon, H., Hartley, J., and Shaw, P. J. (2007). Screening of the transcriptional regulatory regions of vascular endothelial growth factor receptor 2 (VEGFR2) in amyotrophic lateral sclerosis. *BMC Med. Genet.* 8: 23. doi: 10. 1186/1471-2350-8-23

Bruijn, L. I., Becher, M. W., Lee, M. K., Anderson, K. L., Jenkins, N. A., Copeland, N. G., et al. (1997). ALS-linked SOD1 mutant G85R mediates damage to astrocytes and promotes rapidly progressive disease with SOD1-containing inclusions. *Neuron* 18, 327–338. doi: 10. 1016/s0896-6273(00)80272-x

Cardone, M. H., Roy, N., Stennicke, H. R., Salvesen, G. S., Franke, T. F., Stanbridge, E., et al. (1998). Regulation of cell death protease caspase-9 by phosphorylation. *Science* 282, 1318–1321. doi: 10. 1126/science. 282. 5392. 1318

Casella, G. T., Almeida, V. W., Grumbles, R. M., Liu, Y., and Thomas, C. K. (2010). Neurotrophic factors improve muscle reinnervation from embryonic neurons. *Muscle Nerve* 42, 788–797. doi: 10. 1002/mus. 21757

Dal Canto, M. C., and Gurney, M. E. (1995). Neuropathological changes in two lines of mice carrying a transgene for mutant human Cu, Zn SOD and in mice overexpressing wild type human SOD: a model of familial amyotrophic lateral sclerosis (FALS). *Brain Res.* 676, 25–40. doi: 10. 1016/0006-8993(95)00063-V

DeChiara, T. M., Vejsada, R., Poueymirou, W. T., Acheson, A., Suri, C., Conover, J. C., et al. (1995). Mice lacking the CNTF receptor, unlike mice lacking CNTF, exhibit profound motor neuron deficits at birth. *Cell* 83, 313–322. doi: 10. 1016/0092-8674(95)90172-8

Deng, H. X., Zhai, H., Bigio, E. H., Yan, J., Fecto, F., Ajroud, K., et al. (2010). FUS-immunoreactive inclusions are a common feature in sporadic and non-SOD1 familial amyotrophic lateral sclerosis. *Ann. Neurol.* 67, 739–748. doi: 10. 1002/ana. 22051

Devos, D., Moreau, C., Lassalle, P., Perez, T., De Seze, J., Brunaud-Danel, V., et al. (2004). Low levels of the vascular endothelial growth factor in CSF from early ALS patients. *Neurology* 62, 2127–2129. doi: 10. 1212/01. wnl. 0000129913. 44351. a3

Dewil, M., Dela Cruz, V. F., Van Den Bosch, L., and Robberecht, W. (2007). Inhibition of p38 mitogen activated protein kinase activation and mutant SOD1(G93A)-induced motor neuron death. *Neurobiol. Dis.* 26, 332–341. doi: 10. 1016/j. nbd. 2006. 12. 023

Dodge, J. C., Haidet, A. M., Yang, W., Passini, M. A., Hester, M., Clarke, J., et al. (2008). Delivery of AAV-IGF-1 to the CNS extends survival in ALS mice through modification of aberrant glial cell activity. *Mol. Ther.* 16, 1056–1064. doi: 10. 1038/mt. 2008. 60

Dugas, J. C., Mandemakers, W., Rogers, M., Ibrahim, A., Daneman, R., and Barres, B. A. (2008). A novel purification method for CNS projection neurons leads to the identification of brain vascular cells as a source of trophic support for corticospinal motor neurons. *J. Neurosci.* 28, 8294–8305. doi: 10. 1523/jneurosci. 2010-08. 2008

Ernfors, P., Lee, K. F., and Jaenisch, R. (1994a). Mice lacking brain-derived neurotrophic factor develop with sensory deficits. *Nature* 368, 147–150. doi: 10. 1038/368147a0

Ernfors, P., Lee, K. F., Kucera, J., and Jaenisch, R. (1994b). Lack of neurotrophin-3 leads to deficiencies in the peripheral nervous system and loss of limb proprioceptive afferents. *Cell* 77, 503–512. doi: 10. 1016/0092-8674(94)90213-5

Forger, N. G., Prevette, D., Delapeyriere, O., De Bovis, B., Wang, S., Bartlett, P., et al. (2003). Cardiotrophin-like cytokine/cytokine-like factor 1 is an essential trophic factor for lumbar and facial motoneurons in vivo. *J. Neurosci.* 23, 8854–8858.

Fryer, H. J., Wolf, D. H., Knox, R. J., Strittmatter, S. M., Pennica, D., O’leary, R. M., et al. (2000). Brain-derived neurotrophic factor induces excitotoxic sensitivity in cultured embryonic rat spinal motor neurons through activation of the phosphatidylinositol 3-kinase pathway. *J. Neurochem.* 74, 582–595. doi: 10. 1046/j. 1471-4159. 2000. 740582. x

Góra-Kupilas, K., and Joško, J. (2005). The neuroprotective function of vascular endothelial growth factor (VEGF). *Folia Neuropathol.* 43, 31–39.

Gordon, P. H. (2013). Amyotrophic lateral sclerosis: an update for 2013 clinical features, pathophysiology, management and therapeutic trials. *Aging Dis.* 4, 295–310. doi: 10. 14336/ad. 2013. 0400295

Gould, T. W., Yonemura, S., Oppenheim, R. W., Ohmori, S., and Enomoto, H. (2008). The neurotrophic effects of glial cell line-derived neurotrophic factor on spinal motoneurons are restricted to fusimotor subtypes. *J. Neurosci.* 28, 2131–2146. doi: 10. 1523/jneurosci. 5185-07. 2008

Grieshammer, U., Lewandoski, M., Prevette, D., Oppenheim, R. W., and Martin, G. R. (1998). Muscle-specific cell ablation conditional upon Cre-mediated DNA recombination in transgenic mice leads to massive spinal and cranial motoneuron loss. *Dev. Biol.* 197, 234–247. doi: 10. 1006/dbio. 1997. 8859

Gros-Louis, F., Laurent, S., Lopes, A. A., Khoris, J., Meininger, V., Camu, W., et al. (2003). Absence of mutations in the hypoxia response element of VEGF in ALS. *Muscle Nerve* 28, 774–775. doi: 10. 1002/mus. 10498

Grundström, E., Askmark, H., Lindeberg, J., Nygren, I., Ebendal, T., and Aquilonius, S. M. (1999). Increased expression of glial cell line-derived neurotrophic factor mRNA in muscle biopsies from patients with amyotrophic lateral sclerosis. *J. Neurol. Sci.* 162, 169–173. doi: 10. 1016/s0022-510x(98)00333-5

Gurney, M. E., Pu, H., Chiu, A. Y., Dal Canto, M. C., Polchow, C. Y., Alexander, D. D., et al. (1994). Motor neuron degeneration in mice that express a human Cu, Zn superoxide dismutase mutation. *Science* 264, 1772–1775. doi: 10. 1126/science. 8209258

Haase, G., Dessaud, E., Garces, A., De Bovis, B., Birling, M., Filippi, P., et al. (2002). GDNF acts through PEA3 to regulate cell body positioning and muscle innervation of specific motor neuron pools. *Neuron* 35, 893–905. doi: 10. 1016/s0896-6273(02)00864-4

Hawryluk, G. W., Mothe, A., Wang, J., Wang, S., Tator, C., and Fehlings, M. G. (2012). An in vivo characterization of trophic factor production following neural precursor cell or bone marrow stromal cell transplantation for spinal cord injury. *Stem Cells Dev.* 21, 2222–2238. doi: 10. 1089/scd. 2011. 0596

Holasek, S. S., Wengenack, T. M., Kandimalla, K. K., Montano, C., Gregor, D. M., Curran, G. L., et al. (2005). Activation of the stress-activated MAP kinase, p38, but not JNK in cortical motor neurons during early presymptomatic stages of amyotrophic lateral sclerosis in transgenic mice. *Brain Res.* 1045, 185–198. doi: 10. 1016/j. brainres. 2005. 03. 037

Hou, S. T., Jiang, S. X., and Smith, R. A. (2008). Permissive and repulsive cues and signalling pathways of axonal outgrowth and regeneration. *Int. Rev. Cell Mol. Biol.* 267, 125–181. doi: 10. 1016/s1937-6448(08)00603-5

Ikeda, O., Murakami, M., Ino, H., Yamazaki, M., Nemoto, T., Koda, M., et al. (2001). Acute up-regulation of brain-derived neurotrophic factor expression resulting from experimentally induced injury in the rat spinal cord. *Acta Neuropathol.* 102, 239–245.

Jones, K. R., Farinas, I., Backus, C., and Reichardt, L. F. (1994). Targeted disruption of the BDNF gene perturbs brain and sensory neuron development but not motor neuron development. *Cell* 76, 989–999. doi: 10. 1016/0092-8674(94)90377-8

Kablar, B., and Rudnicki, M. A. (1999). Development in the absence of skeletal muscle results in the sequential ablation of motor neurons from the spinal cord to the brain. *Dev. Biol.* 208, 93–109. doi: 10. 1006/dbio. 1998. 9184

Kaspar, B. K., Llado, J., Sherkat, N., Rothstein, J. D., and Gage, F. H. (2003). Retrograde viral delivery of IGF-1 prolongs survival in a mouse ALS model. *Science* 301, 839–842. doi: 10. 1126/science. 1086137

Kilic, U., Kilic, E., Jarve, A., Guo, Z., Spudich, A., Bieber, K., et al. (2006). Human vascular endothelial growth factor protects axotomized retinal ganglion cells in vivo by activating ERK-1/2 and Akt pathways. *J. Neurosci.* 26, 12439–12446. doi: 10. 1523/jneurosci. 0434-06. 2006

Kim, S. H., Won, S. J., Sohn, S., Kwon, H. J., Lee, J. Y., Park, J. H., et al. (2002). Brain-derived neurotrophic factor can act as a pronecrotic factor through transcriptional and translational activation of NADPH oxidase. *J. Cell Biol.* 159, 821–831. doi: 10. 1083/jcb. 200112131

Koh, S. H., Roh, H., Lee, S. M., Kim, H. J., Kim, M., Lee, K. W., et al. (2005). Phosphatidylinositol 3-kinase activator reduces motor neuronal cell death induced by G93A or A4V mutant SOD1 gene. *Toxicology* 213, 45–55. doi: 10. 1016/j. tox. 2005. 05. 009

Korsching, S. (1993). The neurotrophic factor concept: a reexamination. *J. Neurosci.* 13, 2739–2748.

Kotzbauer, P. T., and Holtzman, D. M. (2006). Expectations and challenges in the therapeutic use of neurotrophic factors. *Ann. Neurol.* 59, 444–447. doi: 10. 1002/ana. 20794

Krakora, D., Mulcrone, P., Meyer, M., Lewis, C., Bernau, K., Gowing, G., et al. (2013). Synergistic effects of GDNF and VEGF on lifespan and disease progression in a familial als rat model. *Mol. Ther.* 21, 1602–1610. doi: 10. 1038/mt. 2013. 108

Kramer, E. R., Knott, L., Su, F., Dessaud, E., Krull, C. E., Helmbacher, F., et al. (2006). Cooperation between GDNF/Ret and ephrinA/EphA4 signals for motor-axon pathway selection in the limb. *Neuron* 50, 35–47. doi: 10. 1016/j. neuron. 2006. 02. 020

Laaksovirta, H., Soinila, S., Hukkanen, V., Roytta, M., and Soilu-Hanninen, M. (2008). Serum level of CNTF is elevated in patients with amyotrophic lateral sclerosis and correlates with site of disease onset. *Eur. J. Neurol.* 15, 355–359. doi: 10. 1111/j. 1468-1331. 2008. 02080. x

Lai, E. C., Felice, K. J., Festoff, B. W., Gawel, M. J., Gelinas, D. F., Kratz, R., et al. (1997). Effect of recombinant human insulin-like growth factor-I on progression of ALS. A placebo-controlled study. The North America ALS/IGF-I Study Group. *Neurology* 49, 1621–1630. doi: 10. 1212/wnl. 49. 6. 1621

Lambrechts, D., Poesen, K., Fernandez-Santiago, R., Al-Chalabi, A., Del Bo, R., Van Vught, P. W., et al. (2009). Meta-analysis of vascular endothelial growth factor variations in amyotrophic lateral sclerosis: increased susceptibility in male carriers of the -2578AA genotype. *J. Med. Genet.* 46, 840–846. doi: 10. 1136/jmg. 2008. 058222

Leitner, M. L., Molliver, D. C., Osborne, P. A., Vejsada, R., Golden, J. P., Lampe, P. A., et al. (1999). Analysis of the retrograde transport of glial cell line-derived neurotrophic factor (GDNF), neurturin, and persephin suggests that in vivo signaling for the GDNF family is GFRalpha coreceptor-specific. *J. Neurosci.* 19, 9322–9331.

Li, B., Xu, W., Luo, C., Gozal, D., and Liu, R. (2003). VEGF-induced activation of the PI3-K/Akt pathway reduces mutant SOD1-mediated motor neuron cell death. *Brain Res. Mol. Brain Res.* 111, 155–164. doi: 10. 1016/s0169-328x(03)00025-1

Liao, B., Zhao, W., Beers, D. R., Henkel, J. S., and Appel, S. H. (2012). Transformation from a neuroprotective to a neurotoxic microglial phenotype in a mouse model of ALS. *Exp. Neurol.* 237, 147–152. doi: 10. 1016/j. expneurol. 2012. 06. 011

Lunetta, C., Serafini, M., Prelle, A., Magni, P., Dozio, E., Ruscica, M., et al. (2012). Impaired expression of insulin-like growth factor-1 system in skeletal muscle of amyotrophic lateral sclerosis patients. *Muscle Nerve* 45, 200–208. doi: 10. 1002/mus. 22288

Masu, Y., Wolf, E., Holtmann, B., Sendtner, M., Brem, G., and Thoenen, H. (1993). Disruption of the CNTF gene results in motor neuron degeneration. *Nature* 365, 27–32. doi: 10. 1038/365027a0

Matsuzaki, H., Tamatani, M., Yamaguchi, A., Namikawa, K., Kiyama, H., Vitek, M. P., et al. (2001). Vascular endothelial growth factor rescues hippocampal neurons from glutamate-induced toxicity: signal transduction cascades. *FASEB J.* 15, 1218–1220. doi: 10. 1096/fj. 00-0495fje

Mitsumoto, H., Ikeda, K., Holmlund, T., Greene, T., Cedarbaum, J. M., Wong, V., et al. (1994). The effects of ciliary neurotrophic factor on motor dysfunction in wobbler mouse motor neuron disease. *Ann. Neurol.* 36, 142–148. doi: 10. 1002/ana. 410360205

Mohajeri, M. H., Figlewicz, D. A., and Bohn, M. C. (1999). Intramuscular grafts of myoblasts genetically modified to secrete glial cell line-derived neurotrophic factor prevent motoneuron loss and disease progression in a mouse model of familial amyotrophic lateral sclerosis. *Hum. Gene Ther.* 10, 1853–1866. doi: 10. 1089/10430349950017536

Moreau, C., Gosset, P., Kluza, J., Brunaud-Danel, V., Lassalle, P., Marchetti, P., et al. (2011). Deregulation of the hypoxia inducible factor-1alpha pathway in monocytes from sporadic amyotrophic lateral sclerosis patients. *Neuroscience* 172, 110–117. doi: 10. 1016/j. neuroscience. 2010. 10. 040

Morrison, B. M., Janssen, W. G., Gordon, J. W., and Morrison, J. H. (1998). Time course of neuropathology in the spinal cord of G86R superoxide dismutase transgenic mice. *J. Comp. Neurol.* 391, 64–77. doi: 10. 1002/(sici)1096-9861(19980202)391: 1 <64:: aid-cne6> 3. 0. co; 2-p

Morselli, L. L., Bongioanni, P., Genovesi, M., Licitra, R., Rossi, B., Murri, L., et al. (2006). Growth hormone secretion is impaired in amyotrophic lateral sclerosis. *Clin. Endocrinol. (Oxf)* 65, 385–388. doi: 10. 1111/j. 1365-2265. 2006. 02609. x

Mudò, G., Bonomo, A., Di Liberto, V., Frinchi, M., Fuxe, K., and Belluardo, N. (2009). The FGF-2/FGFRs neurotrophic system promotes neurogenesis in the adult brain. *J. Neural Transm.* 116, 995–1005. doi: 10. 1007/s00702-009-0207-z

Nagano, I., Shiote, M., Murakami, T., Kamada, H., Hamakawa, Y., Matsubara, E., et al. (2005). Beneficial effects of intrathecal IGF-1 administration in patients with amyotrophic lateral sclerosis. *Neurol. Res.* 27, 768–772. doi: 10. 1179/016164105x39860

Nagara, Y., Tateishi, T., Yamasaki, R., Hayashi, S., Kawamura, M., Kikuchi, H., et al. (2013). Impaired cytoplasmic-nuclear transport of hypoxia-inducible factor-1alpha in amyotrophic lateral sclerosis. *Brain Pathol.* 23, 534–546. doi: 10. 1111/bpa. 12040

Namikawa, K., Honma, M., Abe, K., Takeda, M., Mansur, K., Obata, T., et al. (2000). Akt/protein kinase B prevents injury-induced motoneuron death and accelerates axonal regeneration. *J. Neurosci.* 20, 2875–2886.

Nguyen, Q. T., Parsadanian, A. S., Snider, W. D., and Lichtman, J. W. (1998). Hyperinnervation of neuromuscular junctions caused by GDNF overexpression in muscle. *Science* 279, 1725–1729. doi: 10. 1126/science. 279. 5357. 1725

Oosthuyse, B., Moons, L., Storkebaum, E., Beck, H., Nuyens, D., Brusselmans, K., et al. (2001). Deletion of the hypoxia-response element in the vascular endothelial growth factor promoter causes motor neuron degeneration. *Nat. Genet.* 28, 131–138. doi: 10. 1038/88842

Oppenheim, R. W. (1991). Cell death during development of the nervous system. *Annu. Rev. Neurosci.* 14, 453–501. doi: 10. 1146/annurev. neuro. 14. 1. 453

Oppenheim, R. W., Haverkamp, L. J., Prevette, D., Mcmanaman, J. L., and Appel, S. H. (1988). Reduction of naturally occurring motoneuron death in vivo by a target-derived neurotrophic factor. *Science* 240, 919–922. doi: 10. 1126/science. 3363373

Oppenheim, R. W., Wiese, S., Prevette, D., Armanini, M., Wang, S., Houenou, L. J., et al. (2001). Cardiotrophin-1, a muscle-derived cytokine, is required for the survival of subpopulations of developing motoneurons. *J. Neurosci.* 21, 1283–1291.

Raoul, C., Buhler, E., Sadeghi, C., Jacquier, A., Aebischer, P., Pettmann, B., et al. (2006). Chronic activation in presymptomatic amyotrophic lateral sclerosis (ALS) mice of a feedback loop involving Fas, Daxx, and FasL. *Proc. Natl. Acad. Sci. U S A* 103, 6007–6012. doi: 10. 1073/pnas. 0508774103

Rosen, D. R., Siddique, T., Patterson, D., Figlewicz, D. A., Sapp, P., Hentati, A., et al. (1993). Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* 362, 59–62. doi: 10. 1038/362059a0

Saccà, F., Quarantelli, M., Rinaldi, C., Tucci, T., Piro, R., Perrotta, G., et al. (2012). A randomized controlled clinical trial of growth hormone in amyotrophic lateral sclerosis: clinical, neuroimaging, and hormonal results. *J. Neurol.* 259, 132–138. doi: 10. 1007/s00415-011-6146-2

Sato, K., Morimoto, N., Kurata, T., Mimoto, T., Miyazaki, K., Ikeda, Y., et al. (2012). Impaired response of hypoxic sensor protein HIF-1alpha and its downstream proteins in the spinal motor neurons of ALS model mice. *Brain Res.* 1473, 55–62. doi: 10. 1016/j. brainres. 2012. 07. 040

Sendtner, M., Schmalbruch, H., Stockli, K. A., Carroll, P., Kreutzberg, G. W., and Thoenen, H. (1992). Ciliary neurotrophic factor prevents degeneration of motor neurons in mouse mutant progressive motor neuronopathy. *Nature* 358, 502–504. doi: 10. 1038/358502a0

Shook, S. J., and Pioro, E. P. (2009). Racing against the clock: recognizing, differentiating, diagnosing and referring the amyotrophic lateral sclerosis patient. *Ann. Neurol.* 65(Suppl. 1), S10–S16. doi: 10. 1002/ana. 21545

Siciliano, G., Carlesi, C., Pasquali, L., Piazza, S., Pietracupa, S., Fornai, F., et al. (2010). Clinical trials for neuroprotection in ALS. *CNS Neurol. Disord. Drug Targets* 9, 305–313. doi: 10. 2174/187152710791292648

Sreedharan, J., and Brown, R. H. Jr. (2013). Amyotrophic lateral sclerosis: problems and prospects. *Ann. Neurol.* 74, 309–316. doi: 10. 1002/ana. 24012

Stephens, B., Guiloff, R. J., Navarrete, R., Newman, P., Nikhar, N., and Lewis, P. (2006). Widespread loss of neuronal populations in the spinal ventral horn in sporadic motor neuron disease. A morphometric study. *J. Neurol. Sci.* 244, 41–58. doi: 10. 1016/j. jns. 2005. 12. 003

Storkebaum, E., Lambrechts, D., Dewerchin, M., Moreno-Murciano, M. P., Appelmans, S., Oh, H., et al. (2005). Treatment of motoneuron degeneration by intracerebroventricular delivery of VEGF in a rat model of ALS. *Nat. Neurosci.* 8, 85–92. doi: 10. 1038/nn1360

Su, H., Zhang, W., Guo, J., Guo, A., Yuan, Q., and Wu, W. (2009). Neural progenitor cells enhance the survival and axonal regeneration of injured motoneurons after transplantation into the avulsed ventral horn of adult rats. *J. Neurotrauma* 26, 67–80. doi: 10. 1089/neu. 2008. 0656

Suzuki, M., and Svendsen, C. N. (2008). Combining growth factor and stem cell therapy for amyotrophic lateral sclerosis. *Trends Neurosci.* 31, 192–198. doi: 10. 1016/j. tins. 2008. 01. 006

Suzuki, M., Mchugh, J., Tork, C., Shelley, B., Hayes, A., Bellantuono, I., et al. (2008). Direct muscle delivery of GDNF with human mesenchymal stem cells improves motor neuron survival and function in a rat model of familial ALS. *Mol. Ther.* 16, 2002–2010. doi: 10. 1038/mt. 2008. 197

Suzuki, M., Mchugh, J., Tork, C., Shelley, B., Klein, S. M., Aebischer, P., et al. (2007). GDNF secreting human neural progenitor cells protect dying motor neurons, but not their projection to muscle, in a rat model of familial ALS. *PLoS One* 2: e689. doi: 10. 1371/journal. pone. 0000689

The BDNF Study Group. (1999). A controlled trial of recombinant methionyl human BDNF in ALS: the BDNF study group (phase III). *Neurology* 52, 1427–1433. doi: 10. 1212/WNL. 52. 7. 1427

Tokumine, J., Sugahara, K., Kakinohana, O., and Marsala, M. (2003). The spinal GDNF level is increased after transient spinal cord ischemia in the rat. *Acta Neurochir. Suppl.* 86, 231–234. doi: 10. 1007/978-3-7091-0651-8\_50

Tolosa, L., Mir, M., Asensio, V. J., Olmos, G., and Llado, J. (2008). Vascular endothelial growth factor protects spinal cord motoneurons against glutamate-induced excitotoxicity via phosphatidylinositol 3-kinase. *J. Neurochem.* 105, 1080–1090. doi: 10. 1111/j. 1471-4159. 2007. 05206. x

Tolosa, L., Mir, M., Olmos, G., and Llado, J. (2009). Vascular endothelial growth factor protects motoneurons from serum deprivation-induced cell death through phosphatidylinositol 3-kinase-mediated p38 mitogen-activated protein kinase inhibition. *Neuroscience* 158, 1348–1355. doi: 10. 1016/j. neuroscience. 2008. 10. 060

Tortarolo, M., Veglianese, P., Calvaresi, N., Botturi, A., Rossi, C., Giorgini, A., et al. (2003). Persistent activation of p38 mitogen-activated protein kinase in a mouse model of familial amyotrophic lateral sclerosis correlates with disease progression. *Mol. Cell. Neurosci.* 23, 180–192. doi: 10. 1016/s1044-7431(03)00022-8

Tovar-Y-Romo, L. B., and Tapia, R. (2010). VEGF protects spinal motor neurons against chronic excitotoxic degeneration in vivo by activation of PI3-K pathway and inhibition of p38MAPK. *J. Neurochem.* 115, 1090–1101. doi: 10. 1111/j. 1471-4159. 2010. 06766. x

Tovar-Y-Romo, L. B., and Tapia, R. (2012). Delayed administration of VEGF rescues spinal motor neurons from death with a short effective time frame in excitotoxic experimental models in vivo. *ASN Neuro* 4, 121–129. doi: 10. 1042/an20110057

Tovar-Y-Romo, L. B., Zepeda, A., and Tapia, R. (2007). Vascular endothelial growth factor prevents paralysis and motoneuron death in a rat model of excitotoxic spinal cord neurodegeneration. *J. Neuropathol. Exp. Neurol.* 66, 913–922. doi: 10. 1097/nen. 0b013e3181567c16

Veglianese, P., Lo Coco, D., Bao Cutrona, M., Magnoni, R., Pennacchini, D., Pozzi, B., et al. (2006). Activation of the p38MAPK cascade is associated with upregulation of TNF alpha receptors in the spinal motor neurons of mouse models of familial ALS. *Mol. Cell. Neurosci.* 31, 218–231. doi: 10. 1016/j. mcn. 2005. 09. 009

Vicario-Abejón, C., Fernández-Moreno, C., Pichel, J. G., and De Pablo, F. (2004). Mice lacking IGF-I and LIF have motoneuron deficits in brain stem nuclei. *Neuroreport* 15, 2769–2772.

Wang, L. J., Lu, Y. Y., Muramatsu, S., Ikeguchi, K., Fujimoto, K., Okada, T., et al. (2002). Neuroprotective effects of glial cell line-derived neurotrophic factor mediated by an adeno-associated virus vector in a transgenic animal model of amyotrophic lateral sclerosis. *J. Neurosci.* 22, 6920–6928.

Wang, Y., Mao, X. O., Xie, L., Banwait, S., Marti, H. H., Greenberg, D. A., et al. (2007). Vascular endothelial growth factor overexpression delays neurodegeneration and prolongs survival in amyotrophic lateral sclerosis mice. *J. Neurosci.* 27, 304–307. doi: 10. 1523/jneurosci. 4433-06. 2007

Wu, D. C., Re, D. B., Nagai, M., Ischiropoulos, H., and Przedborski, S. (2006). The inflammatory NADPH oxidase enzyme modulates motor neuron degeneration in amyotrophic lateral sclerosis mice. *Proc. Natl. Acad. Sci. U S A* 103, 12132–12137. doi: 10. 1073/pnas. 0603670103

Yanpallewar, S. U., Barrick, C. A., Buckley, H., Becker, J., and Tessarollo, L. (2012). Deletion of the BDNF truncated receptor TrkB. T1 delays disease onset in a mouse model of amyotrophic lateral sclerosis. *PLoS One* 7: e39946. doi: 10. 1371/journal. pone. 0039946

Yu, F., Sugawara, T., Maier, C. M., Hsieh, L. B., and Chan, P. H. (2005). Akt/Bad signaling and motor neuron survival after spinal cord injury. *Neurobiol. Dis.* 20, 491–499. doi: 10. 1016/j. nbd. 2005. 04. 004

Zachary, I. (2005). Neuroprotective role of vascular endothelial growth factor: signalling mechanisms, biological function and therapeutic potential. *Neurosignals* 14, 207–221. doi: 10. 1159/000088637

Zheng, C., Nennesmo, I., Fadeel, B., and Henter, J. I. (2004). Vascular endothelial growth factor prolongs survival in a transgenic mouse model of ALS. *Ann. Neurol.* 56, 564–567. doi: 10. 1002/ana. 20223