# Letter to the Editor: Autoimmune pathogenic mechanisms in Amyotrophic Lateral Sclerosis

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Dear Editor,

With this letter we would like to describe the most recent evidences highlighting the crucial role of autoimmunity in Amyotrophic Lateral Sclerosis (ALS) pathogenesis.

ALS is a neurodegenerative disorder characterised by a progressive death of motor neurons, resulting in fatal paralysis in a few years. Hereditary ALS, account for 10% of the cases while in the remaining non-hereditary 90% ALS and does not show any conventional hereditary pattern [1]. The only established risk factors to date are older age, male gender, and a family history of ALS [1].

The cause of ALS and the specific mechanisms of neuronal death remain unknown. Considerable evidences support the existence of autoimmune mechanisms contributing to pathogenesis in ALS, including biochemical, morphological, pharmacological, and physiological studies [1]**.** Typical hallmarks of autoimmunity, such as circulating immune complexes, higher frequency of a particular histocompatibility type, or association with other autoimmune diseases, have also been reported [2]**.**

An important marker of autoimmunity is the degree of T-lymphocytic infiltration in the anterior horn of the spinal cord of ALS patients [3]**.** Hence, inflammation in the ALS spinal cord and brain appears to be primarily due to T-cells and macrophages [4]**,** and aberrant macrophage activity is believed by many investigators to contribute to the pathology underlying ALS.

This may explain the recent promising results of an ALS phase 2 clinical trial of NP001, a regulator of inflammatory macrophage activity [5]**.** Although the predefined endpoints in this study did not reach statistical significance, administration of NP001 was associated with cessation in disease progression in 27% of patients, approximately 2.5 times greater than the percentage in patients on a placebo. Two major plasma markers of inflammation, IL-18 and lipopolysaccharide, differentiated NP001 responders from non-responders, suggesting that the subgroup of patients with greater baseline biomarkers of neuroinflammation experienced the most benefit [5]**.**

Additional evidence pointing toward pathologic involvement of autoimmune processes is the finding that immunoglobulins from ALS patients have been shown to cause apoptosis of motor neurons in primary spinal cord cultures and that passive transfer of immunoglobulins to mice

caused degeneration of motor neurons [6]. These findings suggest that antibodies can contribute to disease pathogenesis. Increased levels of interleukins IL-17 and IL-23 have also been found in serum and cerebrospinal fluid of ALS patients. This increment is thought to be a sign of T-helper 17 activation, a subset of T-cells suggested to be crucial in destructive autoimmunity.

Additional support for the autoimmune pathogenesis hypothesis is the finding that ALS has recently been included in the spectrum of neurologic manifestations associated with voltage-gated potassium channel (VGKC) autoimmunity [7].

Ample evidence now points to a contribution of the innate immune system in ALS. In line with this, microglial cell activation can be found at the sites of neurodegeneration. In addition, the importance of microglia in ALS has recently been highlighted by a study demonstrating that classical NF-κB activation is required to induce motor neuron death in a mutant superoxide dismutase 1 ($SOD1^{G93A}$) mouse model of ALS. These findings are further substantiated by PET imaging of patients with ALS, and studies have suggested that microglial cell activation is increased in affected brain areas. In addition, the extent of microglial cell activation positively correlated with the severity of clinical symptoms in these studies [8].

The innate immune system may affect the function and survival of motor neurons in ALS by at least three mechanisms. First, there is evidence to suggest that aggregates of mutant SOD1—which is derived from microglial and astroglial cells—activate neighbouring microglia by binding to TLR2, TLR4, and CD14, and subsequently promote neuronal cell death [9]. Second, the release of pro-inflammatory cytokines may drive motor neuron damage. Third, although poorly understood, a mechanism has been suggested on the basis of the functional analysis of microglial cells that express mutant SOD1 [10]. These cells showed impaired overall motility and a reduced capacity to clear neuronal cell debris. Impairment of microglial cell phagocytosis may therefore contribute to the accumulation of further immunostimulatory proteins, including mutant SOD1, chromogranin A, and dsRNA, thereby resulting in disease progression.

**References**

[1] Pagani MR, Gonzalez LE, Uchitel OD. Autoimmunity in amyotrophic lateral sclerosis: past and present. Neurol Res Int 2011;2011:497080. doi:10.1155/2011/497080.

[2] Antel JP, Arnason BG, Fuller TC, Lehrich JR. Histocompatibility typing in amyotrophic lateral sclerosis. Arch Neurol 1976;33:423–5.

[3] Troost D, van den Oord JJ, de Jong JM, Swaab DF. Lymphocytic infiltration in the spinal cord of patients with amyotrophic lateral sclerosis. Clin Neuropathol n.d.;8:289–94.

[4] Graves MC, Fiala M, Dinglasan LA V, Liu NQ, Sayre J, Chiappelli F, et al. Inflammation in amyotrophic lateral sclerosis spinal cord and brain is mediated by activated macrophages, mast cells and T cells. Amyotroph Lateral Scler Other Motor Neuron Disord 2004;5:213–9. doi:10.1080/14660820410020286.

[5] Miller RG, Block G, Katz JS, Barohn RJ, Gopalakrishnan V, Cudkowicz M, et al. Randomized phase 2 trial of NP001-a novel immune regulator: Safety and early efficacy in ALS. Neurol Neuroimmunol Neuroinflammation 2015;2:e100–e100. doi:10.1212/NXI.0000000000000100.

[6] Pullen AH, Demestre M, Howard RS, Orrell RW. Passive transfer of purified IgG from patients with amyotrophic lateral sclerosis to mice results in degeneration of motor neurons accompanied by Ca2+ enhancement. Acta Neuropathol 2004;107:35–46. doi:10.1007/s00401-003-0777-z.

[7] Nwosu VK, Royer JA, Stickler DE. Voltage gated potassium channel antibodies in amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2010;11:392–4. doi:10.3109/17482960903452283.

[8] Brettschneider J, Toledo JB, Van Deerlin VM, Elman L, McCluskey L, Lee VM-Y, et al. Microglial activation correlates with disease progression and upper motor neuron clinical symptoms in amyotrophic lateral sclerosis. PLoS One 2012;7:e39216. doi:10.1371/journal.pone.0039216.

[9] Zhao W, Beers DR, Henkel JS, Zhang W, Urushitani M, Julien J-P, et al. Extracellular mutant SOD1 induces microglial-mediated motoneuron injury. Glia 2010;58:231–43. doi:10.1002/glia.20919.

[10] Sargsyan SA, Blackburn DJ, Barber SC, Grosskreutz J, De Vos KJ, Monk PN, et al. A comparison of in vitro properties of resting SOD1 transgenic microglia reveals evidence of reduced neuroprotective function. BMC Neurosci 2011;12:91. doi:10.1186/1471-2202-12-91.