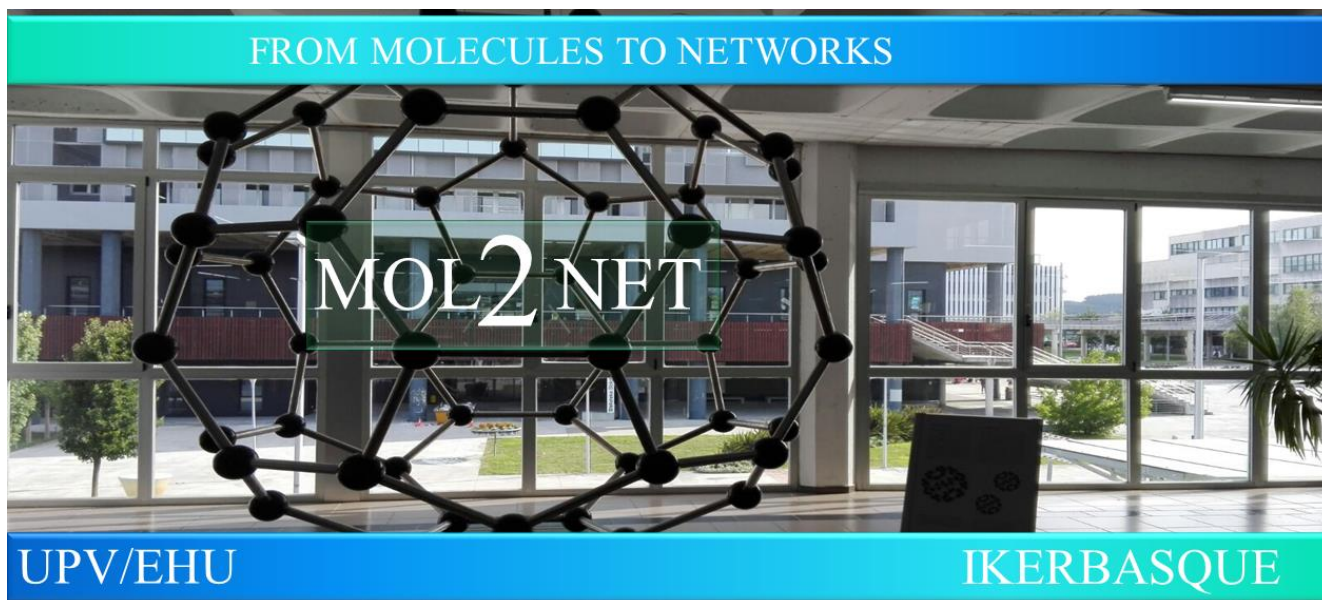




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### LAG-3 Role in Neurological Diseases

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## Abstract.

*Lymphocyte activation gene 3 (LAG-3) is a cell surface inhibitory receptor with multiple biological activities over T cell activation and effector functions. LAG-3 plays a regulatory role in immunity and emerged some time ago as an inhibitory immune checkpoint molecule. A systematic research was performed using PubMed and ClinicalTrial.gov databases. Up-to-date published articles meeting the inclusion criteria were investigated. LAG-3 expression has been linked to increased pathology in neurological diseases. Emerging preclinical and clinical evidence suggests that LAG-3 is associated with an increased risk of Parkinson's disease (PD) (Guo et al, J. Neuroinflammation 2019; Chocarro et al, Int J Mol Sci 2021). A disruption of the immune homeostasis caused by LAG-3 dysfunction in the central nervous system could initiate neuron-to-neuron  $\alpha$ -synuclein aggregation and PD progression. Thus, LAG-3 could serve as a possible therapeutic target to slow the progression of  $\alpha$ -synucleinopathies. In addition, germline allelic variation of the LAG-3 gene has been described to confer susceptibility to multiple sclerosis (Zhang et al, Genes Immun. 2005; Chocarro et al, Int J Mol Sci 2021.) Here, we will discuss the impaired control of cell-mediated immunity associated with high accumulation of LAG-3 in neurological diseases (Chocarro et al, Int J Mol Sci 2021). Interestingly, in vitro blockade of PD-1/LAG-3 interactions enhances cytokine production in response to cancer and infections, and it is showing promising results in several clinical trials for the treatment of various cancers, suggesting it could have a similar effect in neurological disorders (Chocarro et al, IOTTECH 2022). A deeper understanding of the basic mechanisms underlying LAG-3 intracellular signaling will provide insight for further development of novel strategies for autoimmune and neurological disorders (Chocarro et al, Int J Mol Sci 2021).*

**Keywords:** LAG-3; Neurological Diseases; Parkinson's disease;  $\alpha$ -synucleinopathies; Multiple Sclerosis

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