

# ***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

**40° Cycle**

## **Project proposal for a PhD scholarship**

**Title of the research: Investigating the interplay between Epstein-Barr Virus infection and host immune system imbalance in multiple sclerosis pathogenesis**

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### **Summary (max 500 words)**

Multiple sclerosis (MS) is a complex chronic inflammatory disease of the central nervous system (CNS) resulting from still poorly understood interactions between predisposing genes and promoting environmental factors. Among the latter, Epstein-Barr virus (EBV) shows the strongest association with MS. A recent study has provided compelling evidence of the key role of EBV in disease initiation however, the mechanisms linking EBV infection to MS pathology are still unclear and it remains to be determined whether EBV has a role in ongoing disease. Studies from our and other groups showed the presence of EBV-infected B cells and preferential accumulation of EBV-specific CD8 T cells in the post-mortem MS brain tissue. This evidence supports a model of MS in which an active and persistent EBV infection in CNS-infiltrating B cells results in a dysregulated cytotoxic CD8 T-cell response that leads to bystander tissue damage and progressive disability in MS. To shed light on the mechanisms linking EBV to MS, his project aims to further explore the intricate interactions between EBV infection and host-immune system in MS, and in particular:

1. The presence of both EBV and anti-EBV immune response as well as the presence of specific T cell subtypes in post-mortem brain tissue donated by people with secondary progressive MS and collected at the UK MS Tissue Bank of London using both conventional (immunohistochemistry/immunofluorescence, EBER ISH) and innovative (in situ pentamer binding staining, RNAscope) techniques.
2. The EBV infection status (viral DNA/RNA levels) and antibody response to EBV (serum EBNA1 and VCA IgG titers) in the peripheral blood from people with MS (PwMS) at the disease onset and sex and age matched healthy donors (HD).
3. The expression of a large panel of immune genes (about 50) in PBMC from PwMS and HD using high-throughput real-time PCR system

The research activity will be carried out within the framework of funded projects, with particular focus on a project funded by European Union, within the HORIZON Europe programme, coordinated by the German Cancer Research Center (DKFZ, Heidelberg, Germany), which aims at better understanding the association between EBV and MS,

identifying the mechanisms that cause the disease and developing more effective and safer therapies.

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### **Pertinent Publications of the proponent (last 5 years)**

1. Serafini B, Benincasa L, Rosicarelli B, Aloisi F. EBV infected cells in the multiple sclerosis brain express PD-L1: How the virus and its niche may escape immune surveillance. *J Neuroimmunol.* 2024; 389:578314. doi: 10.1016/j.jneuroim.2024.578314.
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9. Veroni C.\*, Serafini B\*, Rosicarelli B, Fagnani C, Aloisi F. Transcriptional profile and Epstein-Barr virus infection status of laser-cut immune infiltrates from the brain of patients with progressive multiple sclerosis. *Journal of Neuroinflammation* 2018; 15(1):18. <https://doi.org/10.1186/s12974-017-1049-5> PMID: 29338732 \*These authors share first authorship.