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

**XXXIX Cycle**

**Project proposal for a PhD scholarship (with no financial support from Sapienza)**

**Title of the research:**

Astrocytes and interleukin-9: a novel axis regulating neuroinflammation in progressive multiple sclerosis

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**Summary**

Progressive multiple sclerosis (MS) affects an estimated one million people in the world and has limited treatment options. The ideal future of progressive MS therapy would involve combination of drugs, which attenuate neuroinflammation, and induce neuroprotection and remyelination.

We previously discovered that interleukin-9 (IL-9) is expressed in brain of progressive MS patients, and is inversely correlated with meningeal inflammation and neurodegeneration.

We demonstrated that IL-9 reduces inflammation in human lymphocytes and microglia/macrophages. Astrocytes are also responsive to IL-9, given their large expression of IL-9 receptor in brain tissue of progressive MS patients. However, the role of IL-9 in astrocytes has not been investigated in detail.

Since astrocytes play a crucial role in progressive MS disease through several mechanisms, involved in both neuroinflammation and neuroprotection, we hypothesised that IL-9 could have a crucial role in regulating astrocyte functionality during disease.

In the present project we aim at exploring the molecular and functional effect of IL-9 in astrocytes using an *in vitro* model of human astrocytes (Aim1). Moreover, the results obtained from *in vitro* experiments will be validated *in vivo* using murine primary astrocytes purified from mice (Aim2).

In order to transfer acquired knowledge to human pathology, we plan to analyse the expression of soluble factors, identified and validated in previous aims as expressed by astrocytes and modulated by IL-9, in serum and cerebrospinal fluid of progressive MS patients. The values of those factors will be correlated to the levels of markers of glial activation, such as glial fibrillary acidic protein (GFAP), as well as to clinical parameters of each MS patients (Aim3).

This project will better elucidate the role of IL-9 in progressive forms of MS, and might lead to the identification of new pathways regulating astrocyte functions, and involved in progressive MS disease.

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

1. Pattarini L, Trichot C, Bogiatzi S, Grandclaudon M, Meller S, Keuylian Z, Durand M, Volpe E, Madonna S, Cavani A, Chiricozzi A, Romanelli M, Hori T, Hovnanian A, Homey B, Soumelis V. TSLP-activated dendritic cells induce human T follicular helper cell differentiation through OX40-ligand. J Exp Med.,2017

2. Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. Scanning the Immunopathogenesis of Psoriasis. Int J Mol Sci., 2018

3. Bielli P, Panzeri V, Lattanzio R, Mutascio S, Pieraccioli M, Volpe E, Pagliarulo V, Piantelli M, Giannantoni A, Di Stasi SM, Sette C. The splicing factor PTBP1 promotes expression of oncogenic splice variants and predicts poor prognosis in patients with non-muscle invasive bladder cancer.Clin Cancer Res., 2018

4. Volpe E, Cesari E, Mercatelli N, Cicconi R, De Bardi M, Capone A, Bonvissuto D, Fraziano M, Mattei M, Battistini L, Paronetto MP, Sette C. The RNA binding protein Sam68 controls T helper 1 differentiation and anti-mycobacterial response through modulation of miR-29. Cell Death Differ., 2018

5. Becher J, Simula L, Volpe E, Procaccini C, La Rocca C, D'Acunzo P, Cianfanelli V, Strappazzon F, Caruana I, Nazio F, Weber G, Gigantino V, Botti G, Ciccosanti F, Borsellino G, Campello S, Mandolesi G, De Bardi M, Fimia GM, D'Amelio M, Ruffini F, Furlan R, Centonze D, Martino G, Braghetta P, Chrisam M, Bonaldo P, Matarese G, Locatelli

F, Battistini L, Cecconi F. AMBRA1 Controls Regulatory T-Cell Differentiation and Homeostasis Upstream of the FOXO3-FOXP3 Axis. Dev Cell., 2018

6. Corsetti M, Ruocco G, Ruggieri S, Gasperini C, Battistini L, Volpe E. Resiquimod-Mediated Activation of Plasmacytoid Dendritic Cells Is Amplified in Multiple Sclerosis. Int J Mol Sci., 2019

7. Capone A, Bianco M, Ruocco G, De Bardi M, Battistini L, Ruggier L, Gasperini C, Centonze D, Sette C, Volpe E. Distinct Expression of Inflammatory Features in T Helper 17 Cells from Multiple Sclerosis Patients. Cells, 2019

8. Kunkl M, Frascolla S, Amormino C, Volpe E, Tuosto L. T helper cells: the modulators of inflammation in multiple sclerosis. Cells, 2020

9. Capone A, Volpe E, Transcriptional regulators of T helper 17 cell differentiation in health and autoimmune diseases. Frontiers in Immunology, 2020

10. Donninelli G, Saraf Sinik I, Mazziotti V, Capone A, Grasso M G, Battistini L, Reynolds R, Magliozzi R, Volpe E. Interleukin-9 regulates macrophage activation in the progressive multiple sclerosis brain. Journal of Neuroinflammation, 2020

11. Cortese A, Lova L, Comoli P, Volpe E, Villa S, Mallucci G, La Salvia S, Romani A, Franciotta D, Bollati V, Basso S, Guido I, Quartuccio G, Battistini L, Cereda C, Bergamaschi R. Air pollution as a contributor to the inflammatory activity of multiple sclerosis. Journal of Neuroinflammation 2020

12. De Paola E, Forcina L, Pelosi L, Pisu S, La Rosa P, Cesari E, Nicoletti C, Madaro L, Mercatelli N, Biamonte F, Nobili A, D'Amelio M, De Bardi M, Volpe E, Caporossi D, Sette C, Musarò A, Paronetto MP. Sam68 splicing regulation contributes to motor unit establishment in the postnatal skeletal muscle. Life Science Alliance, 2020

13. Capone A. and Volpe E. Identification and purification of human memory T helper cells from peripheral blood. In:Annunziato, Francesco, Maggi, Laura, Mazzoni, Alessio editors. T-Helper Cells. Methods in Molecular Biology, 2021

14. Donninelli G, Studer V, Brambilla L, Zecca C, Peluso D, Laroni A, Michelis D, Mantegazza R, Confalonieri P, Volpe E. Immune soluble factors in the cerebbrospinal fluid of progressive multiple sclerosis patients segregate into two groups. Front Immunol., 2021

15. Capone A, Naro C, Bianco M, De Bardi M, Noel F, Macchi P, Battistini L, Soumelis V, Sette C, Volpe E. Systems analysis of human T helper17 cell differentiation uncovers distinct time-regulated transcriptional modules. iScience 2021

16. Carbone ML, Madonna G, Capone A, Bove M, Mastroeni S, Levati L, Capone M, Ascierto PA, De Galitiis F, D'Atri S, Fortes C, Failla CM, Volpe E. Vitiligo-specific soluble biomarkers as early indicators of response to immune checkpoint inhibitors in metastatic melanoma patients. Sci Rep. 2022

17. De Marco L, D'Orso S, Pirronello M, Verdiani A, Termine A, Fabrizio C, Capone A, Sabatini A, Guerrera G, Placido R, Sambucci M, Angelini DF, Giannessi F, Picozza M, Caltagirone C, Salvia A, Volpe E, Balice MP, Rossini A, Rötzschke O, Giardina E, Battistini L, Borsellino G. Assessment of T-cell Reactivity to the SARS-CoV-2 Omicron Variant by Immunized Individuals. JAMA Netw Open. 2022

18. Sabatini A, Guerrera G, Corsetti M, Ruocco G, De Bardi M, Renzi S, Cavalieri D, Battistini L, Angelini DF, Volpe E. Human conventional and plasmacytoid dendritic cells differ in their ability to respond to Saccharomyces cerevisiae. Frontiers in Immunology 2022.

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3. Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Munch, A. E., Chung, W. S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., Stevens, B. and Barres, B. A., Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 2017. 541: 481-487.

4. Colombo, E. and Farina, C., Astrocytes: Key Regulators of Neuroinflammation. *Trends Immunol* 2016. 37: 608-620.

5. Rosengren, L. E., Lycke, J. and Andersen, O., Glial fibrillary acidic protein in CSF of multiple sclerosis patients: relation to neurological deficit. *J Neurol Sci* 1995. 133: 61-65.

6. Jack, C. S., Arbour, N., Manusow, J., Montgrain, V., Blain, M., McCrea, E., Shapiro, A. and Antel, J. P., TLR signaling tailors innate immune responses in human microglia and astrocytes. *J Immunol* 2005. 175: 4320-4330.