

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 02 of 16/01/2026 PO 20 Page 4 of 8</p>
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PROJECT

Supervisor: Federica Esposito

Title: Central and peripheral immunophenotyping to unravel intra-disease heterogeneity in multiple sclerosis and neuromyelitis optica spectrum disorder

Curriculum: Neuroscience and Experimental Neurology

Link to the personal page of the University or relevant hospital site website:

<http://research.hsr.it/en/institutes/institute-of-experimental-neurology/human-genetics-of-neurological-disorders.html>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Multiple sclerosis (MS) is characterized by broad heterogeneity in clinical manifestations, pathophysiology, neuroradiological features and treatment response, suggesting that distinct molecular and immunological profiles underlie individual disease trajectories. This variability likely reflects differences in patients' immunological status, which remain only partially understood. A comparable heterogeneity is increasingly recognized in neuromyelitis optica spectrum disorder (NMOSD), particularly in aquaporin-4 antibody (AQP4-IgG) seropositive patients, where clinical severity, lesion distribution and disease course are not fully explained by antibody presence alone. However, how immunological diversity translates into phenotypic variability within and across these diseases remains largely undefined.

Rationale and hypothesis

We hypothesize that the phenotypic heterogeneity observed in MS reflects an underlying immunological heterogeneity driven by distinct immune repertoires and their interactions. A similar concept may apply to NMOSD, where antibody-mediated and cellular mechanisms could variably contribute to disease expression. Dissecting immune heterogeneity at the single-cell and individual level may provide a framework to capture phenotypic variability and to study this phenomenon at a higher magnitude of resolution.

Objectives and specific aims

The study aims to investigate whether distinct immune repertoire profiles are associated with disease heterogeneity in MS and, in an exploratory manner, in NMOSD. In MS patients at diagnosis, we will analyze T and B cell immune repertoires in CSF and peripheral blood. Single-cell omics will be performed on CSF-derived cells, and bulk sequencing on T and B cells from PBMCs, characterizing T-cell receptor (TCR) and B-cell receptor (BCR) repertoires in terms of diversity and architecture across different phenotypes (PPMS, elderly RRMS, young RRMS). These profiles will be correlated with clinical activity and disease progression over 2-year follow-up. In parallel, NMOSD patients will be included for an exploratory characterization of peripheral immune profiles and their association with clinical and radiological variability. In selected cases, additional analyses may further address qualitative features of the humoral immune response.

Expected outcomes



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CSF immune profiling is expected to provide insights into CNS-compartmentalized processes, while paired blood analyses will inform on CNS-periphery relationships. This integrative approach may identify immune signatures associated with clinical and radiological phenotypes and support the discovery of accessible biomarkers.

Extending the analysis to NMOSD may clarify shared and disease-specific mechanisms underlying immune-driven heterogeneity, contributing to a more mechanism-based patient stratification and personalized therapeutic approaches.

Skills that the student should acquire (max. 600 characters including spaces):

The student will acquire expertise in advanced large-scale data analysis and integrative immunological profiling. She/he will learn how to analyze next-generation sequencing data, including quality control and statistical interpretation, and how to integrate multi-layer datasets (e.g. immune repertoire, clinical and MRI data) to investigate disease heterogeneity.

References (max. 15)

- [1] Hauser SL, Oksenberg JR. The Neurobiology of Multiple Sclerosis: Genes, Inflammation, and Neurodegeneration. *Neuron*. 2006
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- [4] Gross CC, Schulte-Mecklenbeck A, Steinberg OV et al. Multiple sclerosis endophenotypes identified by high-dimensional blood signatures are associated with distinct disease trajectories. *Sci Transl Med* 2024
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- [7] Vaknin-Dembinsky A, Brill L, Kassis I, et al. T-cell responses to distinct AQP4 peptides in patients with neuromyelitis optica. *Mult Scler Relat Disord*. 2016
- [8] Varrin-Doyer M, Spencer CM, Schulze-Topphoff U, et al. Aquaporin 4-specific T cells in neuromyelitis optica exhibit a Th17 bias and recognize Clostridium ABC transporter. *Ann Neurol*. 2012
- [9] Nakajima A, Yanagimura F, Saji E, et al. Stage-dependent immunity orchestrates AQP4 antibody-guided NMOSD pathology. *Acta Neuropathol*. 2024