PROGETTO

Supervisore:	Federica Esposito
Titolo/*Title*:	Evaluation of changes induced by Ocrelizumab on the T and B-lymphocyte repertoire in Relapsing-Remitting multiple sclerosis patients
Curriculum:	Neuroscience and Experimental Neurology
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/institutes/institute-of-experimental-neurology/human-genetics-of-neurological-disorders.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Multiple Sclerosis (MS) is an autoimmune disorder of the central nervous system characterized by inflammation, demyelination and axonal degeneration [1]. Therapies with a high anti-inflammatory effect could significantly impact disease course and improve MS prognosis, blocking the accumulation of brain damage and reducing inflammation-related neurodegeneration. Among these drugs, ocrelizumab (OCRE) is a recombinant humanized anti-CD20 monoclonal antibody that selectively binds B cells expressing CD20 [2].

Rationale and hypothesis

Our hypothesis is that OCRE therapy is able to induce changes in immune cells that could be used as markers of drug efficacy. We believe that the evaluation of the drug-induced effects directly measured at patient level may reveal the underlying drug mechanism and facilitate the identification of markers of efficacy to be implemented in the clinical practice.

Objectives and specific aims

The present study is aimed at investigating the immunological changes of the T and B cell repertoire induced by OCRE treatment in MS patients, in order to define markers of drug efficacy that could be used in clinical practice to improve treatment management.

The project includes the analysis of the immune repertoire of T and B-lymphocytes in MS patients for which blood samples have already been collected at baseline (before starting the

treatment), after 6 months, and after 2 years under treatment. Specifically, *"BULK DNA analysis"* will be performed on $CD4^+$ memory T cells ($CD3^+$, $CD4^+$, $CD45RO^+$) and $CD8^+$ memory T cells ($CD3^+$, $CD8^+$, $CD45RO^+$) in 20 MS patients, while in a smaller subset of patients (n=6) a single cell analysis will also be performed (*"SINGLE CELL analysis"*) starting from sorted $CD4^+$ T cells and B cells. Clonal persistence, as well as clonality and diversity of repertoires at the 3 timepoints will be evaluated with the aim of identifying significant immunological changes induced by OCRE treatment. The student will be involved in the analysis of genetic and genomic data, in statistical analyses and in the interpretation of the results.

Expected outcomes

TCR and BCR sequencing represents a novel methodology. This kind of approach represents an unique opportunity to broaden our knowledge on the biological mechanisms affected by Ocrelizumab treatment in the context of MS and to investigate the basis of its long-term effect. Results may help to identify biomarkers able to monitor the treatment effect, towards an early identification of patients who are more likely to respond to the drug.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The student will learn how to design and perform next-generation sequencing approaches. She/he will acquire expertise in large–scale data analyses, with a focus on the analysis of the immune repertoire at bulk and single-cell configurations, as well as on the assessment of tanscriptomic profiling. Dedicated tools and approaches will be used.

Bibliografia (max. 15)

[1] Hauser SL, Oksenberg JR. The Neurobiology of Multiple Sclerosis: Genes, Inflammation, and Neurodegeneration. Neuron. 2006

[2] Syed YY. Ocrelizumab: A Review in Multiple Sclerosis. CNS Drugs. 2018