Tittle: To assess antigenic specificity of CNS-autoreactive antibodies in MS patients

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Despite indisputable improvements in multiple sclerosis (MS) management owing to effective disease modifying therapies (DMTs), there is still no cure for this disease. A key feature of MS is the presence of immune cells in the central nervous system (CNS) that mediate inflammation and demyelination, resulting in oligodendrocyte loss, astrogliosis and ultimately axonal damage. It is commonly thought that MS is triggered by a combination of a genetic background and environmental factors. Among the latter, Epstein-Barr virus (EBV) seems to play a crucial role. Indeed, an accumulation of data establishes that infection with EBV is a necessary, although not sufficient, condition to develop MS. Here, we propose to address two central questions in the field of MS: i) is there a cellular and/or humoral immune response against CNS auto-antigens? and ii) would the implication of EBV in the etiopathogenesis of MS be mediated by molecular mimicry between this virus and the CNS? In an attempt to answer these questions, we focus in the lab on two major components of the immune response: CD8+ T cells and antibodies, being the focus of this project, two key components of the adaptive immune response in MS. The quest of CNS auto-antigen and molecular mimicry between EBV and the CNS has already been examined by different authors, but we hypothesize that the conditions to successfully address these two questions were generally not met. Indeed, here, we propose resorting to a platform with CNS cells differentiated from human induced pluripotent stem cells (hiPSCs) being reprogrammed from erythroblasts of MS patients and healthy donors (HD). With this unique setting, a very large array of CNS potential auto-antigens can be presented i) in a non-hypothesis driven fashion and, ii) with the correct conformation to antibodies. We have already reprogrammed hiPSC from 8 MS patients and 6 HD and have been able to differentiate them into astrocytes, neurons, oligodendrocytes and endothelial cells from the blood-brain barrier (the latter in a collaborative work). We have already identified up to 20% of MS patients harboring antibodies directed against neurons or astrocytes in the serum or CSF.

Building on these findings, we propose that the MD PhD student will **assess antigenic specificity of CNS-autoreactive antibodies in MS patients, specifically he / she will:**

AIM I. assess the CNS-reactive antibody profile of MS patients versus controls in blood and CSF

AIM II. determine the antigen targeted by selected CNS-specific antibodies to help in refining MS subsets

AIM III. identify cross-reactivity from CNS-specific monoclonal antibodies to EBV motifs in MS patients

We believe that the proposed studies have the potential to lead to the identification of epitopes targeted by auto-antibodies. Study results could contribute to design very selective DMTs with higher efficacy and less side effects than the current ones. Our findings could also conduct to the establishment of biomarkers of the disease. Finally, this setting should establish whether molecular mimicry between EBV and the CNS does exist, at least as antibodies are concerned, which may have profound therapeutic implications.