

ADIS Abstract

Alzheimer's Disease (AD) and related dementias are heterogeneous multifactorial diseases, involving a range of etiopathogenic mechanisms that lead to neuronal death and loss of cognitive function. It is assumed that the disease starts decades before diagnosis, which imposes a great challenge for treatment. Identification of prognostic biomarkers for AD is thus of utmost importance. Sleep-wake alterations are common in AD due to the dysfunction of the noradrenergic system. The early degeneration of the main noradrenergic brainstem nucleus (i.e., locus) and its consequent noradrenergic dysfunction, is an important driver of sleep-wake alterations and AD pathogenesis. There is increasing evidence regarding the involvement of the systemic immune system into the pathophysiology and resolution of AD. Thus, understanding the mechanisms linking cognitive impairment, sleep disturbances and inflammation could facilitate earlier diagnosis of the disease. While some immunological events were associated with disease progression, recruitment of immune-regulating cells is required for reducing local central nervous system (CNS) inflammatory response, eliminating toxic elements and enhancing cell renewal and repair. This suggests that peripheral immune profiles can reflect characteristics of the disease. Indeed, it was recently demonstrated that a peripheral immune signature of a subtype of cytotoxic CD8 effector memory T (TM) cells is associated with AD. Another type of cytotoxic lymphocytes are Natural Killer (NK) cells, which their role in AD is poorly understood. Importantly, both ImmunoBrain Checkpoint (IBC) and SCAI demonstrated the link of NK cells to AD, in independent studies on unrelated cohorts, using totally different approaches, either experimentally or artificial intelligence (AI), respectively. In the current program we will thoroughly characterize the role of peripheral blood cytotoxic lymphocytes as potential markers for prediction of AD and investigate the influence of sleep disturbances on these markers. Using a multidisciplinary approach for multi-omics deep immune profiling, combined with AI and Agent-Based-Modeling (ABM), this project is expected to reveal novel immune and digitally assessed physiology signatures for early prediction of the disease that can appear early in the course of the disease and are associated with rapid clinical decline.