Background and Description of Invention. Microvesicles (MVs) have been indicated as important mediators of intercellular communication and are emerging as new biomarkers of tissue damage. MVs released by microglia/macrophages in vivo were detected in cerebrospinal fluids (CSF) of healthy controls. In relapsing and remitting experimental autoimmune encephalomyelitis (EAE) mice, the concentration of myeloid MVs in the CSF was significantly increased and closely associated to disease course. Analysis of MVs in the CSF of 28 relapsing patients and 28 patients with clinical isolated syndrome (CIS) from two independent cohorts, revealed higher levels of myeloid MVs than in 13 matched-age controls, indicating a clinical value of MVs as companion tool to capture disease activity diagnosis. Myeloid MVs were found to spread inflammatory signals both in vitro and in vivo, at the site of administration, while mice impaired in MV shedding were protected from EAE, suggesting a pathogenic role for MVs in the disease. Interestingly, FTY720 (a specific inhibitor of A-SMase, the enzyme that controls MV production, and the first approved oral MS drug), significantly reduced the amount of MVs in the CSF of EAE treated mice. These findings identify myeloid MVs as a valuable marker and therapeutic target of brain inflammation (Verderio et al., Annals of Neurology 2012; Agosta et al., Annals of Neurology 2014).


Stage of Development. To verify whether the findings obtained in the mouse model can be extended to humans, scientists collected CSF from two independent cohorts of healthy donors, patients with CIS, patients with definite primary progressive or relapsing-remitting multiple sclerosis (PPMS and RRMS, respectively), the latter during a stable phase of the disease (stable RRMS), or during an acute attack (acute RRMS) and patients from other neurologic diseases. These data indicate CSF MVs as novel exploratory biomarker of microglia/macrophage activation. Myeloid MVs were significantly increased in the CSF from both cohorts of CIS and relapsing RRMS patients (Figure below). Furthermore, the pathogenic role of MVs in the inflammatory response was demonstrated in vivo by showing that injection of microglia-derived MVs induces the formation of inflammatory foci at the site of delivery.
We seek a potential commercial partner focused on companion diagnostic and novel therapeutic approaches for treating neuroinflammation in neurological disorders.

Potential Applications and Competitive Advantages. CSF myeloid MVs can be exploited as novel exploratory biomarkers of microglia/macrophage activation in vivo. In MS, the most common neuroinflammatory disease, CSF MVs may be useful as companion tool to monitor disease diagnosis activity drugs efficacy, or to identify very active patients likely to need a prompt shift to second line treatments or CIS patients needing early treatment.

Microglia activation, however, is also associated to several other CNS diseases, like, for example, neuromyelitis optica, or brain tumors, that in fact display increased CSF MVs. Thus CSF MVs monitoring may provide valuable information in several different neurological disorders.

The inventors also propose that MVs produced by microglia/macrophages and leaking into the CSF may represent a rich source of information on microglia/macrophage activation in the brain, which may lead to the identification of specific disease cell signatures through the analysis of their content.

Several advantages can be envisaged:
- The concentration of microglia/macrophage-derived MVs in mouse CSF reflects the course and severity of EAE. Consistently, the amount of MVs in human CSF is higher in patients presenting with the first clinical symptom of MS or in relapsing patients as compared to patients in a stable phase of the disease or healthy controls.
- Given MVs are a unique way for exchanging integrated signals, targeting MVs may represent a therapeutic strategy more advantageous than classical approaches aimed at neutralizing single inflammatory molecules in MS.

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