A high-molecular weight and soluble hexameric form of endogenous retroviral protein, pHERV-W ENV, is specifically extracted from demyelinating MS lesions and can be detected in sera from active MS patients.

Running title: *Soluble hexameric pHERV-W ENV antigen in MS.*

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In Multiple Sclerosis (MS), pHERV-W-ENV (formerly MSRV-Env) is abnormally expressed. It displays pro-inflammatory and neurodegenerative effects (reviewed in Küry et al. Trends Mol Med 2018). pHERV-W ENV is being targeted by a humanized monoclonal antibody in clinical trials in MS patients (NCT01639300 ; NCT02782858).

We characterized pHERV-W-Env immunobiochemical profile from MS demyelinating lesions and sera with WES capillary immunoelectrophoresis. Snap-frozen brain blocks were obtained from Netherlands Brain Bank (VUMC-ethics committee, Amsterdam). Frozen sera were collected from a longitudinal prospective observational study (AMIR), with signed informed consents.

In transfected cells, insoluble monomer and trimer and a soluble hexamer (360-400KDa) were observed. Monoclonals targeting pHERV-W specific epitopes in SU and TM domains did not cross-react with syncytin or GFP. Deglycosylation disrupted recombinant hexamers and trimers with parallel increase in monomers.

Similar oligomers were seen from active MS lesions. The soluble fraction only contained the hexamer detected by anti-SU monoclonal but unlike transfected cells, the TM region was only detected after deglycosylation within a maintained hexameric form. Oligomers were not detected in MS NAWM or WM from non-MS controls. Since HERV-W was first identified from virion-like particles produced by leptomeningeal and B-lymphocyte cultures (Perron et al. 1997. PNAS) and its envelope was shown to block remyelination (Kremer et al. 2013 Ann. Neurol), this raises question about its possible identity with the MS-B-cell secreted factor (>300KDa) associated with sub-pial cortical demyelination (Lassmann Exp Neurol. 2014).

In pilot series, this soluble hexamer was detected in sera of active RRMS, SPMS and PPMS, but not in 20 healthy controls. 10/14 RRMS subjects classified as active were HERV+, versus 4 of 30 clinically and radiologically stable RRMS patients (Chi-2 y.c. $p<0.001$). In progressive patients 9/10 subjects were HERV+, suggesting that this soluble pHERV-W-ENV hexamer could also be a biomarker for disease activity and progression.

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