**Regulatory T cells in multiple sclerosis: from methylation to (re)myelination**

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*Funding Statement: This work was funded by grant from GMSI (Grant for Multiple Sclerosis Innovation), by Merck KGaA (CrossRef Funder ID: 10.13039/100009945) to support research addressing unmet needs*

Multiple sclerosis (MS) is an autoimmune-induced demyelinating disease of the central nervous system (CNS). Focal demyelination, the primary hallmark of MS, results in neurodegeneration as a result of oligodendrocyte death and loss of axonal function. In MS, regulatory T cells (Tregs), which possess regenerative functions, are compromised. In homeostatic conditions, Tregs promote remyelination through the secretion of factors such as nephroblastoma overexpressed (NOV/CCN3), leukaemia inhibitory factor (LIF), inhibitor of differentiation 2 (ID2) and transforming growth factor β (TGF-β). However, it is thought that in MS, the epigenetic imprinting of Tregs is altered during the course of the disease causing a decrease in the function of Tregs. Targeting the remyelination pathway of Tregs may have ground-breaking implications for progressive MS (pMS) patients, for whom there are currently no approved treatments to target repair. Recently, we have investigated the methylation pattern of ID2 in MS patients (RRMS and SPMS) and controls through pyrosequencing. We have shown that SPMS derived Tregs display a hypermethylated pattern of inhibitor of differentiation 2 (ID2) compared to RRMS and healthy control derived Tregs. As ID2 is a regulator of Treg function, these results are intriguing and may indicate that other Treg-associated genes are also differentially methylated between MS patients and controls. Therefore, we aim to determine which Treg-associated remyelination-inducing genes have an altered epigenetic imprinting in MS patients and whether epigenetic editing of those genes is able to promote remyelination through the adoptive transfer of epigenetically edited Tregs into models of MS. Ultimately, we aim to investigate a potential cell-based autologous Treg therapy for remyelination in pMS.

**Keywords:** Regulatory T cells, epigenetics, multiple sclerosis