MicroRNAs regulate human brain endothelial cell barrier function in inflammation: implications for multiple sclerosis
Arie Reijerkerk1*, M. Alejandro Lopez-Ramirez2*, Bert van het Hof1, Joost A.R. Drexhage1, Wouter Kamphuis1, Gijs Kooij1, Joost B. Vos1, Tineke C.T.M van der Pouw Kraan3, Anton J. van Zonneveld4, Anton J. Horrevoets3, Alex Prat7, Ignacio A. Romero2, and Helga E. de Vries1&

1Blood-Brain Barrier Research Group, Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands. 2Department of Life, Health & Chemical Sciences, The Open University, Milton Keynes, United Kingdom. 3Department of Pediatric Oncology/Hematology, Sophia Children’s Hospital, Rotterdam, the Netherlands. 4Division of Gene Regulation, Netherlands Cancer Institute, Amsterdam, the Netherlands. 5Department of Nephrology and Eindhoven Laboratory for Experimental Vascular Research, Leiden University Medical Center, the Netherlands. 7Neuroimmunology Research Laboratory, CHUM-Notre-Dame Hospital, Montréal, Canada.

Background
The blood-brain barrier (BBB) tightly controls the homeostasis of the central nervous system (CNS) and actively limits entry of blood-borne molecules and circulating leukocytes. In essence the BBB is formed by specialized endothelial cells that are sealed together by intercellular tight junction protein complexes. Disruption and immune activation of the BBB is a central and early feature of multiple sclerosis (MS), a chronic inflammatory disorder of the central nervous system (CNS). Grasping of the underlying mechanisms of barrier disruption in MS may lead to the development of novel and selective routes of intervention to prevent the influx of inflammatory cells into the CNS. MicroRNAs, endogenous non-coding small RNAs, are now recognized to play a critical role in key cellular functions by specifically repressing gene expression. There are several microRNAs that have been identified in endothelial cells and they have been implicated in primary endothelial cell function and angiogenesis, but to date no microRNAs that regulate barrier function have been identified.

Material and Methods
The tissues were obtained from The Netherlands Brain Bank (NBB), Netherlands Institute for Neuroscience, Amsterdam. Brain capillaries were isolated from periventricular non-neurological patient tissue, periventricular normal appearing white matter (NAWM) and periventricular MS lesions from post-mortem MS patients. Using a genomics approach, we defined a microRNA signature which is altered at the BBB of MS patients.

Results and conclusion
Our novel data show that a set of microRNAs modulates BBB function under normal and inflammatory conditions. Most importantly, levels of BBB-associated microRNAs were diminished in isolated MS patient capillaries. Together, our findings uncover an unprecedented and exciting regulatory mechanism of brain endothelial cell barrier function in health and disease and provide novel opportunities to treat neurovascular-dependent brain diseases through microRNAs.

Reference: Reijerkerk et al., J Neuroscience 2013