

## “Stroke and the cell therapy saga: towards a safe, swift and efficient utilization of cells”

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The first clinical trials of cell therapy in stroke were first published in the 2000s and consisted of neural stem cells transplanted via the intracerebral pathway. Since mesenchymal stem cells showed similar capacities to differentiate into neural cells and allowed autologous cell transplantation, they were then preferentially studied, including diabetes and hypertension. More recently, bone marrow derived mononuclear cells were successfully transplanted in stroke with no need of culture processing, and simple collection by density gradient centrifugation rendering them immediately ready for use. They improve post-stroke neurological deficit in rodents and clinical trials have shown the feasibility of intra-arterial or intravenous administration. The underlying mechanisms are not yet understood. We investigated the therapeutic potential of peripheral blood derived mononuclear cells (PB-MNC) harvested from diabetic patients and stimulated by ephrin-B2 (PB-MNC+). We showed that intravenously injected PB-MNC+ after cerebral ischemia reduced infarct volume at day 3, increased cell proliferation in the peri-infarct area and the subventricular zone, decreased microglial cell density, and upregulated TGF- $\beta$  expression. At D14, microvessel density was increased and functional recovery enhanced, whereas plasma levels of BDNF were increased in treated mice. Ephrin-B2 induced phenotype switching of PB-MNC by upregulating genes controlling cell proliferation, inflammation and angiogenesis, as confirmed by adhesion and Matrigel assays. PB-MNC+ transplantation in stroke is a promising approach and should be investigated for the development of rapid, non-invasive bedside cell therapy strategies in stroke.