Millard, S. M. and N. M. Fisk (2013). "Mesenchymal stem cells for systemic therapy: shotgun approach or magic bullets?" Bioessays 35(3): 173-182.

Given their heterogeneity and lack of defining markers, it is surprising that multipotent mesenchymal stem/stromal cells (MSCs) have attracted so much translational attention, especially as increasing evidence points to their predominant effect being not by donor differentiation but via paracrine mediators and exosomes. Achieving long-term MSC donor chimerism for treatment of chronic disease remains a challenge, requiring enhanced MSC homing/engraftment properties and manipulation of niches to direct MSC behaviour. Meanwhile advances in nanoparticle technology are furthering the development of MSCs as vehicles for targeted drug delivery. For treatment of acute injuries, systemic cell-free exosome delivery may ultimately displace current emphasis on empiric donor-cell transplantation for anti-inflammatory, immunomodulatory and repair-promoting effects. Exploration of potential clinical sources of MSCs has led to increased utilisation of perinatal MSCs in allogeneic clinical trials, reflecting their ease of collection and developmentally advantageous properties.

Xin, H., et al. (2013). "Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats." J Cereb Blood Flow Metab 33(11): 1711-1715.

Here, for the first time, we test a novel hypothesis that systemic treatment of stroke with exosomes derived from multipotent mesenchymal stromal cells (MSCs) promote neurovascular remodeling and functional recovery after stroke in rats. Adult male Wistar rats were subjected to 2 hours of middle cerebral artery occlusion (MCAo) followed by tail vein injection of 100 mug protein from MSC exosome precipitates or an equal volume of vehicle phosphate-buffered saline (PBS) (n=6/group) 24 hours later. Animals were killed at 28 days after stroke and histopathology and immunohistochemistry were employed to identify neurite remodeling, neurogenesis, and angiogenesis. Systemic administration of MSC-generated exosomes significantly improved functional recovery in stroke rats compared with PBS-treated controls. Axonal density and synaptophysin-positive areas were significantly increased along the ischemic boundary zone of the cortex and striatum in MCAo rats treated with exosomes compared with PBS control. Exosome treatment significantly increased the number of newly formed doublecortin (a marker of neuroblasts) and von Willebrand factor (a marker of endothelial cells) cells. Our results suggest that intravenous administration of cell-free MSC-generated exosomes post stroke improves functional recovery and enhances neurite remodeling, neurogenesis, and angiogenesis and represents a novel treatment for stroke.

Lankford, K. L., et al. (2018). "Intravenously delivered mesenchymal stem cell-derived exosomes target M2-type macrophages in the injured spinal cord." PLoS One 13(1): e0190358.

In a previous report we showed that intravenous infusion of bone marrow-derived mesenchymal stem cells (MSCs) improved functional recovery after contusive spinal cord injury (SCI) in the non-immunosuppressed rat, although the MSCs themselves were not detected at the spinal cord injury (SCI) site [1]. Rather, the MSCs lodged transiently in the lungs for about two days post-infusion. Preliminary studies and a recent report [2] suggest that the effects of intravenous (IV) infusion of MSCs could be mimicked by IV infusion of exosomes isolated from conditioned media of MSC cultures (MSCexos). In this study, we assessed the possible mechanism of MSCexos action on SCI by investigating the tissue distribution and cellular targeting of DiR fluorescent labeled MSCexos at 3 hours and 24 hours after IV infusion in rats with SCI. The IV delivered MSCexos were detected in contused regions of the spinal cord, but not in the noninjured region of the spinal cord, and were also detected in the spleen, which was notably reduced in weight in the SCI rat, compared to control animals. DiR "hotspots" were specifically associated with CD206-expressing M2 macrophages in the spinal cord and this was confirmed by co-localization with anti-CD63 antibodies labeling a tetraspanin characteristically expressed on exosomes. Our findings that MSCexos specifically target M2-type macrophages at the site of SCI, support the idea that extracellular vesicles, released by MSCs, may mediate at least some of the therapeutic effects of IV MSC administration.

Sun, X., et al. (2018). "Intravenous mesenchymal stem cell-derived exosomes ameliorate myocardial inflammation in the dilated cardiomyopathy." Biochem Biophys Res Commun 503(4): 2611-2618.

Mesenchymal stem cells (MSCs) have been shown to be efficacy to attenuating cardiovascular inflammation; however, there are many limitations to stem cell treatment. Present study was to prove MSC-derived exosomes (MSC-Exos) could alleviating inflammatory cardiomyopathy by improving the inflammatory microenvironment of myocardium, especially by regulating the activity of macrophages. Mice were intraperitoneal injected of doxorubicin (DOX) to establish a dilated cardiomyopathy (DCM) model, and then received intravenous injection of either MSC-Exos or PBS as control. Mice receiving MSC-Exos showed improved cardiac function via echocardiography and attenuated cardiac dilation via HE staining, as well as reduced cardiomyocytes apoptosis. Expression levels of inflammatory factors were reduced. And there was a significant decrease of the inflammatory cells infiltration in the MSC-Exos treatment group comparing to the PBS group. Meanwhile, MSC-Exos could remarkably attenuate the pro-inflammatory macrophages amount in both blood and heart, which was proved that MSC-Exos relied on the JAK2-STAT6 pathway mediating macrophages activation. MSC-Exos improved the inflammatory microenvironment of dilated cardiomyopathy by regulating the polarization of the macrophage, which may hold promise for dilated cardiomyopathy clinical therapy.